Collaborative Bioethics 2

Erick Valdés
Juan Alberto Lecaros *Editors*

Handbook of Bioethical Decisions. Volume I

Decisions at the Bench

Springer

Collaborative Bioethics

Volume 2

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The aim of **Collaborative Bioethics**, is to draw attention to an underexplored but increasingly important area of scholarly thought and action: bioethics as a co-creative activity of ethicists working with scientists rather than as always a reaction to biomedical developments after the fact. The scope of this series is determined by each major subfield of science and medicine that raises ethical uncertainties for researchers, regulators, and the public.

Collaborative Bioethics is a series that will provide a central hub for timely publications addressing ethical issues that are emerging right alongside the science. As such, this series will be of interest to a wide swath of readers: bioengineers and scientists at all professional levels; bioethicists intrigued by bioengineering and medical advances; research regulators and funders; and the general public.

Erick Valdés • Juan Alberto Lecaros
Editors

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Foreword

The term "Bioethics" appears to have first been used in 1927 by Fritz Jahr, a German protestant pastor, in an article titled "Bio-ethics: A Review of the Ethical Relationships of Humans to Animals and Plants." Jahr (1927: 2–4) was calling for the development of what today would be called an ecological ethic. That was also the sense in which Van Rensselaer Potter, an American biochemist and oncologist, used it in the 1970s, apparently without knowing of Jahr's earlier usage, to urge that we broaden our understanding of ethics to include not just how we should act with regard to our fellow-humans but also towards our environment, and the biosphere of our planet (Potter, 1970). Potter in turn acknowledged his debt to Aldo Leopold, the ecologist who wrote of a "land ethic" that would govern our relation "to land and to the animals and plants which grow upon it" (Leopold, 1949).

To coin a term is one thing; to control how it is used is another. In 1969, just a year before Potter first used the term "bioethics" in print, Willard Gaylin and Daniel Callahan founded the Institute of Society, Ethics and the Life Sciences, initially located in Hastings on Hudson, New York. The founding of the Hastings Center, as the Institute became known, reflected and facilitated the rapid growth of interest in the interdisciplinary field covered by "Society, Ethics and the Life Sciences." But that field needed a shorter name, and "bioethics" was the one that caught on. By 1978, when the first *Encyclopedia of Bioethics* was published, it was clear that the term was being used to refer to an area of studies concerned with ethical, social, and legal issues in the biological and life sciences. Issues in medicine and health care were particularly prominent among them (Reich, 1978).

Potter himself recognized that the term he proposed had developed a meaning other than the one he had intended. He tried to rescue the term by adding the prefix "Global" to distinguish bioethics in the sense that he was concerned with – our ethical approach to the world as a whole, and to the global biological systems on which we depend – from ethical issues in the biological and life sciences. But "global bioethics," in the sense that Potter intended it, was never widely used (Potter, 1988).

I start with this look back at the origin of the term because the *Handbook of Bioethical Decisions* edited by Erick Valdés and Juan Alberto Lecaros goes some way towards reuniting the two senses of "bioethics." This first volume includes

many of the core ethical issues in bioethics, as the term is now understood, including gene editing, experimentation with human embryos, cloning, genetic enhancement, the extension of human life, and the ethics of experimentation on nonhuman animals; but a substantial part of this volume is headed "Animals, Food and Environment." That includes several chapters examining our relations with animals, some of which are concerned with the broader question of the moral status of animals. The final section, on "GMOs for Global Challenges," is concerned with the ethical issue of feeding the world in a time of climate change, and also considers whether the use of genetically modified foods poses environmental risks, and what it means for sustainable agriculture – issues that are not always regarded as part of "bioethics" as it is narrowly conceived but which, as I have shown, fall squarely within the original use of the term, and which, in view of their great significance for the future of our planet and all who live on it, richly deserve their inclusion in this volume.

The *Handbook of Bioethical Decisions* is a monumental project, bringing together, over its two volumes, a total of 68 full-length chapters on a wide range of issues in bioethics, focused on the ethics of biomedical research. You will find here a variety of different, and often conflicting, approaches to some of the key questions discussed. For example, now that the technique known as CRISPR makes gene editing possible with a level of precision that previously was only a dream, this newfound ability raises a variety of deep, ethical questions. Brendan Parent presents a balanced view of several of these ethical issues. He does not find a decisive objection to gene editing but emphasizes the importance of distributing its benefits fairly, especially to vulnerable and marginalized populations. In contrast, Calum MacKellar regards the use of gene editing to avoid genetic disabilities as form of eugenics, unless the parents wish to avoid having a disabled child is due solely to their belief that they would be unable to cope with a child with the anticipated disability. If they have the capacity to cope, but prefer a child without the disability because, for example, they believe that the disability will reduce the child's quality of life, or the child's ability to live independently, that is, in MacKellar's view, contrary to the principle that all humans have equal dignity and worth, and therefore, always wrong. That view is in turn opposed by Ferdinando Insanguine in his chapter about gene therapy and germline cells research. Erick Valdes also takes a more liberal position when he writes about the use of preimplantation genetic diagnosis to avoid genetic disabilities.

A separate set of essays discuss the possibility of using gene editing or other techniques for enhancing our children or future generations. Nick Bostrom, Anders Sandberg, and Matthew van der Merwe convincingly set aside the objection that we are unlikely to be able to improve on human nature as selected by evolution, while Daniel Loewe weighs the case for enhancing mood. Because severe, prolonged depression is responsible for more years of suffering than almost any other illness, the case for enhancing the mood of people suffering from this condition is very strong. But if we learn how to safely change mood, should we limit ourselves to eliminating such clearly negative abnormal mental states, or would it also be permissible to select for children with a tendency to be more positive and cheerful than

the median for human beings? Further, Elena Atienza Macias asks, would selecting for psychological states that confer a competitive advantage in certain sports be a form of cheating, like doping?

At the end of this section on enhancement, Allen Porter writes about research aimed at enabling us to live longer – perhaps much longer. In contrast to almost all of the other chapters in this volume, Porter does not express any opinion on whether research with this goal is, or is not, ethically defensible or even obligatory. Instead, he rejects the idea that we can search for true, or more defensible, or better argued, views on normative ethical questions. This belief is, Porter holds, a legacy of the Enlightenment idea that it is possible to offer a rational justification for a secular morality on grounds that will appeal to rational beings. Those who, like Porter, believe that we are living in a "postmodern" world consider this hope for rational justification to be untenable. The claim that it is untenable is, however, an assumption rather than a position for which Porter argues in any depth. Moreover, even if we cannot provide rational foundations for particular moral theories that will convince everyone, it will still be valuable to explore and clarify the ethical implications of widely held ethical views. Debates about normative ethical questions, including the question whether it is desirable to enable humans to live to 150, or even longer, can be seen as doing just that. It is, no doubt, to the credit of the editors that they have been sufficiently open-minded to include in their *Handbook* a chapter that attacks the foundations of the volume itself, but given the inclusion of Porter's essay, I would have liked to also see an explicit defense of rational argument in secular ethics.[1]

During the COVID-19 pandemic, there was no higher research priority than the development of a safe and effective vaccine against the virus that was causing so many deaths. Although vaccines were developed in a shorter time than many had expected, the organization 1Day Sooner encouraged people to register their willingness to participate in human challenge trials, as such trials could have enabled us to have vaccines even sooner. (The name of the organization was intended to make the point that every day's delay in getting a safe and effective vaccine to market would cost thousands of lives). Many people registered their willingness to take part in human trials, mostly young, healthy people at low risk of death or serious illness from COVID-19. (At the time of writing, nearly 40,000 volunteers, from 166 countries have registered).[2] Yet, as Erick Valdes describes, there was a surprising reluctance to make use of these fully informed consenting volunteers. Some people suggested that to make use of them would violate the Kantian principle of using people as a means, even though in this case they were giving their informed consent. When acting on what some believe to be an ethical principle is going to cost many lives – as the initial refusal to hold human trials did – we need to have an extremely high level of confidence that the principle is both sound and sufficiently important

[1] For one such defense, based on the views of the Victorian philosopher Henry Sidgwick, see: de Lazari-Radek and Singer (2014).

[2] www.1daysooner.org, Accessed January 19, 2023.

to take precedence over saving the lives at stake. I do not believe that the arguments against using volunteers in human challenge trials were so strong that any reasonable person could have the required degree of confidence in them.

In contrast to this extreme reluctance to use informed human volunteers in low-risk, high value medical research, more than 100 million animals are used each year, without their consent, in experiments that cause them severe suffering and death, often in research that has low or negative value. Several chapters in this volume discuss the ethics of this use of animals. That in itself is to be applauded, because it is wrong to limit our ethical concern to members of our own species. Pain is, in itself, a bad thing, irrespective of the species of the being experiencing it. Nevertheless, I cannot refrain from expressing the opinion that some of the chapters discussing the use of animals in research fail to present a realistic picture of research on animals as it is carried out today. They may give readers the impression that the various regulations and guidelines described are sufficient to prevent any unnecessary infliction of pain or suffering on animals. Thus, they are able to conclude that the practice of experimenting on animals is ethically acceptable. Yet as Jeff Sebo points out in his powerfully argued chapter on "Integrating Human and Nonhuman Research Ethics," in the area of research on animals, the necessity of using animals, or even of inflicting pain on them, is interpreted to mean what is necessary to achieve the goal of the research, without assessing whether this goal is itself worthwhile. For example, poisoning hundreds of animals may be "necessary" for testing the safety of a drug, but the drug may be a "me-too" drug that a company wishes to bring to market in order to obtain a share of a lucrative market that is currently dominated by a patented drug manufactured by a competitor. These "me-too" drugs do not need to perform better than the existing drug, and may even be less effective, but the poisoning of the test animals will still have been considered "necessary" because the drug could not be marketed without it (Aronson & Green, 2020).

Severe suffering can also be deliberately inflicted on animals when it is judged "necessary" for research that has only a very remote prospect of yielding any benefit to anyone other than the experimenters who are making their career by experimenting on animals. To give just one of a huge number of examples, and one that is far from being the worst: researchers at Florida State University put prairie voles (small rodents native to American grasslands) in plastic tubes and used plastic mesh and Velcro straps to, in their own words, "completely immobilize the subject." They then kept them, unable to move at all, for a full hour. They did this because they were studying depression, and this kind of immobilization had been found, in previous research, to cause stress to the voles. Prairie voles are predominantly monogamous and form pair-bonds, and the study showed that the presence of a partner reduced the signs of stress in the immobilized vole. The researchers conclude that "As social environments are a critical part of our lives, we must continue to explore this area of research to understand how social bonds may ultimately shape our health outcomes and well-being."

Voles may resemble humans in being predominantly monogamous, but their monogamy is not an adequate reason to subject them to an hour of severe stress – and if vole pair-bonds really are anything like human relationships, the partners

observing the immobilized voles must also be undergoing a stressful experience. This research was funded by the US National Institutes of Health and presumably was approved by the usual institutional animal care committee, and certified as complying with US regulations for the care of animals in experiments. Yet it is only one of several experiments involving stressed voles by various authors, and in turn only one of a much larger number of experiments conducted, over many decades, and in many countries, that deliberately cause stress and anxiety to a very large number of animals, without achieving significant benefits for humans (Donovan et al., 2023).

On this issue of the ethics of using animals in research, as with all the other issues considered in the *Handbook of Bioethical Decisions*, the material included will stimulate many valuable discussions. It is my firm belief that open, reasoned, and civil exchanges between people of different opinions lead to better outcomes than not having such exchanges. It is in this spirit that I encourage you to read the chapters that follow with an open mind, to engage critically with the arguments they contain, and yet at the same time to be prepared to learn from them.

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Acknowledgments

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We are also very grateful to the impressive line-up of authors who participate in this volume, all of them leaders in their corresponding areas. Their commitment, patience, and especially their brilliant work have undoubtedly made it possible for the *Handbook* to become a vibrant reality.

Santiago, Chile — Erick Valdés

Santiago, Chile — Juan Alberto Lecaros

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Chapter 1
Introduction: Biomedical Research in One World: Current and Future Challenges

Erick Valdés and Juan Alberto Lecaros

Abstract Biomedicine has sparked interest around the world as it may offer knowledge about fundamental biological processes as well as latest generation breakthroughs to human health. Yet with these developments many questions arise about some technical aspects of achieving desired results and avoiding unwanted effects, and about a variety of uses that may include not only healing, but also preventing disease in current and future generations, or even altering traits unrelated to health needs. As the issue of biomedical regulation displays itself at national and international levels, collaborative bioethics must harmonize regulation in a context of different countries laws. Although problems and concerns are different in heterogeneous social and cultural contexts, the application of new biomedical breakthroughs is similar. Therefore, transnational and intercultural regulation is necessary, especially considering global epistemological and regulatory scopes of bioethics.

Keywords Biomedical research · Bioethics · Biomedicine · Enhancement technologies · Biomedical regulation

As current pandemic goes through, planetary risk looming over the world has become an indisputable reality, so thinking of future devastating scenarios for mankind seems to be a task far from trivial. Global catastrophe is no longer mere literature and thinking that the entire globe is not facing any threat encompasses counterfactual and counterintuitive arguments. Prophesying our future then is not a frivolous endeavor as biotechnological and biomedical breakthroughs display not only the ability to fight diseases and improve life, but also comprise a whole brand-new constellation of hazards never faced before in our species' history.

The exponential growth of the contemporary biotechnological device seemed, at first, to herald the arrival of a promised dawn for humanity. Yet, such innocent

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conjecture turned into a prelude to disturbing events. All super powerful bio-tools originally aimed at improving lives and fighting disease hide the underlying risk of a malicious use. This scenario demands, now more than ever, positive actions from different regions of human thought.

Reflection on bioethics and new technologies applied over life should be based on different forms of interaction with natural and animal world, as well as with society and other human beings, rather than on the powers offered by these new technologies. However, such inventions make possible an important transformation of natural environment that distort the objectivity of human gaze before the planetary deployment of contemporary technological apparatus.

New technologies are capable of building new social universes and challenging human beings to build unprecedented vital projects, in tune with new demands of the twenty-first century. In this scenario, it is necessary to sustain more specific theoretical positions that help understand and regulate a profuse array of technological events, whose scope and consequences seem like fracturing traditional ethical analysis. Such inexorable mutation drives the need to reestablish a moral congruence between ethics, policy and latest generation technologies, which are not external regarding the settings they work in, but, in contrast, they modify individual and social capacities to face moral dilemmas emerged from biomedical and biotechnological applications. New technological gadgets are not simply instruments; they also redefine reason's limits continually shaped by interactions between humans and their environment.

An 'ethics/biomedicine' constellation appears in contemporary times, traversed by an unprecedented element: the extension of human action' scopes, made possible by technological progress. This very revolution reaches all spheres of human existence, which become fractured by such technological colonization that embraces all levels of human networks and relationships. Therefore, a collaborative bioethics able to provide a right understanding of biomedical practices and aimed at integrating different lines of research, as well as relating bioethical issues to regulatory debates is needed. The dematerialization of science through data-based research brings up new challenges for biomedicine's governance in an open science context. Collaborative bioethics, then, comes into play in new open science atmospheres, oriented to common good and to interjurisdictional regulation, goals that Covid pandemic has made visible, by sharpening the need for a global collaborative research. The importance of a global scientific community to carry out biomedicine that engenders immediate translation, as well as innovative therapies reaching the market and the patient quickly, is, therefore, undeniable.

Such a task seems to necessarily require unmasking what is behind biomedical research, as the form of rationality underlying human intellection of it, is often exclusively intended to calculable and measurable results. While biomedicine is conceived as a determining factor in the configuration and transformation of the world, the need for collaborative bioethics to participate in such transformation must now be seriously considered.

This encounter bioethics-biomedicine mobilizes public debate beyond ethics and law, as it significantly concerns the entire social spectrum, mainly regarding the true scope of powerful and revolutionary inventions, which encompass not only ethical

but also anthropological challenges, such as cloning, chimeras, gene editing research, enhancement, dysgenic biogenetics, and different disturbing modifications of the environment, in an era of anthropocene, that seems like forcing us to improve human nature.

Biomedicine has sparked interest around the world as it may offer knowledge about fundamental biological processes as well as latest generation breakthroughs to human health. Yet with these developments many questions arise about some technical aspects of achieving desired results and avoiding unwanted effects, and about a variety of uses that may include not only healing, but also preventing disease in current and future generations, or even altering traits unrelated to health needs (National Academies of Science and Medicine, 2017: xi).

As a matter of fact, any therapeutic germline gene editing can also be done for non-therapeutic purposes, opening up a wide range of potential bioethical issues. Also, the reception of the ethical scope of this technique is complex, since, for its extension to biotechnological industry and its massive commercialization, the old figure of a tacit social pact is used, assuming an implicit agreement of society to be introduced into daily life. In this scenario, an argumentative and discursive model of consensus is preferable, where all those who may be affected by these new tools (including non-human animals and nature) should be represented in a deliberative process ending in explicit and reasoned decisions about the eventual proliferation and regulation of biomedicine, especially when it gets a non-therapeutic dimension.

Some principles that can serve as a basis to articulate policy and regulatory frameworks to carry out biomedical practices with more ethical and legal certainty, may be the following (Valdés, 2021: 179–180):

Beneficence: that is, promoting the welfare of society, maximizing biomedicine's benefits and minimizing its risks.

Transparency: openness in the exchange and dissemination of information before carrying out any genetic editing practice, understandable and accessible enough for those potentially affected.

Precaution: protecting society from possible risks associated with biomedical applications. Thus, research should only be carried out when there is solid scientific evidence on those applications' aftermaths. Otherwise, research should not be carried out.

Autonomy: respect for people and their individual decisions.

Equality: all people have the same moral value in bioscientific research, regardless of their genetic qualities.

Distributive justice: similar cases must be treated equally, without any exogenous element contaminating the balance of benefits and risks.

Transnational cooperation (The National Academies of Sciences, 2017): nations should be committed to work together to articulate interjurisdictional regulatory to be applied in different cultures and traditions.

As for articulating elements for international and integrative regulatory models, some rules to be considered may be (Valdés, 2021: 180):

- Implement gene editing procedures and applications to promote health.
- Guide practices for treatment and prevention of diseases.
- Minimize risks with a high degree of scientific certainty.
- Ensure a reasonable balance of risks and benefits.
- Deliver and disclose confidential information timely.
- Assume public input or feedback as a very important element of judgment.
- Proceed with caution, allowing systematic monitoring of biomedical practices, by considering cultural and social views.
- Ensure high-quality experimental design and analysis, permanently reviewing and evaluating scientific protocols.
- Give the same value to all subjects involved in research.
- Respect and promote self-determined decisions.
- Prevent different forms of abusive research practices.
- Do not stigmatize disability.
- Impartially distribute benefits and burdens of research.
- Guarantee broad and equitable access to clinical applications resulting from research.
- Respect different national policies to articulate interjurisdictional regulatory models.
- Coordinate standards and regulatory procedures between different countries whenever possible.
- Ensure transnational collaboration to share data and samples.

On the other hand, concerns about regulation of enhancement technologies have boosted. In this book there is consensus on policy and oversight must integrate and specify, in terms of content, general bioethical principles already expressed in international documents: primacy of human being in the field of scientific and technological progress, respect for physical integrity, non-commercialization and arbitrary manipulation of the human body and its parts, informed and responsible autonomy, and justice, among others. Likewise, collaborative bioethics must define and specify meanings for such principles, with special reference to enhancement technologies. The protection of integrity and identity must be made explicit with reference to autonomy instead of a vague concept of dignity. In addition, justice must be understood as a compatibility between the right to enhancement and the right to refuse it, as a conscious option to refrain from using enhancement technologies, without causing discrimination, disadvantage or marginalization.

Collaborative bioethics may represent a general horizon for regulation, which must be clarified in relation to individual technologies. Given biomedical development's dynamism, it is essential that bioethics methodologically develops towards an updated monitoring of scientific research. Scientific advisory committees, in continuous dialogue with bioethicists, are indispensable for this purpose. As it will be seen in the Volume II of the *Handbook*, creating national and international bioethics committees is also relevant, as they can contribute to critical reflection on these issues in a context of ethical and legal pluralism.

Bioethical debates must also be opened and extended towards the public space, through ample information and, at the same time, it must consider and monitor social expectations and concerns. In this fashion, collaborative bioethics must balance scientific assessment and public consultation; it is essential to seek a balance in the relationship between science and society. Furthermore, it is key that democratic participation be informed, inclusive and active. This is possible by promoting public debate in any regulatory standardization process.

As the issue of biomedical regulation displays itself at national and international levels, collaborative bioethics must harmonize regulation in a context of different countries laws. Although problems and concerns are different in heterogeneous social and cultural contexts, the application of new biomedical breakthroughs is similar. Therefore, transnational and intercultural regulation is necessary, especially considering global epistemological and regulatory scopes of bioethics.

Many legal systems around the world – one world – have been modified or updated, especially stimulated by new genetic technologies applied to life. New regulatory regimes have been developed to understand and resolve still emerging concerns raised by practices such as genetic testing and the use of genetic information. Additionally, social implications of these new inventions have also been subject of debate, to define and implement security policies and protocols for their use. In this way, disturbing confines of genetic engineering have led to debate on reproductive cloning, experimental subjects' safety, implementation of human challenge studies, redesign of human genome, and genetic intervention of life as a whole, among others.

The emergence of predictive genetic tests - which reveal the increasing risks or, in some cases, the virtual certainty of suffering future diseases - has caused widespread concern about the potential use of genetic information among insurance companies, health institutions, employers, and, eventually, other social institutions, as the potential detriment of future generations of humans seems to be closer than before. Such consternation has been important enough to prompt, in the United States and some Western European countries, the installation of a legislative agenda to discuss the scope and eventual consequences of the Human Genome Project and other related programs.

Some reasons for this agenda are, basically: 1. As health care in several countries has been increasingly effective, the threat of genetic diseases being excluded from coverage has also grown; 2. Predictive genetic tests threaten to move many people from healthy to asymptomatic, as they are destined to suffer certain diseases in the future; and 3. Concerns of health institutions, researchers, scientists, and the genetic testing industry in general, related to healing, investigating, and expanding tests, have been equated with the worries of individuals who are patients, eventual test subjects, and potential clients. These factors have generated a powerful initial impetus to implement legislative reform measures, as well as have challenged health and insurance companies about the role and social responsibility they will have in this new scenario.

As the problem of regulating challenging practices and scenarios (artificial intelligence creating in silico and in vitro models to perform research, paradoxes in

animal research, producing chimeras, and at the same time, refining the requirements to use animals in laboratories, and environmental and sustainability challenges GMOs entail), scales nationally and internationally, collaborative bioethics must harmonize jurisdictions to conduct biomedical research.

The *Handbook of Bioethical Decisions* (Vol. I: Decisions at the Bench) is aimed at addressing and analyzing the most important ethical concerns and moral quandaries arisen in biomedical and scientific research. Part One, Research with Human Subjects, addresses topics such as genetic and cell research, enhancement research, research with human biological samples, and biomedical challenges in research, among others. Part Two, Animals Food and Environment, analyzes the use of animals in scientific research, decision making and alternatives to animal use in research, and GMOs and environmental issues. We are aware of that some of the chapters dedicated to the use of animals in research may give the reader the wrong impression that, as Peter Singer asserts in his Foreword, current regulations and instruments are enough to prevent animals from suffering when research on them is carried out. We are far from that assumption. Yet we decided not setting aside visions different from ours in order to enrich such an important section of the *Handbook*.

As this volume identifies and problematizes on a comprehensive range of ethical issues researchers must deal with in different critical contexts, the *Handbook* may be helpful for them to make decisions and deliberate in complex practical scenarios. In this fashion, we reunite different points of view, even some that evidently collide with the very basis of this work. However, instead of including only essays tuned with our own position we have assumed an inclusive criterion under the strong conviction that such a thing will give readers room enough to get a better knowledge and take without any sort of external manipulation their own side on pressing bioethical issues of the day.

Consequently, and far from an oblique view, this work seeks to engender dense ethical epistemology scientists can count on when conducting latest generation biomedical research. By bringing together an impressive array of contributions on the most important elements and categories for “at the bench” bioethical decisions as well as offering chapters by some of the most world renowned and prominent experts in bioethics, the *Handbook* will probably become a paradigmatic text in its area, so we are proud to present it to the public.

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Part I
Biomedical Research: *Genetic and Cell Research*

Chapter 2
Learning from Icarus: The Impact of CRISPR on Gene Editing Ethics

Brendan Parent

Abstract After centuries of crude genetic engineering through crossbreeding, the ability to directly intervene in life's fundamental blueprint led to breakthroughs including longer lasting produce, cheaper insulin without using animal organs, and research animal models demonstrating disease progressions. But this was slow, resource-intensive work. After four decades of moderate technique advancements, CRISPR-Cas9 burst on the scene and blew the doors off previous gene editing (GE) mechanisms. Suddenly, long-standing philosophical thought experiments about whether we should put wings on donkeys and design virtuoso violinists became more concrete possibilities. Most say the ease, speed, and great potential of CRISPR do not fundamentally change the gene editing ethics questions, they just make it more urgent to answer them. But CRISPR traits do change the ethics. They play to our hopes, make us take risks, and might threaten our commitment to solidarity. This chapter explores long-standing GE ethics considerations including utilitarian calculations, "Playing God," transparency and democracy, informed consent, treating disease versus accepting difference, and most importantly fairness and equity. Each ethics issue will be demonstrated through current and near-future gene editing applications, and will focus on how these interplays are impacted by the unique attributes of CRISPR based tools.

Keywords CRISPR-Cas9 · Gene editing · GE mechanisms · Gene therapy · Gene editing ethics

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Introduction

Gene editing has the capacity to make extraordinary advances for human well-being. It also makes us question our identity, values, and role on the planet. In some cases, it might just go wrong and harm people. Each decade since the conceptualization of recombinant DNA has been marked both by gene editing (GE) progress and renewed concerns about whether we should be engaging at all and if so, what limitations and expectations will best support human flourishing. Strict opponents have generally been overwhelmed by proponents with at least some attention to how to mitigate risks. Only human germline engineering — edits to embryos that would be inherited by future generations — has received a temporary stop supported by majorities of the public and scientific community. But significant ethics concerns remain for each GE endeavor, which have stagnated in terms of their power to shape practice.

Meanwhile, CRISPR-Cas9 has redefined expectations for gene editing. The unprecedented speed, efficiency, and low cost of "Clustered Regularly Interspaced Short Palindromic Repeat" (CRISPR) sequences combined with Cas proteins streamline almost every aspect of gene editing research. This gene editing tool and its subsequent relatives, hereafter CRISPR, have led to exponential growth in GE research and practice. It has been argued that CRISPR has not changed the GE ethics landscape, it just makes existing concerns more urgent. But immediacy has transformed the ethics landscape in critical ways. The simplicity and accessibility of CRISPR-based editing make it easier to ignore risks in favor of potential benefits, while little has changed about the actual risk-benefit balance. CRISPR could revolutionize agriculture, healthcare, environmental preservation, and energy production. But it also plays on our predilection for hope and if deployed irresponsibly, it could undermine our obligations to justice and solidarity.

This chapter will first provide a brief history of gene editing. It will then describe what, if anything, is ethically unique about CRISPR, and discuss how property rights to CRISPR affect ethical considerations. It will then consider long standing GE ethics considerations — utilitarian calculations, "playing God," transparency and democracy, informed consent, treating disease versus accepting difference, fairness and equity — in context of several current and near future applications. These include gene drives, somatic and germline human interventions, and nonhuman animal modification for xenotransplantation. Every CRISPR application could be examined through the light of countless ethical considerations. This chapter will only be able to examine a few of these interplays and will focus on how they are impacted by the unique attributes of CRISPR based tools.

Brief History of Gene Editing and CRISPR

While genetic *engineering* is old — going back to unintentional domestication of canines 20,000 years ago, to intentional pea plant breeding in the mid-1800s — gene *editing* is relatively new. The discovery of life's common denominator in genes

composed of nucleic acid structures in the 1950s led to a fair question: Why can't we replace genes we don't want with genes we do want?

Preparatory work in the 1960s involving gene isolation, ligation, and methylation and restriction enzymes launched the era of laboratory gene splicing and recombinant DNA in the 1970s. This capacity widened everyone's eyes. Should we edit life's foundational structure? The message from the 1975 Asilomar conference of leading scientists was to proceed, but cautiously (Berg et al., 1975). The 1980s brought development of genetically engineered products like insulin to treat diabetes that drastically reduced the need for pig and cow pancreases, and intergeneric marvels like knock-out mice that enabled examination of disease processes and interventions.

Fascination and excitement surrounded the possibility that these milestones were paving the way to editing humans — the elimination of fatal diseases or maybe smarter and more compassionate societies. Yet, into the 90 s and early 2000s even pioneering geneticists recognized the technology — largely driven by protein engineering of homing endonucleases or DNA binding proteins like zinc finger nucleases and TALENS nucleases (Bak et al., 2018) — was too clunky, too imprecise to risk editing the germline of our own species. Not to mention the risks of a new eugenics where a few empowered people dictate desirable characteristics and available edits, exacerbating marginalization and discrimination of disempowered communities (Sufian & Garland-Thomson, 2021). These concerns led to regulations in several countries that, to various degrees, prohibit clinical application of germline editing (Araki & Ishii, 2014). But many countries still permit extensive germline editing research and many acknowledge a future where the technology will be safe enough to translate into medical practice (Araki & Ishii, 2014). All the while, work on nonhuman applications like phosphorescent tobacco plants and heartier and larger farmed salmon continued in earnest (Van Eenennaam & Muir, 2011; Ow et al., 1986).

In 2012/13 — after a global series of CRISPR-related work going back to 1993 — CRISPR-Cas9 was characterized at the biochemical level and harnessed for editing eukaryotic cells ("CRISPR Timeline", n.d.). This system captured the ability of a bacterial adaptive immune system to recognize potentially harmful invading viruses, break the DNA of such viruses, and incorporate a "snapshot" of this DNA into the bacteria's own DNA to then use for future invader identification (Memi et al., 2018). Doudna and Charpentier at Berkeley and Zhang at MIT proved that such a system could be engineered to break DNA at desired locations and replace specific sequences. Almost overnight, a 45 year-long philosophical thought experiment — whether to genetically edit human embryos — developed the weight of reality.

Not all forms of human GE remained off limits. Somatic gene editing or "gene therapy" — genome manipulation of an individual that is not passed on to future generations — has been researched since 1990. But in 1999, a young person with a mild genetic disorder, which was managed with diet and medication, enrolled in a gene therapy experiment at a major research university in the United States. He received the maximum dose and had an immune response that caused massive organ

failure and his death (Gelsinger & Shamoo, 2008). Some say this and other gene therapy studies that led to cancer and death set the field back a decade (Couzin & Kaiser, 2005). These events were critical warnings about unknowns and risks.

Gene therapy cases undoubtedly informed the consensus statement of leading genetics researchers, attorneys, and ethicists who met in 2015 to discuss CRISPR's potential for a different kind of human GE — germline editing. Their recommendations were to hold off on clinical germline editing, bolster transparent research, educate the public, and convene more stakeholder meetings (Baltimore et al., 2015). Since then, two Chinese teams modified nonviable embryos with limited success; an American team did so with greater success (Servick, 2017). None of these researchers intended to bring embryos to fruition. But all their efforts were intended to pull such a future closer, approaching but respecting legal lines. And then came the 2018 Second International Summit on Human Gene Editing in Hong Kong.

At this event, Chinese Scientist He Jiankui revealed that he had used CRISPR to modify nonidentical twin girl embryos, and that they were born (Greely, 2021). He's audacity was both shocking and completely predictable. He was universally condemned and excommunicated from the scientific community. China apologized on the global stage and ultimately sentenced He to prison (Cyranoski, 2020). The specific facts, ethical violations, and aftermath of this case will be revisited later in this chapter. The overarching narrative demonstrates the key ethical challenge posed by CRISPR — how ought we to handle such a powerful, accessible, and imperfectly understood tool? Are we capable of exercising adequate restraint and accurately weighing risks and benefits? Just as He has been punished, germline editing research continues and CRISPR-based gene therapy trials in humans are currently underway (Uddin et al., 2020).

Human applications are but a small fraction of current GE research and practice. CRISPR-based developments are exploding in genetically modified foods (Mah, 2019), attempts to edit wild animal and insect populations (von Gleich & Schröder, 2020), synthetic biology (Schmidt & Platt, 2017), xenotransplantation (Ryczek et al., 2021), and even pet animals (Sohal et al., 2020). The number of academic publications about genome editing has increased exponentially after CRISPR's appearance (Duensing et al., 2018). Each of these arenas will have significant consequences for the human condition.

What Is Ethically Unique About CRISPR?

A common refrain is that CRISPR does not pose new ethics challenges with regard to gene editing, it only recapitulates and makes more urgent longstanding concerns (Mulvihill et al., 2017). But this urgency does create new ethics challenges that revolve around the values we prioritize. More than four decades have built toward the ability to predetermine aspects of life's manifestations with promises of healthier and longer lasting food, disease-free mosquitoes, industrialized microorganisms that can produce fuel and reduce pollution, and eliminating human diseases.

The pace has been a valiant, resource-intensive, and inexorable trudge, thanks to deep emotional and financial investments. Suddenly, CRISPR obliterates the overhead costs yet the expansive hope and money remain. Our capacity to anchor the brilliant possibilities with recognition of risks had previously been supported by technical limitations. With the anchor severed, we might be finding ourselves sprinting into environmental releases without adequate public engagement (Caplan et al., 2015), and back into clinical trials without adequate understanding of off-target mutations (Lander et al., 2019). Such haste is explainable by deeply human psychological characteristics. Hope creates blinders that can make us fixate on benefits and ignore risks, and hope is empowered when goals are made more accessible (Caplan, 2021). Taking significant risks is not necessarily unethical, particularly when possible benefits are immense. The problem arises when the most vulnerable in society are likely to be the worst affected by decisions that prioritize progress over caution, and when such decisions are made without adequate consideration for, and input from, these populations.

Who Owns CRISPR, and Does This Matter?

Despite a 2013 Supreme Court decision that genes cannot be patented (Mulvihill et al., 2017), thousands of CRISPR and CRISPR-Cas gene editing systems are patented (Mischel, 2021). While products of nature cannot be owned, many legal systems want to reward ingenuity and protect interventions that employ these products for new ends — like wielding CRISPR systems in human and nonhuman animal cells where they do not naturally occur— as intellectual property (Mulvihill et al., 2017). The patent owners will drive what is done with these tools. Concentrating CRISPR GE power in individual hands, and allowing markets to drive such decisions, makes it easier for hope — and avarice — to overwhelm caution.

The original CRISPR-Cas9 fight between Doudna/Charpentier of Berkeley and Zhang of MIT has yet to be fully resolved, but there are now patents on tweaks to their system and on more prominent tweaks using different Cas proteins (X,Y,12,14) that could be more efficient and effective for specific applications (Mischel, 2021). This makes it unlikely that the CRISPR world itself will be owned by any one individual or even just a few. But the fact that such systems can be owned, marketed, and licensed does not incent attention to ethical concerns for any person or group likely to make extraordinary sums of money.

Diversifying ownership of gene editing does not by itself create structures that ensure adequate review of research results for off-target editing effects, containment strategies for newly created organisms, engagement plans for local communities where research is taking place, or development of effective informed consent protocols for human subjects. Generally, CRISPR-based GE can take place at nonprofits like research universities without licenses as long as they do not profit (Horizny, 2020/2021), and these institutions tend to have ethics oversight mechanisms that sometimes function better than nothing (Caplan & Redman, 2018). But most private

sector biotechnology work is subject to significantly less scrutiny. The scale and speed of the private sector is great for innovation, and most prominent actors have awareness of some risks (Baltimore et al., 2015). But the consequences of one GE misstep or one inadequately supervised GE human research trial could be significant. Furthermore, those who own and supply CRISPR technology are less likely to be attuned to the needs of vulnerable populations most likely to be affected by poorly designed/understood GE human subject research trials, accidentally released GE microorganisms, or intentionally released but uncontrollable GE organisms.

Technical Concerns, Risks, and Benefits

The most discussed GE ethical consideration is weighing risks against benefits, and specifically risks that stem from technical challenges. These consequentialist concerns are the easiest for many to grasp, rooted in the desire to obtain the best outcome for society. Moratoriums on human germline editing are founded on the notion that the technology is not yet accurate enough and the genotype to phenotype relationship is not yet well enough understood to make genetic changes that could persist for generations. But the implication is that these technical obstacles will be, and should be, overcome. The same line of reasoning is echoed across CRISPR GE applications — the new tools are more effective and efficient than previous editing tools, but they are not yet perfect and nor is our knowledge of how genes interact with each other or how they are affected by the environment. In practice, this means continuing research in earnest and as soon as possible translating to marketed goods, drugs, and interventions.

GE technical risk concerns are by nature, and perhaps by design, conquerable. If we characterize the potential benefits as great enough — improving food supply, curing disease, creating renewable energy (Lorenzo et al., 2018) — they subdue the risks. Simultaneously, with more research and investment, we assume we can reduce the design flaws and better understand the role of genes, thereby decreasing the risks. The ultimate challenge is determining when the balance has shifted enough to justify GE action. There is no universal risk-benefit arbiter; instead, society decides when benefits outweigh the risks. Researchers and investors, policy and law makers, advocates, and the public sometimes push in different directions. These stakeholders must align sufficiently to shift the balance, and some of these stakeholders have more power to influence the rest. The enticing attributes of CRISPR are playing a strong role in how the balance of GE risks and benefits are described and perceived, despite the actual balance not shifting much with CRISPR's arrival.

Although CRISPR is more accurate and efficient than other GE techniques (Hrouda, 2016), CRISPR is still found cutting in unintended locations — creating "indels" — deleting and rearranging wrong sequences (Memi et al., 2018). For any organism edited by CRISPR, essential genes could be deactivated or unwanted genes like those that cause cancer might be activated (Baylis, 2018). The edited organism could also have innate or adaptive immunity to specific CRISPR-Cas

systems (Memi et al., 2018). Incomplete editing across the cellular network can lead to "mosaicism" and uncertainty whether the desired change or perhaps some other harmful phenotype will manifest. Even if indels, mosaicism, and immune responses can be prevented, we cannot know all the effects of editing a single targeted gene. We have characterized the roles of many genes, but each gene might have multiple unknown roles. For example, modifying a gene involved in a signaling pathway for cell division could also affect tumor suppression (Tue et al., 2017). For any given GE endeavor, we must ask how to ensure that unintended effects will either be prevented or will be inconsequential. CRISPR's ease of use, low cost, and potential cannot be allowed to obscure significant technical risks.

Lawmakers and regulatory bodies are important in deciding the course of CRISPR-based GE, but they cannot solely be responsible for calculating risks versus benefits. Their moral compasses are not necessarily better calibrated than other stakeholders, they can be influenced and persuaded, and their power is limited. For government-funded and non-profit research endeavors, oversight committees help with risk-benefit calculations. These entities are limited to overseeing publicly funded research, are oriented to template considerations of research subject risk, and are rarely trained in the science of GE. Furthermore, it is unclear whether they should be considering the potential benefits of a given study in addition to the risks, and if so, how to do this in a methodological and consistent way. There is also a complicated web of GE regulation where pieces of oversight are delegated to different institutions ("Human and Agriculture Gene Editing: Regulations and Index", n.d.), sometimes with uncertain overlap (Waltz, 2021), and sometimes without resources for rule enforcement especially across borders (Marchant, 2021). Alone, law and regulation might thus be outmatched by CRISPR-bred hope and money when determining when GE jumps from research to application.

All relevant stakeholders should subject each CRISPR application to careful risk benefit analysis throughout development. Despite significant challenges including how to actually compare the weight of risks against benefits, and how to determine likelihood of risk or benefit manifestation, the combined utilitarian assessments of multiple affected parties can help inform societal GE decisions. Sometimes, collective determinations cut clearly in one direction. For example, near global moratoriums on germline engineering represent the strong likelihood that performing such intervention right now is wrong.

When He Jiankui decided to modify the CCR5 gene (involved in the ability of HIV to affect cells) of two human embryos toward pregnancy and birth, this was universally recognized as an unethical catastrophe. He circumvented ethics review and formal peer review and misrepresented the experiment to the childrens' parents (Rusconi & Giacomelli, 2020). In one of the children, there is incomplete CCR5 deletion meaning HIV might still be able to enter her cells, and the other child is likely mosaic for the CCR5 gene, meaning some cells are edited as intended and others are not (Xie et al., 2019). These actions harmed the parents' dignity, potentially physically harmed the children and their offspring, harmed the reputation of He's institution, and harmed the field of GE. The claimed goal and intended benefit of this trial was protection against HIV for the resulting children, which could have

been achieved via other means (Rusconi & Giacomelli, 2020). Another more plausible goal was to provide proof of concept for CRISPR-based germline editing, which had low probability due to preceding CRISPR lab data. Lack of sufficient oversight and the allure of CRISPR overwhelmed better judgment, and those most affected were the parents, vulnerable in their desire to have healthy children, and the children themselves who had no choice. Here, consensus outcome analysis should have prevented unethical behavior leading to harmful outcomes.

Transparency and Public Deliberation

Consensus or public approval do not necessarily dictate the right course of action. But risky action — even if well intended and potentially helpful — should rarely be taken without consensus or permission from those who will be affected. CRISPR gene drives — editing a species and releasing it into the wild with a mechanism that ensures its featured mutation is inherited by future generations — are being designed and researched to 1 day help people and environments by preventing disease spread, beating back invasive species, and potentially reversing pesticide resistance (Champer et al., 2016). It would likely be unethical to release a gene drive in a community without their knowledge, but it is unclear what constitutes adequate public engagement, and when the public has or should have the power to veto such projects.

We must understand the nature of a community-impacting project to determine the need for transparency and role of public deliberation. The most prevalent gene drive example is modifying disease-carrying mosquitoes and releasing them into communities to mate with wild types that transmit malaria, dengue, zika, and yellow fever. If the drive succeeds, future generations that inherit the edited genes cannot transmit infection, do not bite because they are all male (only females bite), or just die off (Patrão Neves & Druml, 2017). We cannot question the value of a mosquito gene drive's goal; reducing disease-spread is critical. And traditional pest control methods have become less effective with the development of evolutionary resistance to pesticides (Waltz, 2021).

But concerns exist about the efficacy and safety of gene drives, which matter to locales where drives are proposed. Some research shows gene drives being naturally edited out after a few generations (McLean & Jacobs-Lorena, 2016). Would the release of these bugs have minimal impact on disease vectors and just become additional (although non-biting) nuisances? Would destroying a natural mosquito population damage the ecosystem? Would the edits lead to some kind of worse mutation through unknowable effects of the edited gene when integrating into the wild? Researchers are attempting to create safety mechanisms, like "reversal drives" (release new bugs to undo the first bugs) and "daisy drives" (drives that die out over generations) in case damage control is needed (Scudellari, 2019). Preferably, catastrophes would be prevented in the first place, so researchers are testing gene drives in controlled environments. But we cannot synthesize the exact parameters of the wild. The only way to know what would happen with a gene drive is to do one.

These are critical facts to relay to communities facing the possibility of gene drives in their neighborhoods.

Also critical to note is that as of this writing no gene drive has yet been released in the wild. But genetically modified species — without gene drive technology that replicates the gene modification onto both chromosomes in progeny — have been released in Burkina Fasso, Malaysia, Brazil and most recently the Florida Keys. Existing trials have all been preceded by community engagement efforts. There was significant community pushback before the Florida Keys trials, with one community passing a referendum to prevent the trial from taking place, so the trial moved to a nearby community (Waltz, 2021).

CRISPR could change the speed and scale of gene drive impact, meaning benefits like elimination of disease transmission could be achieved sooner. However, if any of the previously mentioned risks were to manifest, they also might be harder to control or reverse. What mechanisms must be in place to guarantee that host communities are given this information in ways they can understand, are able to ask questions, and voice concerns? Can we trust companies designing and implementing gene drive technology, or the governing bodies with which they partner, to host such conversations in objective and respectful ways? If the lay public would not be able to fully comprehend the risks, and the gene drive would happen regardless of the community's reaction, is this real public deliberation or just a symbolic show?

Community leaders and government organizations perform many services for their constituents without explicit constituent agreement, and thus without permission. It would be too unwieldy to require such permission for all aspects of basic necessary services and unhelpful to do so for some urgent public health matters. The questions are: (1) Whether the problems that CRISPR gene drives try to address fall into one of these camps; and (2) whether the drives themselves are equivalent in nature to other provided services. Efforts to control mosquito populations might be considered a basic service, and if vector-borne disease is sufficiently widespread, this could well be an urgent public health matter. The CRISPR-based solution's speed and comprehensiveness, combined with the fact that mosquitoes are developing resistance to pesticides, might make it easy to assume a paternalistic approach to implementation — disease-impacted communities need this whether they know about it or agree with it.

We might more intuitively hold that CRISPR gene drives are sufficiently unique and untested such that communities ought not only be engaged, but should have input into final implementation decisions. Community members might even be considered pseudo-research subjects, as edited mosquitoes are released into their neighborhoods and the ultimate outcome being studied is human infection. With novel research participation, a careful line must be tread between enabling informed consent through adequate disclosure and fear mongering. Facts that would be relevant to most people must be explained and in an accessible manner. Even low probability scenarios should be considered relevant, such as unforeseeable mutations leading to significant ecological or health consequences, because of the gravity and breadth of potential impact. Industry/government partnerships are unable to relinquish conflicts of interest, so they should seek independent assistance in developing effective

community approaches, potentially from teams with expertise in law, ethics, and community advocacy.

GE public deliberation processes must also recognize the inherent power imbalance between the information providers and the recipients, and must seek to right the scales. Regarding gene drives, implementers will not have to face the consequences of a drive gone wrong. Many of those who live in a release zone will not have the resources to just relocate if necessary. In some cases, those personally affected by vector-borne disease might be too eager to seek the kind of solution proffered by CRISPR, meaning an independent advocacy group could play a role in verifying that critical risks are understood. CRISPR-based drives are not at a point where unilateral decision-making would be ethical. Transparency and authentic public deliberation in which community members have power to shape the course of action are essential.

Informed Consent

Informed consent is among the few clear "victories" won by the field of bioethics, now a required component of major clinical care decisions and all human subjects research. Yet it often remains incredibly hard to define and to obtain. As CRISPR-based human interventions take off, they will epitomize this difficulty. Even after more lab-based work demonstrates reduction in the technical challenges associated with CRISPR GE, the initial clinical research applications will still present extraordinary risks, known and unknowable. This means the first human participants will be those for whom standard of care treatments and even other research treatments have failed. These populations are particularly vulnerable, sometimes driven more by hope than by facts, and in need of strong advocates. The risks to these participants are compounded by the difficulty that will accompany adequate information disclosure, because of the uncertainty surrounding how CRISPR and CRISPR-manipulated products will work in the human body, and because researcher/developer hope and investment in success could shape how risks are disclosed.

Understanding of genetics has increased exponentially in the last 15 years, yet the whole field has only unearthed a fraction of the relationship between genes and human characteristics. Of the approximately 20,000 active genes in the genome, only a few hundred have received much research attention (Stoeger et al., 2018). This not only means we have limited understanding of the remaining thousands barely studied, but also limited understanding of the "popular" genes because of how they might be affected by less examined regions of the genome. Even if we identify a clear correlation between a gene or set of genes and the manifestation of a particular disease, it is impossible to say with confidence that the disease is not also modulated in some way by other genomic regions and by the environment. Using GE mechanisms to modify the genome to eliminate disease is a bit like giving children power tools to build a house — they might have a general sense for how the

tools work and what a house should look like, but this does not warrant a license to build.

Sometimes we must do the most we can with tools we have. Since early gene editing catastrophes in the late 90s and early 2000s, current gene editing research involving humans is limited to those with severely deleterious conditions for which existing treatment options are either nonexistent or insufficient. Accordingly, GE might be the only possibility, even if low probability, to stave off death or to reduce significant suffering. Hence enter multiple dilemmas involved in obtaining informed consent.

Informed consent requires that the consenter has decision-making capacity. Capacity requires the ability "to understand and appreciate the nature and consequences of health decisions" and "to formulate and communicate decisions concerning health care." (Ganzini et al., 2005) Capacity can fluctuate with significant emotional distress, experience of significant pain, and other sequelae often associated with severe disease. (Biros, 2018) It is likely that the specific groups to whom gene therapy is available experience these and other capacity modulating features, which might limit their ability to adequately consider the consequences in context of their own values and goals. Potentially compounding the effects of disease sequelae is young age. Children, by definition, lack the ability to consent to research due to limited capacity.

Lack of capacity cannot alone preclude participation in research. If it did, this would prevent some (including children) from accessing the only possible beneficial intervention for their conditions. It would also prevent gathering data about the intervention's effects on populations without capacity, which could unfairly prevent the development of helpful interventions for these populations. All ethical frameworks for deciding how to involve individuals without capacity or with questionable capacity in research require significant support be provided for the research participant. Surrogate decision makers must have capacity themselves and must also be acting in the participant's best interests. Most often, these are family members who can be subject to the same experiences and mental states that affect capacity. In the case of parents making decisions for children, it is possible that parents' rational decision-making abilities are more impaired by grief and desperation than even their sick children.

These features make careful attention to information disclosure incomparably important. All those seeking GE treatment are at an immediate informational disadvantage. The field of somatic cell gene editing — in which genes are edited in bodily cells excluding gametes, such that changes are not passed to progeny — is called "gene therapy," which is misleading. While human participants will almost certainly wish for therapeutic benefit, somatic cell gene editing is currently research. This means that therapeutic benefit is uncertain, and it is unclear whether participating will better serve than other existing therapies or nothing at all. It might even be more harmful and lead to more suffering. Overcoming the inherent bias of this misnomer, there remains the challenge of how to disclose the potential risks and benefits of CRISPR-based gene therapy. It will be impossible to accurately characterize the likelihood of the desired benefits — ie, the elimination of disease or

reduction of symptoms. The only precedents that can be drawn upon are existing approved gene therapies, which use completely different mechanisms of action ("Approved Cellular and Gene Therapy Product" n.d.). The risks will be equally difficult to characterize and quantify in terms of impact on the body. Yet to enable participants and their advocates to make careful decisions that comport with their values and goals, a full picture must be drawn.

These challenges are not unique to CRISPR-based gene therapy. All untested and highly innovative research interventions cannot be perfectly characterized in terms of risks and benefits. But mainstream media has embedded CRISPR in the public's consciousness. It is likely that those desperately seeking treatments have already been exposed to CRISPR promises made in the media. Many articles provide balanced accounts of CRISPR's development, but there are several others describing "wow" treatments and "breakthroughs" (Stein, 2021) (Weintraub, 2021). These characterizations create expectations that are hard to calibrate, regardless of the care taken by research administrators to be honest and objective in obtaining informed consent.

CRISPR-based gene editing appears to offer some potential technical benefits for somatic cell editing over existing methods, but bears its own unique challenges and risks (Uddin et al., 2020). Ideally, these challenges will be significantly remediated before more regular deployment in human trials. But the hype and hope around CRISPR mechanisms could compromise objective assessment of their safety and efficacy, even at high supervisory levels. There is evidence to suggest that the first phase one CRISPR trial for cancer in the United States was too hastily approved with compromised requirements for scientific validity and favorable harm/benefit ratios (Baylis, 2018). If trials are allowed when experts have inappropriately assessed basic safety and risk thresholds, then facilitating proper informed consent will be impossible. Such rash decision-making not only subjects vulnerable research participants to significant and unjustifiable risk, but can also cause political backlash which sets the whole field back again.

Playing God

Of all modern feats of humanity that would make our recent ancestors cower in fear and confusion, none invoke the concern of "Playing God" quite like gene editing. CRISPR GE adds richness to the consideration, due to its relative ease of use (playing) and its relative power (God), and due to the manipulation of a naturally occurring genetic feature to exert our own will. As this concern is common among opponents, it is important to understand what the term means, and its implications for how to proceed with the field.

Playing God is often used to express discontent with something that appears unnatural or outside of normal (Locke, 2020). Using the term "natural" in the most fundamental sense to draw ethical lines would likely undermine countless features of modern society that contribute to human flourishing, including everything from

Tylenol to electricity. When organ donation and transplant was first developing as a field there was shock, fear, and disgust. Having more than 50 years of experience, it is hard to put ourselves back in those shoes but, yes, there is some sense in deeming unnatural (or at least odd) the removal of cadaveric organs to place them in living people. We can be grateful for the pioneers who ultimately ignored the disapproval at the right moment and are responsible for thousands of lives saved through organ transplant every year. It is thus unclear what is inherently moral about naturalness (Takala, 2004). However, an important corollary to *un*naturalness is unfamiliarity, which can imply danger.

Playing God can also mean attempting to use power beyond control, which can be a more useful heuristic for identifying ethical action. Organ donation was attempted for centuries prior to adequate understanding of microbiological compatibility and immunosuppression, leading to worse suffering for patients (victims) than had they just died of organ failure. Similarly, attempting to use the evolutionary machinery of bacteria to edit human genomes without adequate knowledge of genetics or the likely effects of such machinery on the human body might cause more harm than good. In both situations, humans attempt to use power beyond their control.

Using this framework to separate right action from wrong requires that we know when power is within our control. If the rule were established that we could not perform actions in research that we did not fully understand, then very little research would be possible. We must allow for some unknowns, and thus some risks, and come up with methods for determining acceptable risks and for risk control. Redefining the term Playing God in this way perhaps unfairly converts what is otherwise a deontological, or rule-based, determination of right from wrong (natural vs unnatural), back into a utilitarian calculus about outcomes.

Consequential arguments about whether to pursue gene editing are not the only ones with value. In fact, values should play a critical role in our choices and the kind of society we ought to strive for, regardless of outcomes. It might be argued that attempting to manipulate genetic machinery to create better lives demonstrates an unacceptable degree of hubris that perhaps other innovations do not. Or maybe this line from humility to hubris is crossed only with germline engineering and not gene therapy, separating the intention to heal from the intention to redesign (Evans, 2021). It can also be argued that *not* using the discovery of CRISPR to better humanity is denying God's gift (Locke, 2020), and thus an unfaithful or ungrateful choice. Of all the different values we might need to prioritize, those with greatest ethical import promote the rights of all people equitably.

Solidarity and Justice

This chapter began by recognizing the great benefits to humanity that gene editing might provide, and CRISPR-based GE has now built a door where previously stood a wall. In choosing whether and how to walk through this door, we must first

consider how the most marginalized, disadvantaged, and vulnerable members of society will be affected. A commitment to solidarity in the implementation of CRISPR GE is most likely to achieve the best outcomes for society, prioritize the values that distinguish a moral humanity, and satisfy concomitant rights and duties. Achieving just and equitable distribution of benefits and burdens will take different forms in every case, and will require constant attention to power dynamics, implicit biases, and multiple conceptions of marginalization and vulnerability.

In the most immediate phases, critical attention must be paid to how minority groups including communities of color, LGBTQIA, and those with disabilities, as well as the socioeconomically disadvantaged, are represented in, excluded from, and informed about CRISPR research. For example, the field of xenotransplant — transplanting nonhuman organs into humans — is potentially poised for a breakthrough with the application of CRISPR GE to make nonhuman organs more compatible with human beings. This has the capacity to significantly remediate the vast organ shortage across the globe. Minority groups and those in poverty disproportionately suffer the burden of organ failure and also have the least access to life-saving transplants (Bratton et al., 2011). The first-in-human trials of xenotransplants (which will likely come from pigs with modified kidneys) should consider how to proportionately involve disadvantaged populations, understanding that overrepresentation could lead to exploitation and underrepresentation could mirror discriminatory practices in standard of care transplant. It might be accurate to describe this as a lose-lose design dilemma. Again, this challenge is not unique to CRISPR research, but CRISPR heightens the stakes. Fanaticism around its potential could move trials too fast, undermining critical attention to demographic representation. Hastily implemented trials that harm vulnerable and minority research participants can damage political will to continue pursuit of xenotransplant, thereby destroying future access for those most in need.

The least problematic way to make demographic inclusion decisions integrates community members in trial design. Community members who are experts in the actual science should be selected to help design trials and perform the studies, and community members from the public should be given voices through focus groups and surveys, and inclusion on protocol review boards. This integration will also help appropriately tailor the language and content of informed consent processes.

Other forms of marginalization and vulnerability must also be explicitly acknowledged in efforts to constructively permit or restrict CRISPR research. When standard of care treatments like solid organ transplant are available, it is unclear whether patients ineligible for standard organ transplant should ever be enrolled in xenotransplant trials. This potentially includes patients with advanced cancer or advanced age, who have no long-term treatment options and are more vulnerable. If these groups are made eligible for this kind of research transplant, they would need greater support in the form of independent patient advocates to navigate risks and benefits.

We must also consider the lives that are sacrificed to make xenotransplantation possible. If the benefits of CRISPR-based xenotransplant pan out, we then create a

new industry of factory farming, which is another venue for nonhuman animal suffering for human ends. In the most expansive interpretation of solidarity, we must recognize nonhuman animal rights and cannot ethically let xenotransplant become standard of care unless it is a bridge to bioengineered organs that require no nonhuman animal inputs.

CRISPR is currently being explored as a tool to both diagnose and treat COVID-19 (Churi & Taylor, 2020; Lotfi & Rezaei, 2020). If any such tools come to fruition in time, their application and distribution must pay better attention to the disproportionate disease burden suffered by marginalized and disadvantaged populations than all foregoing COVID-19 prevention and treatment efforts. Social disease control methods, vaccination efforts, triage protocols, and education have all insufficiently taken into account existing population health stratification according to minority and socioeconomic statuses. Some tactics, like wealthy nations hoarding vaccine doses (Dyer, 2020) and ventilator triage protocols that discount quality of life outcomes based on age or disability (Fink, 2020) grossly exacerbate this stratification. The degree to which CRISPR applications are driven by market forces could all but ensure their use for ending the pandemic falls victim to the same patterns.

Assuming all technical risks are resolved, we must ask to what ends CRISPR is allowed for use in editing human traits. Some conditions with at least partial genetic bases are unquestionably deleterious diseases such as cancer, Tay-Sachs, heart failure, and Alzheimer's. However, the vast majority of genetic predispositions can better be characterized as contributing to human differences. This includes everything from height to sight, and autism to Down syndrome. Most traits have significant environmental components and highly complex (and sometimes multiple) genetic pathways, meaning attempts to manipulate them will likely lead to unmet expectations (Parent & Turi, 2019). For some traits, the strength of genotype to phenotype correlation could help set a "natural" line to separate editable traits from those we must leave alone. But this would not hold true for something like Down syndrome, which has identified genetic basis, but is not a universally deleterious or dangerous condition.

Can we trust society to set out the criteria for deciding what traits are eligible for elimination or modification without creating discriminatory policies? Once we choose the set of editable genetic predispositions and have all but eliminated genetic disease, will CRISPR's infinite potential cause us to reset the expectation for what is considered healthy? This could lead to an ever-shifting paradigm that makes the range of acceptable human differences decreasingly narrow. Let us say we are able to commit to drawing hard and fast lines: How do we ensure that the most disadvantaged members of society have priority access to these "medical" services, when we have yet to do so for any current essential medical services? When some members of society choose not to accept universally available edits for themselves or their children, it is unlikely that society will kindly accommodate them with social and structural support.

Conclusion

The excitement that CRISPR has generated and its infinite potential might incent the use of GE to attempt solving problems that either do not exist — treating differences as diseases — or prioritizing investment in higher risk/lower probability solutions for issues that could undoubtedly be better solved with more attention to the social determinants of health. It is our duty to focus attention on improving our understanding of the full universe of genetics and genomics, and their roles in individual and public health, to stay one step ahead of practical translation of CRISPR applications. The brilliance of this extraordinary breakthrough should support, and not distract from, our commitment to solidarity and providing universal basic rights like adequate healthcare, nutrition, water, shelter, and structural and social supports to those in greatest need.

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Chapter 3
Bioethical Decision Making and Genome Editing

Calum MacKellar

Abstract Changing the genetic makeup of living beings is expected to transform several fields of biomedicine giving rise to a number of ethical challenges including in therapy and reproductive procedures. Against this background, however, it is important to determine whether a non-heritable (somatic) procedure is taking place, which may be comparable to conventional therapy, or whether the procedure generates a heritable genetic modification which may give rise to the selection or deselection of possible future children. In this last case, the following ethical choices may then be considered. First, individuals and society may choose to believe that all lives are equal in worth and value, making any selection and classification between possible future children meaningless. Secondly, individuals and society may believe that all possible future children are equal in value but choose not to bring a certain kind of child into existence because they recognise that they themselves or society lack the necessary support and/or capacity to look after such a child. Finally, individuals and society may decide not to bring a certain kind of child into existence, because the value of his or her life is considered to be unacceptable even though they have the resources and support necessary to look after such a child. If this last choice is accepted, however, it would also mean sanctioning selective eugenic decisions between possible future children.

Keywords Bioethical decision making · Ethical challenges · Genome editing · Early embryos · During fertilisation

Introduction

The possibility of editing the genomes of living beings is set to revolutionize many areas of biological research (Cong et al., 2013; Jinek et al., 2012). This is because scientists can now efficiently, precisely, and selectively modify parts of these

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genomes by removing or inserting genetic material with the development of the Crispr–Cas9[1] genome editing system which is relatively simple and inexpensive to use. It only requires a guide RNA molecule with a specific genetic sequence (a sort of homing mechanism) and a Cas enzyme (a protein that works as a kind of molecular scissors), with Cas9 being the one most often employed to cut the DNA strands. In this manner, the guide RNA with a particular genetic code searches for the specific target DNA of the genome to be edited and then combines with the Cas9 enzyme. This, subsequently, cuts the DNA enabling a genetic strand with the relevant sequence to be taken out. The DNA can then be joined back together or, alternatively, a new DNA strand with another genetic sequence inserted.

In this way, genome editing can be used in a number of ways, including in research.[2] For example, specific genetic sequences can be disabled or replaced in early animal embryos in order to better understand embryonic development. It may also be possible, in the future, to inactivate disordered genes responsible for a disease and replace them with healthy ones. The prevention of genetic disorders and even new treatments could then be considered (Sas & Lawrenz, 2017; Turocy et al., 2021).

Biomedical research using genome editing on human cells are already underway, such as in the use of edited immune cells to treat cancer (Winblad & Lanner, 2017). But two important milestones were achieved when Chinese scientists became the first to edit the genome of human embryos (Liang et al., 2015) with another research team bringing to birth twin girls whose genomes were the result of an editing procedure (Cyranoski & Ledford, 2018). Other studies have also been reported using either existing human embryos and genetically editing them after fertilization (post-conception) (Kang et al., 2016; Tang et al., 2017) or injecting the gene editing system at about the same time as fertilization or just after (peri-conception) (Ma et al., 2017). A third possibility would be to edit the genes of the sperm or egg cell before conception (pre-conception). In these last two procedures, it is expected that the embryo would develop in such a way that every cell, and every subsequent organ, would contain the edited DNA, including the reproductive cells, enabling a more efficient, uniform genome editing procedure to take place.

Determining the Ethical Challenges for Human Beings

In considering the use of certain genome editing in human beings, it is important to first examine and address the possible ethical challenges that may arise. These will enable the risks and advantages of such procedures to be considered which will include the following.

[1] Clustered regularly-interspaced short palindromic repeats with the Cas 9 protein system.

[2] For a review of possible applications, see: Nuffield Council on Bioethics, 2018, 32–43 and WHO, 2021.

Safety Concerns

To begin with, some concerns relating to safety of the procedure exist. For example, inserting or deleting specific genetic sequences in the correct location of the genome of a developing embryo without upsetting the biological equilibrium of the cell(s) is a difficult operation. A particular genetic sequence may influence a number of different characteristics, meaning that even if a genome was modified to influence a specific dysfunction, this could give rise to unexpected consequences. The overall result would be a modification that may be less than beneficial (The President's Council on Bioethics, 2003, 38–39; National Academies of Sciences, Engineering, and Medicine, 2017, 67; Turocy et al., 2021).

In addition, during the research and development stages of human embryonic genome editing it is unavoidable that a significant number of embryos will be destroyed in the process. This means that their destruction can be seen, by many, as being just as offensive and immoral as the destruction of any other person (Kirtley, 2016).

Distinguishing Different Personal Identities

In examining possible genome editing procedures, it is also important to differentiate between non-heritable (somatic) and heritable (germline) genome editing procedures. But before doing this it is necessary to consider the different kinds of personal identities that may exist in order to distinguish procedures which are therapeutic in nature and those which actually create a new individual who is completely different from the one who would otherwise have existed. In this regard, though a degree of overlap may exist, and there is no consensus in literature, it is possible to differentiate between:[3]

Numerical identity which examines the number of persons who exist and whether they are distinct. For example, it considers whether the continuous sense of a living being remains one and the same being throughout his or her life trajectory in the three dimensions of space and over time. In this case, two perspectives are generally presented, namely:

– A biological perspective which reflects the continuous biological being remaining one and the same whole being over time as a biological entity in space despite some qualitative changes such as those arising from the replication and division of cells making up this being.[4]

[3] For further discussion, see for example Schechtman, 1996, Schermer, 2011, Foresight Future Identities, 2013, pp. 9–10, De Grazia, 2012, pp.70–73 and MacKellar, 2019.

[4] This reflects an 'animalism' perspective which was developed, amongst others, by Paul F. Snowdon, see Snowdon, 1990. For a discussion see Olson, 2003 and Snowdon, 2014.

– A psychological or biographical perspective which reflects the relationship a living being has to itself as remaining one and the same whole individual over time despite some qualitative changes. This generally includes continuity of consciousness, experiential contents or the maintaining of psychological connections or capacities, such as memories.[5]

On this account, a psychosomatic numerical identity may be seen to exist for most individuals which brings together the biological and psychological perspectives.

- Qualitative identity which examines similarities between the same individual in different settings or between distinct individuals. For example, two beings may be similar from a biological perspective but exist in different settings of space and/or time. In this way, identical twins are qualitatively but not numerically identical. Each twin exists in a different setting of the three dimensions of space though they generally live at the same time.[6]

This means that, in examining a procedure from an ethical perspective, it is important to distinguish whether a procedure results in:

1. Numerical identity changes, meaning that a new individual is brought into existence who would not otherwise have existed, or
2. Qualitative identity changes, meaning that the original individual continues to exist.

Thus, in order to decide which of these two possibilities may be relevant it is necessary to study the different aspects of a procedure while seeking to examine the genetic modifications. For example, genome-editing modifications were categorised by the US National Academies of Sciences, Engineering, and Medicine (2017, 69) as follows:

- The specific kinds of cells or tissue(s) which are modified. For example, whether the modification is made in somatic cells and tissues, which do not affect descendants, or in reproductive cells and early embryos which may change future generations.
- The place where the modification takes place. For example, whether it take place in a test tube, and the cells or tissue(s) returned to the patient or does it take place directly in a person.
- The aim of the modification. For example, is the purpose to treat or prevent disorders or is it to introduce new traits.
- The nature of the modification. For example, does the modification address a simple disease-causing mutation or a more a complex disorder.

[5] This reflects a 'psychologically interconnected' perspective. See for example Lewis, 1976. Such a psychologically interconnection would not exist, for example, between an early embryo and an adult human being since the latter would not be able to remember being an embryo.

[6] Even conjoined twins can be considered as distinct if they each experience their own specific identity.

In considering these different kinds of genetic modifications, it is then possible to distinguish whether a procedure is a non-heritable or heritable procedure.

Non-heritable Genome Editing

If a genome editing procedure takes place with the aim of addressing a genetic disorder on a mature embryo, foetus, child, or adult, this would not be expected to modify the genome of any descendants. As a result, such procedures could be considered in a similar manner to already existing somatic gene therapy procedures which do not affect descendants and have generally been accepted by society. Thus, few new ethical problems would arise apart from safety and efficacy.[7]

The numerical identity would remain the same though the qualitative identity would be changed. This form of therapy would then correspond to the aims of classical medicine in the restoration of health to an individual.

Heritable Genome Editing

Some forms of genome editing procedures, on the other hand, would not only change the genetic heritage of the individual for whom it is being considered but would also change the genetic heritage of all his or her descendants. Moreover, if it is eventually possible to remove or change what may be considered as genetic disorders, it may also be possible to change just about any other genetic attribute. Therefore, such changes would need to be carefully considered while weighing up the advantages against the risks.[8]

Advantages of Heritable Genome Editing

Heritable genome editing can prevent the transmission of genetic disorders by preventing the very existence of persons with such disorders. However, this is not the only way to avoid the existence of such persons since it would be possible, for example, to decided not to have children or use donated embryos, eggs, or sperm. These options, however, do not enable both parents to be genetically related to their children, which may be something that is very important to them.

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[7] Somatic genome editing may be able to address specific cell types or tissues but may not be appropriate for treating other genetic disorders affecting a number of different tissues because targeting all the tissue may be difficult, National Academies of Sciences, Engineering, and Medicine, 2017, 88.

[8] For a review see: National Academies of Sciences, Engineering, and Medicine, 2017 and 2020; Baylis, 2019; Evans, 2020; Parens & Johnson, 2019; WHO, 2021.

In addition, it may be possible to consider in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) of the embryos making it then possible to select embryos without a genetic disorder for implantation into the woman seeking to have a child. However, this possibility is not without biomedical risks and costs. Moreover, it may involves discarding the embryos with the disorder, which may be unacceptable to some individuals. Another option is to use prenatal genetic diagnosis to examine the genome of the foetus followed by the selective termination if any foetus is found to have a genetic disorder. However, such a termination may also be considered unacceptable by some individuals (National Academies of Sciences, Engineering, and Medicine, 2017, 86–87).

Thus, if it were safe and efficient to use heritable genome editing to make sure only a child without a serious genetic disorder comes into existence, this possibility may be considered as preferable by some prospective parents. The number of cases where heritable genome editing may be useful may be small, but the concerns of people considering such a procedure are real. This could be achieved by editing the gametes (eggs, sperm), gamete precursors, or very early embryos. However, IVF would still be required to generate the embryos (National Academies of Sciences, Engineering, and Medicine, 2017, 87–88).

Disadvantages of Heritable Genome Editing

Deciding to use a genome editing procedure with the aim of heritable modifications, does however raises significant ethical concerns. This is because proposed heritable modifications may be considered as inherently eugenic in nature. The word *eugenics*, which derives from two Greek roots *eu* (good) and *genesis* (birth), describes selection strategies or decisions aimed at affecting, in ways which are considered to be positive, the genetic heritage of a child, a community, or humanity in general (MacKellar & Bechtel, 2014).

It was the Englishman Sir Francis Galton who first coined the term *eugenics* in 1883 as he sought to implement into human beings, selection procedures for heritable characteristics which had already been used, with success, in animal breeding programs. This resulted in eugenic ideas becoming relatively common and being considered by many prominent personalities at the beginning of the twentieth century.[9] It was only because a deep reaction of aversion took place towards the atrocities implemented by Nazi Germany during the Second World-War that eugenic

[9] Sir Winston Churchill, wartime Prime Minister of the UK, was openly disappointed when Britain resisted eugenic action on the grounds of civil liberties. In 1910, he wrote to the then UK Prime Minister expressing his support for legislation that proposed to introduce a compulsory sterilization program in the UK saying: "The unnatural and increasingly rapid growth of the feeble-minded and insane classes, coupled as it is with a steady restriction among all the thrifty, energetic and superior stocks, constitutes a national and race danger which it is impossible to exaggerate.... I feel that the source from which the stream of madness is fed should be cut off and sealed up before another year has passed." Quoted in Amy Iggulden, "The Churchill You Didn't Know," *The Guardian*, 27 November 2002.

policies were denounced. This was because such policies were often imposed by the state and were seen as discriminatory.

A number of international legal texts eventually condemned the ideology. For example, Article 3 of the EU *Charter of Fundamental Rights* which was accepted in 2000, explicitly states that "in the fields of medicine and biology … the prohibition of eugenic practices, in particular those aiming at the selection of persons" must be respected. (Charter of Fundamental Rights of the European Union, 2000).

Because of this and even though the coercive nature of eugenics is unlikely to return, grave concerns remain as to the consequences for society when it becomes possible to decide what kinds of children are brought into existence (MacKellar & Bechtel, 2014). Ever since the English writer and philosopher Aldous Huxley published his dystopian science fiction book *Brave New World* in 1932, considerable anxiety has developed relating to the prospect of creating a society in which the genetic heritage of individuals could be controlled.

In addition, the Council of Europe's 1997 *Convention on Human Rights and Biomedicine* states in Article 13, regarding "interventions on the human genome," that "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."(Council of Europe (a), 1997) This means, according to paragraph 91 of the *Explanatory Report* to this Convention, that "interventions seeking to introduce any modification in the genome of any descendants are prohibited. Consequently, in particular genetic modifications of spermatozoa or ova for fertilisation are not allowed." (Council of Europe (b), 1997).

The reasons why such texts reject germline modifications, and thereby eugenic procedures, is because unacceptable discrimination may be associated to selection strategies, thereby undermining the equality in worth and value of all human beings—an equality which is the very basis of civilized society. Thus, deliberate germline and eugenic procedures were not only seen as wrong because a degree of coercion existed in some of the past practices, but because they undermined the very basis of equality between all existing or possible future persons.

However, as the abuses which took place in the first half of the twentieth century slowly became an ever-older memory, pressures are now returning for a new eugenics.[10] Moreover, in a report published in 2017, the U.S.-based National Academies of Sciences, Engineering, and Medicine actually recommended the use of heritable genome editing in human beings in certain specific circumstances. This happened even though the above international regulations condemned such a possibility and a 2015 UNESCO International Bioethics Committee report had clearly highlighted

[10] For example, American Nobel Prize Laureate and co-discoverer of the structure of the DNA molecule James Watson wrote: "But diabolical as Hitler was, and I don't want to minimize the evil he perpetuated using false genetic arguments, we should not be held in hostage to his awful past. For the genetic dice will continue to inflict cruel fates on all too many individuals and their families who do not deserve this damnation. Decency demands that someone must rescue them from genetic hells. If we don't play God, who will?" (Watson, 1995).

the eugenic dangers of selective germline procedures. This indicated that if any intentional germline selection was accepted (such as with genome editing), this would "j*eopardize the inherent and therefore equal dignity of all human beings and renew eugenics, disguised as the fulfilment of the wish for a better, improved life.*" (UNESCO International Bioethics Committee, 2015).

Actually, it was in order to address such a danger that the **United Nations Educational, Scientific and Cultural Organization's (UNESCO) 1997** ***Universal Declaration on the Human Genome and Human Rights*** indicates in Article 24 that germline interventions could be considered as a practice that would be "contrary to human dignity." (UNESCO, 1997).

Decision-Making in a Practical Context

Of course, it is possible to ask what is ethically wrong in deciding to make sure only healthy, and not disabled, children are brought into existence. Why not make sure that children who will have short and difficult lives of suffering are not brought into existence? In these specific cases, are selective eugenic procedures always to be considered in a negative manner?

In response to these questions, it is important to recognize that in some circumstance parents may not really be making a eugenics decision. For example, when parents select against a child with certain characteristics (such as with severe disabilities), the reason may simply be a recognition, or belief, that they themselves lack the financial, physical, psychological or the social resources and support necessary to look after such a child. That is to say, they may be recognising their own limitations or that of society, rather than selecting against a possible future child who is considered as substandard or as unworthy of life (Gavaghan, 2007, 113–114).

However, if such extenuating circumstances do not exist, it is difficult to see how parents can decide not to have certain kinds of children without making a value judgement that some children are less desirable. It follows that when parents make a decision that only a certain kind of child should be brought into existence, based solely on genetics factors, this can only mean making a selective eugenic choice and preferring one possible future child over another. In other words, this decision contradicts the important principle that all human lives have the same worth and value, regardless of their state of health or characteristics (Andorno, 2010).

This is extremely important since the inherent and absolute equal value of each human life is the very basis of civilised society. This resonates strongly in Article 1 of the UN's 1948 *Universal Declaration of Human Rights* which states that "all human beings are born free and equal in dignity." (Universal Declaration of Human Rights, 1948) Thus, if all persons are completely equal in value and worth, how can any choice between two supposedly equal future persons ever be made?

At this stage, however, it is important to examine which genome editing procedures could be considered as selective and potentially eugenic. This is because

distinct categories may exist dependent upon the development stages, and these will now be examined in turn.

Gene Editing of Very Early Embryos

If genome editing takes place on a very early post-conception human embryo (such as a two-cell embryo), a number of ethical challenges arise. Indeed, it would be difficult to know whether any significant genetic change would bring about a completely new individual or whether the original embryonic individual continues to exist and is simply modified (Ossorio, 2003). In other words, it would be difficult to determine whether the procedure would have a numerical or only a qualitative effect on identity. In a way, this philosophical conundrum is not new and comes in many different forms. It is similar to the one mentioned by the Greek historian Plutarch (c. 46–120) in his *Life of Theseus* (the mythical founder-king of Athens). Plutarch questions in a thought experiment whether a ship which is restored by replacing every one of its wooden parts remains the same ship. This is especially relevant if the old parts are then used to build another boat. In the same way, it is possible to ask whether an embryo in which a certain number of genes have been edited remains the same embryo or whether a change in numerical identity has taken place.

From an ethical decision-making perspective, if the genetic modification does not give rise to any significant changes in the already existing embryo, it could be seen as being similar to somatic gene therapy in which the original individual remains and the health of the individual is restored. However, if the gene editing procedure substantially modifies the genome of a very early embryo, more questions relating to the continued existence of the original embryonic individual could be asked. The genetic modification may then end the life of the original embryo (a form of death) while creating another. Moreover, if this did happen, then a clear selective eugenic element may exist, if no extenuating circumstances exist, since it would mean preferring one new individual over another based on the quality of his or her genome (MacKellar, 2021).

Genome Editing of Sperm, Eggs, and During Fertilisation

On the other hand, if a genetic modification takes place on the sperm and/or egg cells before they are used for conception or during fertilisation resulting in the formation of a one-cell embryo, a new individual, who would not otherwise have existed, is being brought into existence (McMahan, 2005, 154). This would happen because any change (no matter how small) of any of the variables in bringing an individual into existence would result in a very different individual existing in time (MacKellar, 2019). In other words, any individual brought into existence through

these procedures would be a totally different person, from a numerical identity perspective, to the one who would, otherwise, have existed.

If such a conclusion is accepted then this again may have a clear selective eugenic element, if no extenuating circumstances exist, since a new individual is being brought into existence in preference to another possible person who may, for example, have qualities which were seen as less valuable than the new individual. What is being proposed, therefore, is not a form of therapy. No existing person is being treated for a disorder. Instead, it is making sure that only certain persons are brought into existence based on the quality of their genomes (MacKellar, 2021).

On What Basis Should a Decision Be Made?

Of course, it is possible to argue, as does the U.S National Academies of Sciences, Engineering, and Medicine Report *Human Genome Editing*, that "unconditional love for a disabled child once born and respect for all people who are born with or who develop disabilities are not incompatible with intervening to avert disease and disability prior to birth or conception." (2017, 97) But the report does not explain how or why any deliberate discrimination can be seen as acceptable before birth while suddenly becoming unacceptable after birth. As the Dutch ethicist Hans Reinders explains, it is more than likely that "in any given case, the only reasonable answer to the question of why a disabled child should not be born is by reference to what one thinks about the lives of people living with the same disorder." (Reinders, 2000, 8).

In other words, if parents do decide to avoid having a child affected by a serious genetic disorder, solely because of genetics factors (and no extenuating circumstances exist), there is a very real sense that such a decision is based on the perceived quality of life of people who already exist and not on the worthiness and inherent value and worth of their lives. Moreover, the indirect message being given to persons, who have already been born with the same disorder, would be that they should also not have existed.[11] This is clearly discriminatory and would undermine the inherent equality of all human persons in society (MacKellar, 2021).

Deciding that choice should be available to make sure that certain kinds of children are not brought into existence may also mean that there is such as thing as a life unworthy of life in society.[12] As the legal ethicist Roberto Andorno explains:

[11] For clear evidence of the feeling of offence being taken by persons with disability in a similar situation, see the disability witnesses in the prominent French court case of Nicolas Peruche. Public Hearings of the French Senate on the 18th of December 2001 relating to the jurisprudence of the 'Perruche' case.

[12] The term a "life unworthy of life" (in German "Lebensunwertes Leben") first occurred in the title of a book by German psychiatrist Alfred Hoche and lawyer Karl Binding, *Die Freigabe der Vernichtung Lebensunwerten Lebens*, (Leipzig: Verlag von Felix Meiner, 1920).

> In reality eugenic ideology presupposes stepping from a "worthiness of life" culture to a "quality of life" culture, in other words, to the idea that not every life is worthy of being lived, or to put it more bluntly, that there are some lives that do not have any worth. (Andorno, 2010, 129–141)

Moreover, if certain genetic preconditions are laid down relating to the generation of a possible future child—thus excluding persons with certain conditions – then this child when brought into existence will always know that his or her very existence was not unconditional but conditional on having a certain genome which may give rise to significant existential anxiety.

Naturally, it is difficult not to have a lot of sympathy towards parents who have children affected by severe disability and suffering or to know the extent of the anguish they are experiencing. But, if one asks these parents, it is always the disorder, and not the very existence of the child with the disorder, that has been the cause of so much heartache. Most would never say that they wished their specific child had not existed. On no occasion, would they indicate that they would have preferred to exchange their child for another, healthier, one. They just want to find a treatment for their child.

Certainly, the advancement of autonomy, the reduction of suffering, and the increase in flourishing of human persons are very important goals in any ethical appraisal. But these aims do not give any true value or worth to human life, at least not the kind of value and worth that is equal to all persons. In actual fact, if only autonomy or the lack of suffering were the basis of the value and worth of an existing or possible future person, then every human being could be classified on a scale—classified as having a different value and worth. This would then come into opposition with the very concept of an egalitarian and civilized society.

It is, thus, imperative for society to always decide to equally value, without selection and preconditions, each and every human individual. In the same way, it is the reason why a civilized society must welcome into existence all possible future persons independently of their biological or other characteristics such as their genetic qualities or disorders.

Of course, it is possible to challenge this statement by emphasising that certain forms of prenatal selection are already taking place, including in preimplantation genetic selection, whereby (following IVF) only the 'best' embryos are selected for implantation. Moreover, it may be argued that such procedures have not given rise to any perceived damage to the equality between persons. But these procedures are, in effect, already sending the message that all persons are not equal in value and worth and that some should not be brought into existence. And the more the vulnerable edifice of equality in civilized society is undermined by decisions that weaken its very foundations, the more likely it is that this equality may eventually disappear.

Conclusion

In deciding whether or not to use genome editing it is first important to consider whether the procedure it heritable. If it is not, then the procedure could be used in a very positive medical manner in helping to restore human bodies to a state of health. This would then be comparable to other somatic gene therapy procedures already in existence which should be welcomed.

On the other hand, if the genome editing procedure could give rise to heritable genetic modifications, a number of important alternatives may then be considered:

To begin with, individuals and society may choose to believe that all lives are equal in worth and value, making any selection and classification meaningless if sufficient resources are available to support all children, which is the ideal context of a civilized inclusive society.

Secondly, individuals and society may choose not to bring a certain kind of child into existence because they recognise, or believe, that they themselves lack the financial, physical, psychological or the social resources and support necessary to look after such a child. In other words, they may admit to their own limitations or that of society, rather than selecting against a possible future child who is considered as substandard or as unworthy of life.

Finally, individuals and society may decide not to bring a certain kind of child into existence, because the value of his or her life is considered to be unacceptable even though the prospective parents have the financial, physical, psychological as well as the social resources and support necessary to look after such a child. But this would then mean that selective eugenic decisions are seen as acceptable since it would be possible to classify the worth of all lives.

Notes

The views expressed in this article are those of the author and do not necessarily reflect the positions of the professional organisations with which he is affiliated.

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Chapter 4
Therapeutic Genome Editing

Ellen Wright Clayton

Abstract Efforts to cure single gene disorders by replacing the responsible genes using stem cell transplantation and gene transfer have been pursued for decades. These approaches, however, have been confined to serious diseases due in large part to their toxicity. Somatic gene editing (SGE), which repairs undesirable variants, is changing the landscape. It may well have fewer side effects than prior technologies. Thus, it is possible to consider using this approach to address a much broader array of a single gene variants, including treating milder genetic disorders and even improving function in otherwise healthy people. With these possibilities in mind, we discuss three implications of SGE. The first is the complexity of distinguishing between therapy and enhancement as well as the multifaceted debate about the acceptability of the latter, noting that many in the public are opposed to what they see as unfair advantage. The second, which previously has received little attention, is the tremendous price that is likely to be charged for SGE, which makes the debate about enhancement almost moot because even the needs of the most seriously ill will almost surely not be met, raising serious concerns about equity. The last is ensuring adequate regulation and governance of somatic gene editing.

Keywords Single gene disorders · Somatic gene editing · Gene editing regulation · Governance · Enhancement

Thousands of genes have variants that can contribute to disease. Some of these changes have major phenotypic effects, causing so-called single gene disorders, such as sickle cell (SS) disease, cystic fibrosis, and Tay-Sachs disease, to name just a few of the thousands that are known. Other variants have little phenotypic effect on their own but contribute in combination with many other genes to the development of complex disorders such as hypertension, obesity, and Type 2 diabetes. The advent of technologies such as Zinc finger nucleases, transcription activator-like

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effector nucleases, and CRISPR-Cas9 and their progeny holds out the prospect of promoting health by making it possible to edit or change these variants to their non-pathogenic forms.(National Academies of Sciences, Engineering, & Medicine, 2017) In this essay, I will focus on the ethical issues raised by using these technologies to alter genes after the person is born. Editing gametes and embryos with the intention of bringing the altered child to term, so-called germline gene editing, is potentially both more powerful and more ethically fraught,. (National Academies of Sciences et al., 2017; National Academies of Sciences, Engineering, & Medicine, 2020) Germline modification is also addressed in Chaps. 3 and 6.

Efforts to "fix" diseases caused by pathogenic variants by replacing them have been underway for decades. Early examples include what were then called "bone marrow transplants" (now more commonly called stem cell transplants) to treat disorders such as severe combined immunodeficiency (SCID) by replacing the child's immune system. (De La Morena & Gatti, 2011) These were followed by numerous trials of gene therapy or transfer, which sought to replace only the affected gene. (Gostin et al., 2014) Some disorders for which this approach now appears to be effective include spinal muscular atrophy, a rare form of retinal dystrophy, some lipid disorders, (Cring & Sheffield, 2020) and, quite recently, ornithine transcarbamylase deficiency. (Kaiser, 2021) These efforts provide powerful lessons about the challenges posed by the development and use of therapeutic genome editing.

The role of risk, however, has loomed large in ethical analysis of these approaches. Some of these technologies have been limited by their toxicity. Stem cell transplantation (SCT) has largely been limited to single gene disorders from which children would otherwise die in childhood, such as SCID. By contrast, this approach has been much less commonly used to treat sickle cell disease (SS) even though this disease causes enormous suffering and involves only a single base pair change in stem cells that are readily accessible. This reluctance is due in part to the fact that survival into adulthood is more common, concern about the side effects of SCT, and the availability of other partially effective interventions, such as the use of urea to promote production of fetal hemoglobin. (Jones & DeBaun, 2021; Krishnamurti, 2021) Some advocate for using SCT to treat SS, (de la Fuente et al., 2020) citing improvements in of stem cell transplantation with marrow ablation over the years, but the remaining risks still make technology less palatable to many.

Efforts to replace single genes, so-called gene therapy or transfer, raise a different, but related set of risks. The first are the risks of delivering the "new" gene to a place where it can usefully function. Replacing a gene that is expressed to create a needed enzyme or hormone, as is the case in SCID caused by adenosine deaminase deficiency, is more likely to be effective than one that contributes to the formation of structures like the heart or bone. (Fox & Booth, 2021) Delivery of wild type FGFR3,(MedlinePlus, 2021) for example, will not repair the skeleton of a person with achondroplasia. Accessibility of the target organ also matters – the bone marrow is easier to reach than the central nervous system. Typically, a vector, such as an altered virus or a lipid nanoparticle, is required to ensure that the gene reaches its target without being degraded. These vectors, however, can elicit serous immune responses, as was tragically observed in the case of Jesse Gelsinger, who died

during an early phase I trial of gene transfer to treat ornithine transcarbamylase deficiency. (Wilson, 2010) And a number of cases have been identified in which patients treated with gene transfer have subsequently developed cancer, apparently attributable to the intervention. (Jones & DeBaun, 2021; Marwick, 2003) Misdirected integration of genes, so-called off-target effects, have also occurred, interrupting functional genes, rendering them inactive or altering their regulation.

Many of the efforts at gene replacement/therapy have focused on children in an effort to prevent the progression of disease. For such trials to be acceptable, however, there must be a commensurate possibility of benefit to the children or to others like them. (Office of Human Research Protections, 2021) Thus, some trials are being conducted in adults who can make their own decisions about the balance between risk and benefit. The Jesse Gelsinger case mentioned above was a powerful lesson about both the challenges of obtaining truly informed consent and concerns about the appropriate conduct of clinical trials. (Gelsinger & Shamoo, 2008; Wilson, 2010).

Gene editing, typically using CRISPR or related technologies, holds out the promise of treating genetic disorders by repairing the pathogenic variant directly while avoiding some of the risks of SCT and gene transfer. Bone marrow ablation is not always needed and if necessary, can often be less intense. Many of the adverse immune responses may also be avoidable. In fact, some experimental efforts to edit genes are being conducted *ex vivo*, or outside the body. This involves removing stem cells from the bone marrow, treating them, and then reinfusing them into the patient. Trials are under way to treat SS, beta thalassemia, Leber congenital amaurosis, and transthyretin amyloidosis using gene editing, as well as HIV (Saha et al., 2021).

If it turns out that gene editing poses little risk to the individuals whose genes are altered, questions have already been raised about whether this technology should be used to edit somatic, or body, cells to treat less serious disorders or even to enhance normal human function, raising problems both of line drawing and equity. While the public in general is more supportive of gene editing to treat diseases than to address non-medical traits, (Delhove et al., 2019; Howell et al., 2020; Riggan et al., 2019) the distinction between therapy and enhancement may not always be clear, an issue also discussed in Chap. 13. A classic example used to explore this issue is the use of erythropoietin (Epo), a hormone used to increase red cell production in patients with anemia, but which athletes can use to increase their endurance.

In an effort to place some boundaries around the use of somatic gene editing, many commentators have argued that this technique should be used only to relieve symptoms or to bring the individual to normal human function. (National Academies of Sciences et al., 2017) Using the admittedly fluid concept of normality as a limit has been attacked from many directions. John Evans argues that, once begun, gene editing has no clear boundaries or stopping points, creating a risk that expansion of use will continue unabated. (Evans, 2020, 2021) Others challenge the notion that enhancement is undesirable *per se*, arguing that people appropriately do many things to improve their own life experiences and those of others, usually family members, around them. After all, parents are supposed to enhance the lives of their children, and the job of educators is to enhance the understanding of their students.

Indeed, a few argue that parents are morally obligated to use genetic interventions to enhance their children. (Savulescu, 2009) For most people, however, the question is how to distinguish between acceptable and unacceptable interventions. (Juengst et al., 2018) One line of inquiry that has been instructive is the longstanding debate in sports, also addressed in Chap. 15, where a rough line has been drawn to exclude interventions that confer advantage without effort on the part of the athlete. Thus, just as use of epo is forbidden in many sports, so too would gene editing to increase the production of erythropoietin be banned. (Juengst, 2020; Murray, 2018).

These questions about treatment versus enhancement pale in comparison to issues of access given the likelihood that these interventions will be more available to those with more resources, thereby widening the gaps between haves and have-nots even further. This is particularly the case given the price of gene editing, which will dramatically constrain the availability of these interventions. The current price for gene replacement/therapy for spinal muscular therapy, for example, exceeds $2,000,000 for a single dose, with no guarantee that further doses will not be required. Since gene editing trials are so new, little information is available about what price will be charged for these interventions if these trials prove effective, but it appears certain that the price will be quite high. (Irvine, 2019) And yet the number of people with serious disorders, ones that cause early death, serious morbidity, or lifelong onerous or expensive intervention, that are potentially amenable to gene editing is quite high. To pick just a few out of thousands of candidates affecting people in the US, ~16,500 have PKU, ~10,000 have urea cycle defects, 10,000–25,000 have spinal muscular atrophy, and almost 100,000 have sickle cell disease. Assuming a conservative price of $2,000,000 per dose, treating all these patients would cost over thirty billion dollars in the US alone. This sum is an underestimate in that many other disorders would also be candidates for editing, and the potential need worldwide will be even greater. The World Health Organization estimates that 300,000 babies with severe hemoglobin disorders are born every year around the world. (World Health Organization) It is notable that representatives of Médicins Sans Frontières attended the Paris meeting of the first international genome editing committee. (National Academies of Sciences et al., 2017) Some of the price would be offset by the ability to forgo future treatment, (Chapman et al., 2021) assuming 100% efficacy and no need for retreatment, but the potential price remains prohibitive. Thus, whether these interventions should be devoted primarily or exclusively to treating those who have severe, life-limiting disorders is a pressing question of equity, for which the current unequal distribution of COVID-19 vaccine around the world provides a powerful parallel.

On balance, it seems reasonable to suggest that somatic gene editing when effective should be used to treat individuals who are ill, acknowledging the inherent vagueness of these categories, and that use for other purposes should be disfavored due to the lack of resources needed for patients. Clearly, ongoing efforts to obtain public input on how to deploy these interventions are critical. (National Academies of Sciences et al., 2017; Scheufele et al., 2017) But it is also important to consider how to ensure that these tools are actually allocated appropriately because violating ethical norms and public consensus threatens the fabric of society. Some

mechanisms that have been proposed are the traditional tools of regulation and licensure, perhaps augmented innovatively by a lottery to allocate interventions among those are eligible. (Mehlman, 2018) Others have taken a broader view of the needed governance structures. (Jasanoff et al., 2019; Marchant, 2021) All of these approaches have limitations and their implementation varies widely around the world, so ongoing monitoring is needed.

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Chapter 5
Bioethical Decision-Making About Somatic Cell Genome Editing: Sickle-Cell Disease as a Case Study

Christopher Rudge and Dianne Nicol

Abstract Somatic cell genome editing (SCGE) now allows exquisitely precise and targeted non-heritable changes to be made to human DNA. While SCGE has many possible applications, clinical trials indicate its great potential to provide new forms of medical treatment, as well as cures, for a range of prevalent monogenic diseases, including several disorders of the blood (hemoglobinopathies). This chapter provides an overview of the nature of somatic cells, a discussion of their connection with genetic disease, and a summary of the bioethical issues that attend various therapeutic uses of the system. The chapter takes sickle-cell disease as a case study, identifying the advantages that SCGE promises over the current best treatment, as well as the issues that will likely compel patients, clinicians and others to engage in difficult bioethical decision-making. Lastly, the chapter takes up four bioethical principles—nonmaleficence, beneficence, autonomy and justice—to analyze some of the most pressing bioethical issues associated with SCGE, as well as recent recommendations for governing the technology published by the World Health Organization.

Keywords Somatic cell genome editing · Sickle-cell disease · Programmable nuclease-mediated SCGE · Bioethics of SCGE · Gene therapy

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Introduction

Somatic cell genome editing (SCGE) is a complex linguistic expression for a complex science. Since the 1970s, explorations in gene modification—including studies of gene targeting, genome engineering, or genome surgery—have distinguished between two forms of experimental and clinical genome editing. The term SCGE is generally used to describe those forms of editing carried out on mammalian (including human) somatic cells whose modifications are not heritable (Smithies, 1966). By contrast, human germline genome editing (HGGE) denotes those forms of editing intended to alter DNA in the 'germ' cells of human gametes (or their precursors) that cause heritable changes to the genome.

Another line of distinction captured in the expression SCGE derives from the word 'editing.' Since around the 1980s, 'editing' has denoted the exquisitely precise and targeted nature of the changes made to somatic cell DNA in SCGE applications. It involves the introduction of 'editing machinery' into cells to induce targeted damage at specific sites of, and initiate controlled repairs in, cellular DNA (Li et al., 2020b). Although there are various forms of genome editing, their key features are 'programmable nucleases', designed to create precise breaks in both strands of the DNA molecule (double strand breaks). Thus, SCGE is usually distinguished from 'traditional' somatic cell gene therapy (SCGT) (World Health Organization, 2021a)—or simply 'gene therapy'—which employs random insertion methods, such as by using adenovirus-associated viral vectors or other delivery tools, to replace mutated genes or add new ones—not to alter existing nucleotides (Chang et al., 2018).

Inevitably, degrees of overlap and ambiguity arise in the nomenclature. Some emerging and prospective forms of SCGE may lead to heritable changes, such as where gonadal cells isolated from the male reproductive system are removed, edited, and retransplanted, thus introducing changes that may propagate to future generations (Monckton, 2018). Likewise, some forms of SCGE will be used in conjunction with established forms of gene therapy, such as where adenovirus-associated viruses are used as vectors for programmable nucleases (Li et al., 2020b). Thus, although genome editing is considered more precise than gene therapy, and less genealogically consequential than HHGE, this distinction can sometimes be tenuous and confusing, impacting on patient as well as scientific understanding (Anguela & High, 2019).

This chapter will focus on several bioethical decision-making issues associated specifically with programmable nuclease-mediated SCGE directed towards the treatment of serious pathological genetic disorders. In this way, this chapter might be thought to elide or reinforce the so-called somatic/germline and disease/enhancement 'barriers' that, since the 1970s, have characterised the bioethical discourse on genome editing more generally (Evans, 2021). Nevertheless, our concentration on therapeutic forms of nuclease-mediated SCGE is intended not to mark out any limits in the genome editing debate but instead to enable a focused analysis on SCGE's most pressing challenges for bioethical decision-makers as we see them.

Some now well-established uses of somatic cell modification have been translated without significant bioethical demurral, usually where both a specific medical benefit and a favourable risk-benefit ratio obtains (Coller, 2019). Such is the case in allogeneic (donor-facilitated) hematopoietic stem cell transplantation, which involves the modification of a patient's DNA through the infusion of exogenous DNA from donor cells, creating true biological chimeras (Themeli et al., 2011). Moreover, the development, regulatory approval and clinical translation of several gene therapies, such as Luxturna (voretigene neparvovec)—a medication for a rare form of inherited blindness—reflects the extent to which genome manipulation is already well underway.

For hematopoietic stem cell transplants, the bioethical discourse has primarily focused on the patient's health interests, including clinical safety and efficacy, consent and inclusion and practitioner conflicts of interest (Liso et al., 2017). In the case of gene therapies, similar issues are considered, although the exceptionally high cost of these medications—some of which cost more than 30 times the median US income per dose—is emphasised (Shukla et al., 2019; Machin et al., 2018; Lloyd-Williams & Hughes, 2021; Wong et al., 2021; 'Gene therapies should be for all', 2021). By contrast, broader principles related to 'genetic identity' (Goekoop et al., 2020) and genealogical 'tampering' are far more common in the philosophical bioethical discourse of HHGE (Isa et al., 2020). While we do not suggest that 'the horse has already bolted' (Kirskey, 2020) in relation to SCGE, it is important to acknowledge the extent to which many of these bioethical decisions are far from hypothetical (as they were some 50 years ago when the debate began) and increasingly involve bioethical decision-making in the clinic, or clinical bioethics.

In sections "What are somatic cells?", "Historical development of somatic cell genome editing", and "Sickle-cell disease", we provide some background on somatic cells, disease etiology, the historical development of SCGE, and different cell-environment applications of SCGE. In section "Bioethical decision-making about ex-vivo nuclease-mediated SCGE", we provide a case study of the sickle-cell disorders (sickle-cell disease). Here we discuss the attributes and bioethics of the current best treatment for sickle-cell disorder, the allogeneic hematopoietic stem cell transplant, before discussing the emerging potential of the nuclease-mediated SCGE. In this way, we lay the groundwork for our broader reflection of the bioethics of SCGE in section "Conclusion"—a reflection we develop with reference to sickle-cell disorder, as well as the proposed governance framework for genome editing published in 2021 by the World Health Organization (World Health Organization, 2021a). In this last section, we also adopt a version of the bioethics framework formulated originally by Beauchamp and Childress in their landmark text *Principles of Biomedical Ethics* (2019 [1979]) but reanimated in more recent considerations of genome editing and bioethics, such as by Evans (2020) and others (Getz & Dellaire, 2020). This bioethics framework is used to classify a broad gamut of bioethical considerations under four principles: namely, nonmaleficence, beneficence, autonomy and justice.

What Are Somatic Cells?

Mammals, including humans, have only germ and somatic cells. Each somatic cell in the human body is diploid, containing two inherited genomes (or two sets of chromosomes) from each biological parent. Germ cells are primordial cells in the oocytes (eggs) and spermatocytes (sperm), collectively known as the gametocytes. These cells are haploid, having undergone meiosis, in which a parent cell divides twice to produce four genetically distinct germ cells. Each germ cell has only one sex chromosome and one of each pair of the remaining 44 chromosomes. While germ cells are sometimes called 'germline' cells, that latter term refers to the *lineage* of cells that originates from the primordial gametocytes and eventually form the gametes in the adult, which transmit genetic materials from parent to child (Wessel, 2016).

The other kind of cells, somatic cells, encompass all cells in the human body that are *not* germ cells (Boggio et al., 2019) Named after the word 'soma', meaning body, somatic cells make up the organs, integument (skin, hair, nails), bones, blood and connective tissue (Strome & Lehmann, 2007). They can divide only by mitosis, where a parent cell divides once to produce two genetically identical daughter cells, incapable of sexual reproduction (Wessel, 2016). Unlike germ cell meiosis, which facilitates sexual reproduction, somatic cell mitosis facilitates the growth and replacement of worn-out (senescent) or shed (apoptotic) cells in the body.

Since somatic cells cannot establish continuous lines (Hayden, 2020), alterations made to them are not propagated or transmitted to future generations but instead simply maintained (through repair and replacement but not reproduction) within the body of the person treated. Modifications made to germ cells, by contrast, will be passed to any offspring into the future, thus entering the species' gene pool (Boggio et al., 2019). While SCGE is possible at any stage of human development after birth (and in-utero), alterations to germ cells are, with few exceptions, only possible at the earliest stages of human development. Studies have demonstrated that pre-fertilisation gamete editing is the only promising way in which to effect heritable alterations to the human genome, and that editing mature gametes (i.e., sperm or eggs) is more difficult than editing their early precursors (i.e., spermatagonial stem cells or germinal vesical oocytes) (Vassena et al., 2016). Moreover, the editing of embryos is highly regulated if not unlawful in many jurisdictions, while the maintenance of edited of embryos is unlawful in almost all jurisdictions (Cavaliere, 2017; Yotova, 2017).

In 2006, it was discovered that by encoding certain transcription factors, somatic cells could be converted (or induced) into pluripotent stem cells—cells that, like embryonic stem cells, may give rise to every other cell type in the body and propagate indefinitely (Takahashi & Yamanaka, 2006). While this chapter will not contemplate the seemingly great potential of induced pluripotent stem cells to improve diagnostic and regenerative medicine (Jehuda et al., 2018), it is worth underlining their likely place in future clinical practice—particularly in SCGE therapies (Chen et al., 2021).

SCGE has many applications. It may be used to genetically modify bacteria, plants and animals, improve our understanding of gene functions, model human disease for basic research, aid in drug discovery and, of course, create targeted therapeutic interventions to treat and prevent human disease. In this chapter, we analyse nuclease-mediated SCGE as a particularly important class of *therapeutic* intervention—one that promises to transform the treatment of serious genetic diseases for which no other interventions exist.

Somatic Cells and Disease Etiology

Somatic cell genomes encode the person's cellular functions for the term of their life, facilitating repair and growth but also determining afflictions. Genetically inherited diseases usually occur when a child inherits certain deleterious genetic variants (alleles) from one or both parents; however, sometimes the random appearance of such variants occurs de novo in the embryo (National Academies of Science, 2017).

A genetic variant may be inherited either from one parent alone (heterozygously) or from both parents (homozygously). While some single-copy (heterozygous) genetic variants may be inconsequential (recessive), others are known to cause significant medical issues, as with Huntington's disease and hemophilia. In Huntington's disease, a single variant is 'dominant' (and so will express as disease regardless). In some cases of hemophilia, a single variant is linked to the X chromosome or 'X-linked,' and so will manifest in males (who have only one X chromosome) but not females (who have two) (Tsai et al., 2015). But even when recessive, a single-copy variant may threaten the health of future generations. If two unaffected 'carriers' of a single variant reproduce, there is a 25 percent chance that a child will inherit two copies of the variant and express the relevant disease (National Academies of Science, 2017). Then again, sometimes a single-copy variant may also confer a genetic advantage. The variant for sickle-cell disease, discussed later in this chapter, provides carriers with some genetic protection against malaria if inherited heterozygously (National Academies of Science, 2017). Of course, in homozygosity, where two copies of this same pathogenic variant are inherited, expression of sickle-cell disease will be inevitable.

Monogenic and Polygenic Diseases

While single genetic variants are common in the transmission of diseases, most human disorders are complex or polygenic—that is, caused by multiple variants and affecting numerous cell and tissue types. At present, nuclease-mediated SCGE is poorly suited to treating such polygenic disorders. Recent studies utilising CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and associated Cas

enzymes, the most popular current genome editing technique, do hold some promise for future treatments of polygenic disease. Despite this, nuclease-mediated SCGE is not yet adept at targeting multiple DNA loci (McCarty et al., 2020). Still, with more than 10,000 monogenic diseases identified in the human population (Chen et al., 2020), many of them fatal, the enormous burden of treating diseases caused by single gene mutations is heavy indeed, forming a strong clinical-bioethical rationale for exploring and translating therapeutic SCGE.

Since the 1980s, the prospects for reaching clinical efficacy in monogenic disorders have increased considerably, with more than a dozen diseases now being investigated in clinical trials or preclinical studies, including sickle-cell disease, β-thalassemia, severe combined immunodeficiency, X-linked hyper IgM Syndrome, haemophilia B, cystic fibrosis, HIV, cancer immunotherapy, Duchenne's muscular dystrophy, Huntington's disease, and several neurodegenerative diseases (National Academy of Medicine et al., 2020). In recent years, increasing numbers of clinical trials have been initiated using SCGE for such monogenic disorders. In order to illustrate how this shift in prospects came to pass, the following section outlines the historical development of SCGE and the emergence of the nuclease-mediated platforms.

Historical Development of Somatic Cell Genome Editing

Homologous Recombination

The first applications of genome editing in humans were performed on somatic cells (National Academy of Medicine et al., 2020). In the 1980s, researchers established a proof-of-principle study (Porteus, 2011) confirming that specific gene sequences could be 'targeted' by adopting homologous recombination, a naturally occurring process during meiosis whereby some of the DNA in one chromosome in a pair is exchanged with the equivalent DNA from the other chromosome in the pair (Fehse & Abramowski-Mock, 2018). An early experiment involving homologous recombination achieved a planned modification of the human β-globin locus—a single gene that, if affected by a point mutation, produces sickle-cell disease and related haemoglobinopathies (Smithies et al., 1985). Although the inefficiency of homologous recombination was acknowledged at the time (only one in one thousand cells were changed as intended), the great potential of SCGE—specifically for in vivo modifications of specific genes—was grasped. The investigators foresaw that particular enzymes present in bacteria might enhance the homologous repair activity, auguring more precise forms of homology-directed repair (Kucherlapati et al., 1984).

Even before the adoption of homologous recombination, radiation scientists had verified that human somatic cells could repair DNA damage endogenously where both strands of DNA had been severed synchronously (Lange, 1974; Resnick, 1976). Early studies of this repair mechanism, known as non-homologous

end-joining, underlined both its great potential and its improbability: while repairs would always follow DNA damage, there was no homology between the severed strands, as the name suggests (Resnick, 1976; Lieber, 2010). Soon, non-homologous end-joining was shown to be an imperfect or 'inefficient' repair process because it introduced small, random insertions and deletions, known as indels, into the DNA—products that can disrupt or turn off the repair-affected genes (Rouet et al., 1994; Yang et al., 2020). Due to these errors, this technique was regarded as impracticable for specific repairs, but useful if the goal was to precisely disrupt a gene or genes.

Non-homologous End-Joining

As studies of double strand breaks and non-homologous end-joining repairs improved, investigators found new ways of making site-specific breaks in complex genomes (Jasin & Rothstein, 2013). First discovered in yeast mitochondria (Choulika et al., 1995; Plessis et al., 1992), particular enzymes known as endonucleases were applied to human somatic cells in 1994 (Porteus, 2016). The advantage of these endonucleases was that their so-called recognition sites—the length of the DNA sequence they could target—spanned some 12–40 base pairs. This was longer than the restriction enzymes studied in earlier forms of homologous recombination, which spanned only between 3 and 8 base pairs. This meant that the endonucleases were less likely to be affected by single base-pair changes (Belfort, 1997), opening the door to far more precise and efficient methods of genome editing than ever before (Carroll, 2014).

Interestingly, the human body's 'preferred' mechanism for endogenous DNA repair in somatic cells is non-homologous end joining (Liang et al., 1998). However, investigators realised in the 1990s that a template-assisted form of homologous recombination called homology-directed repair could, at least in optimal conditions, facilitate superior editing frequency (Porteus, 2016). By inserting an extra piece of DNA into the cell during the breakage-repair process—a homologous 'sister chromatid' related but slightly different to the cleaved gene—editing accuracy was improved (Miyaoka et al., 2016). Still, the efficiency of homology-directed repair varies widely among different cell types for reasons not yet well understood (Gu et al., 2020). How and why chromosomes dynamically reorganise during repair, achieving increased mobility, are still mysterious (Smith & Rothstein, 2017). While investigators have recently attempted various ways to improve the DNA donor template, such as by hindering gene expression using interfering RNA (siRNA) (Liu et al., 2019), many unintended products are still introduced into the repair process (National Academy of Medicine et al., 2020).

Some commentators lament what they see as a 'false dichotomy' between non-homologous end-joining and homology-directed repair (Berthel et al., 2019). Indeed, some of most promising SCGE technologies to date harness the repair of double strand breaks using both techniques. A 'diverse genome editing toolbox' now exists with which investigators can achieve site-specific double strand break

repairs (Porteus, 2016). The four best-established platforms comprise the meganucleases, zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and, most transformatively, the CRISPR-Cas system, the engineered molecular-bacterial machinery mentioned earlier in this chapter.

Nuclease-Mediated SCGE

While each nuclease-mediated platform has its own advantages and disadvantages (see Table 5.1) (Adli, 2018), each has been greeted with initial enthusiasm and adoption followed by subsequent realisations of their limitations (Guha & Edgell, 2017). Computational analysis of each platform's precision is developing, promising new insights on their efficacy and improvement (Bao et al., 2021). Undoubtedly, the most revolutionary platform has been the CRISPR-Cas system. More than any other nuclease-based editing platform, CRISPR-Cas systems have revolutionised genome editing, largely because their target sequences may be programmed more simply, reliably, and effectively than ever before through the use of easily designed guide RNAs (Saha et al., 2021).

Some emerging SCGE techniques, such as base editing (using, for instance, 'CRISPR Nickase' systems) and prime editing (using a fused Cas9 nuclease), also rely on modified versions of the CRISPR or Cas systems (Satomura et al., 2017; Anzalone et al., 2019). As neither of these techniques requires double strand breaks to modify genomes, but rather only partially nicks the genome, they appear to considerably reduce the risk of errors associated with double strand break repair.

Ex Vivo, In Vivo and In Utero Applications of SCGE

Nuclease-mediated SCGE may occur outside the body (ex vivo) or inside the body (in vivo). A third route, in which edited somatic cells may be administered to fetuses (in utero), is also under investigation (Rossidis et al., 2018). In utero SCGE may offer transformative therapeutic benefits where an unborn child, through prenatal genetic testing, is diagnosed with a monogenic disease that would be irreversible or untreatable after birth, such as inborn errors of metabolism (Houtkooper, 2018; World Health Organization, 2021a; Coller, 2019; Hartman et al., 2018). However, in utero editing may also pose increased risks of germline modifications if the germ cells have not been entirely sequestered from the somatic cells (Coller, 2019).

The most frequently used approach to sickle-cell disease is ex vivo SCGE, which involves extracting or harvesting somatic cells from a patient's body, then isolating, expanding and editing those cells with a programmable nuclease in a medium (in vitro), and then selecting and reintroducing those cells into the patient's tissues through a route of infusion (Li et al., 2020c). In vivo approaches involve introducing the nuclease platform directly into the patient's tissues through systemic or local

Table 5.1 Attributes of different nuclease platforms

Nuclease	Year of first use in human somatic cells	Specificity	Biasing events (repair)	Target site length	Ease of reengineering	Cost effectiveness	Multiplex potential	Therapeutic delivery	Stage of clinical development
Homing endonucleases and meganuclease	1994	Not determined	HDR	Short (>18)	Very difficult	Poor	High	Easy	Target validation
ZFN	2003	Moderate	NHEJ	Short (18–36)	Difficult	Poor	Low	Moderate	Phase I/II
TALENs	2011	High	HDR	Long and repetitive (24–38)	Easy	Moderate	Low	Moderate	Phase I/II
CRISPR-Cas9	2013	Very High	NHEJ	Long (22)	Easy	High	High	Easy	Phase I/II

Adapted from Guha and Edgell (2017), Porteus (2016), and Li et al. (2020a)

(more invasive) delivery methods so that a therapeutic effect may be exerted on-site. This approach faces tremendous challenges in transporting the nuclease to the nuclei of the targeted cells and avoiding delivery to off-target cell types (Li et al., 2020c). Furthermore, in vivo approaches do not enable investigators to test the cells for quality or for immunological compatibility before they are reinfused into the patient (albeit that validating millions of cells may be extremely difficult) (Carlson-Stevermer et al., 2020). These challenges are exacerbated in diseases involving different organs (National Academy of Medicine et al., 2020). Where an organ is readily accessible and hermetically distinct from other organs and tissues, however, such as in the case of the eye or liver (Editas Medicine, Inc., 2020), the prospects of an effective in vivo SCGE may be stronger (Sangamo Therapeutics, 2021a, b, c).

Regardless of administration type, all CRISPR-mediated SCGE techniques face major challenges to clinical translation that bear on clinical and bioethical decision-making. These include patient pre-existing immunity (Li et al., 2020b; Charlesworth et al., 2019), in vivo delivery efficiency (Tong et al., 2019), off-target or unintended edits (Cradick et al., 2013), structural abnormalities (inversions) and chromosomal translocations of the kind seen in cancer, such as chromothripsis (Leibowitz et al., 2021). More specific concerns include that double strand breaks in CRISPR-Cas systems are potentially or even inevitably 'genotoxic' (Sheridan, 2021; Blattner et al., 2020), prone to causing large deletions (Adikusuma et al., 2018) and liable to make unexpected truncations of genetic material (Cullot et al., 2019).

Bioethical Decisions About Nuclease-Mediated SCGE in General

These disturbing and real risks frame the way in which bioethical decisions can and should be made about the introduction of these treatments into humans for therapeutic use in the clinic. Indeed, while many fundamental mysteries still enshroud the molecular mechanisms of double strand break repair, it is arguable that much more research is needed before these treatments should be permitted to be delivered. As one investigator asks, 'How does the cell 'know' what to do when confronted with broken DNA? What is the mechanism governing increased chromosome mobility? To what is the circuitry responding when it triggers the repair event?' (Jasin & Rothstein, 2013). As will be discussed below, these epistemological gaps coincide with a growing body of evidence demonstrating real and potential genetic harms of SCGE.

But why should these potential harms be important for bioethics and decision-making? Since the avoidance of harm or 'nonmaleficence' (Evans, 2021) has long been at the centre of health practitioner ethics, this first principle is also reflected in broader bioethical considerations about the use of SCGE, whether they occur in the legal, regulatory, clinical, or patient-doctor (consent) context. But to take up this principle, and to recognise these harms, is also to approach the bioethical concept of

'vulnerability'—a phenomenon that was described as 'undertheorised' some ten years ago (Rogers et al., 2012) but has more recently been developed and expanded beyond clinical research (Boldt, 2019). Focusing on the risks and potential harms to patients is to give form to the bioethical consideration of vulnerability, which is connected implicitly to the principle of nonmaleficence.

Still, these concerns for harm and patient vulnerability must also be weighed against the principle of beneficence, especially in view of increasing evidence for the benefits of SCGE for certain diseases, such as sickle-cell disease, as well as the tremendous potential for medical advancement that SCGE represents more generally, including through the broader prospect of eradicating or diminishing the enormous burden of widespread genetic diseases such as sickle-cell disease. In order to explore these bioethical tensions, we now take up the example of the treatment of sickle-cell disease, exploring the disease itself, its current best treatment, and the emerging alternative treatment in SCGE.

Sickle-Cell Disease

The sickle-cell diseases are a group of inherited genetic disorders that relate to red blood cells. Red blood cells contain hemoglobin, which helps carry oxygen from the lungs to the tissues of the body (and remove carbon dioxide). In sickle-cell disease, red blood cells express so-called abnormal sickle hemoglobin (known as HbS) due to the genetic inheritance of the homologous HbS gene—a variant of the hemoglobin beta gene (HBB) (Wen et al., 2017). Where a person has two copies of the HbS gene, they will have sickle-cell anemia; or, where a person has only a heterozygous (single) copy of HbS, they will likely exhibit varying manifestations of the disorder, including phenotypic symptoms associated with the β-thalassemias.

The HbS variant is caused by a single substitution in the hemaglobin molecule: glutamic acid is replaced by valine. This change in protein structure results from a small change in the DNA sequence coding for the protein—from GAG to GTG on the HBB gene (on chromosome 11p15.5) (Ingram, 1959). This substitution causes hemoglobin to form polymers under reduced oxygen conditions (Higgs & Wood, 2008). As a result, red blood cells become contorted, taking on a sickle shape. These 'sickled' red blood cells can then obstruct normal blood circulation and cause ischemia (reduced blood flow) in tissues around the vascular blockages known as vascular-occlusive crises, causing significant health complications (Driss et al., 2009). While sickle-cell disease is sometimes considered a relatively simple monogenic disorder, the clinical phenotypes are extremely variable, with symptoms ranging from death in early childhood through to a normal lifespan with few complications (Serjeant et al., 2007). This makes sickle-cell disease an extremely complex disorder to treat (Driss et al., 2009).

Together with the related β-thalassemias, sickle-cell disease hemoglobinopathies are the most prevalent and clinically significant genetic diseases in the world, affecting approximately 100,00 people in the US an estimated more than 25 million

people worldwide (Modell & Darlison, 2008). Although common in Europe and North America, sickle-cell disease is most prevalent in sub-Saharan Africa, India and the Mediterranean (Osunkwo et al., 2021). In a recent comprehensive study involving over 2000 patients with sickle-cell disease globally known as the Sickle Cell World Assessment Survey (SWAP), it was found to have a profound negative effect on quality of life, with some 60% reporting that the disease impacted on their emotional wellbeing, some 48% reporting they worried about dying, and 94% of patients reporting a need for ongoing treatment. Fewer than half reported receiving the mainstay medication for the general treatment of sickle-cell disease—an anti-metabolite that increases fetal hemoglobin called hydroxyurea (Osunkwo et al., 2021).

Current Therapeutic Approaches to Sickle-Cell Disease

While several treatment pathways are available for patients with sickle-cell disease, including pain medications, blood transfusions, hydroxyurea and, most recently, L-glutamine oral powder (Sadaf & Quinn, 2020), the only known curative treatment is allogeneic hematopoietic stem cell transplantation (Karamperis et al., 2021). This intervention is typically known as a 'bone marrow transplant' because it uses stem cells normally harvested from a donor's bone marrow—although stem cells from cord blood or mobilised peripheral blood are also used (Fitzhugh et al., 2014). Hematopoietic stem cells give rise to all the blood cells in the body, making up about 0.1% of cells in the bone marrow (myeloid tissue) (Hawley et al., 2006). An allogenic hematopoietic stem cell transplantation involves replacing a patient's sickle-affected hematopoietic stem cells with 'healthy' cells. These replacement hematopoietic stem cells are donated by a person whose tissues are 'matched' to patient's based on their human leukocyte antigen tissue type.

In most cases of hematopoietic stem cell transplantation, the patient receives myeloablative (blood-cell reducing) conditioning before being infused with the donated hematopoietic stem cells. The purpose of this intensive regimen is to cause irreparable damage to the recipient's hematopoietic stem cells so that, when the healthy donor cells are engrafted, these exogenous cells may then 'rescue' and restore bone marrow function and replace the now-unrecoverable pre-existing cells (as well as prevent aplasia-related death) (Bacigalupo et al., 2009). The conditioning also supresses the recipient's immune system, minimising any immunological barriers to the transplant and allowing engraftment to occur. (Bacigalupo et al., 2009) In early iterations of hematopoietic stem cell transplantation, patients were subject to high-dose chemotherapy and radiotherapy—procedures associated with immediate and long-term complications, including infertility and death, and significant sources of patient decision-making anxiety (Meier et al., 2015). In recent years, however, lower intensity regimens have been adopted (nonmyeloablative), decreasing the risks of complications (Bacigalupo et al., 2009).

Allogeneic hematopoietic stem cell transplantation is administered more often to children than adults due to the higher risks in the latter cohort of complications, such as chronic organ damage, lower tolerance to conditioning and infertility. Adults also have more limited coverage by public and private health insurance (Saraf & Rondelli, 2019). Another very significant problem with hematopoietic stem cell transplantation treatments for sickle-cell disease is that more than 80% of treatment candidates cannot find a human leukocyte antigen-matched donor (Demirci et al., 2018). Accordingly, hematopoietic stem cell transplantation presents very high risks of graft-versus-host disease and treatment-related mortality (Robinson & Fuchs, 2016). As such, there is clearly a critical need for other treatment options for people affected by sickle-cell disease globally.

Bioethical Decision-Making About Hematopoietic Stem Cell Transplantation-Based Cures for Sickle-Cell Disease

Clinical bioethical discourse on hematopoietic stem cell transplantation for sickle-cell disease engages with a broad range of these challenges, as well as several problematic uses of the treatment, such as its application in children with 'less severe' sickle-cell disease (Nickel et al., 2014). Nickel and Kamani (2018) have developed a hematopoietic stem cell transplantation decision calculus that identifies a number of potential risks and benefits, as well and other important variables, such as whether the patient harbours any psychosocial, adherence or financial concerns, or whether direct consent is impossible, such as in paediatric patients, and substituted consent is needed. The authors also identify a range of factors that compound these bioethical challenges, such as the unpredictability of certain outcomes in hematopoietic stem cell transplantation, the absence of any validated prognostic criteria, and the fact that sickle-cell disease disproportionately afflicts minority and disadvantaged populations (Nickel & Kamani, 2018).

A 2015 study of patient attitudes towards hematopoietic stem cell transplantation for sickle-cell disease provides some useful guidance on changing community attitudes towards risk (Meier et al., 2015). The study found that while significant numbers of patients were unwilling to accept any risk of mortality or morbidity for the possibility of a cure, the number of respondents willing to accept a 15% or greater risk of graft-versus-host disease had increased since 1991, when hematopoietic stem cell transplantation first emerged as a treatment. While this might reflect improvements in hematopoietic stem cell transplantation outcomes and its increased availability, it may also reflect the commonly implied notion that, with time and familiarity, many potentially harmful treatments gain marginally increased acceptance, while bioethical concerns may diminish in significance (Nickel & Kamani, 2018).

The Nuclease-Mediated SCGE Approach to Sickle-Cell Disease

All the bioethical issues just described with reference to hematopoietic stem cell transplantations are similarly important for patients and clinicians engaged in decision-making about ex vivo SCGE for sickle-cell disease curative therapy. Indeed, while the unprecedented spatial precision of SCGE may appear to somewhat surpass the unpredictable outcomes of the current best cure, a conspicuous lack of data about SCGE for sickle-cell disease means that it is neither possible nor prudent to identify its safety and efficacy other than in the most general and conceptual terms. As will be discussed below, the current lack of well-established evidence represents a significant limitation for bioethical decision-making about SCGE in the clinic, rendering the discussion more speculative than practical. Having said that, it should also be acknowledged that ex vivo SCGE relies in many respects on the established protocols of hematopoietic stem cell transplantation, which allows any bioethical discussion to home in on the narrower aspects of the treatment.

While clinical trials for an ex vivo SCGE treatment for sickle-cell disease are now underway (Vertex Pharmaceuticals Incorporated, 2021a, b), so too are many ex vivo gene therapy trials for the treatment of sickle-cell disease and related hemoglobinopathies (Williams, 2021). Notably, both the SCGE and gene therapy treatments under investigation target the BCL11A gene—a potent 'silencer' or transcriptional repressor of fetal hemoglobin (HbF). It has been known for some time that HbF reduces the severity of sickle-cell disease but is not expressed in adult cells. These treatments are thus designed to induce the production of endogenous HbF in adults. Both forms of treatment involve manipulation of the BCL11A gene, which is known to regulate or 'switch' HbF expression; however, the precise mechanisms by which BCL11A achieves this effect are still being explored (Basak & Sankaran, 2016).

One significant difference between SCGE and conventional hematopoietic stem cell transplantation is that SCGE does not require donor hematopoietic stem cells as these are autologous treatments. By harvesting hematopoietic stem cells from the patient who is undergoing treatment, the very significant engraftment and donor-compatibility challenges posed by an allogenic stem cell transplant are sidestepped. Be that as it may, the significant difficulties associated with undergoing a myeloablative conditioning regimen remain. As for the difference between gene therapy and SCGE, the latter evidently achieves a more precisely targeted alteration to the BC11A gene than the former. While the SCGE treatment uses a CRISPR-Cas9 nuclease to create the edit, gene therapy relies on random insertion via adenovirus-associated virus vectors to modify BC11A.

Safety data on 22 patients undergoing ex vivo SCGE for sickle-cell disease using a CRISPR-Cas9 platform known as CTX001 were reported in a press release from the sponsors of the CLIMB sickle-cell disease-121 study in June 2021, after more than 3-months follow-up post-treatment (Vertex Pharmaceuticals Incorporated 2021a). While these safety data are not yet published in a peer-reviewed study, the initial data suggest that ex vivo SCGE applications may have a generally consistent safety profile when compared with autologous hematopoietic stem cell

transplantation and myeloablative conditioning. The clinical trial is a Phase 1/2 trial involving patients aged 12–35 years with severe sickle-cell disease, defined as a history of more than two vaso-occlusive crises per year in the previous two years (Vertex Pharmaceuticals Incorporated 2021b). The trial protocols were outlined in a proof-of-principle publication (Frangoul et al., 2021) and, following the carrying out of the procedure, described in a follow-up editorial (Malech, 2021). The protocols involved the collection of heterogenous cells from patients via mobilisation and apheresis (from peripheral blood) before being shipped to a manufacturing location. The heterogenous cells were then separated from the vascular fraction so that enriched hematopoietic stem cells (CD34+ cells) were isolated. Following enrichment, the cells were then edited by means of a specialised instrument called an electroporator, which delivers a precise electrical pulse to the enriched cells in a protective medium that contains the CRISPR-Cas9–guide RNA complex.

Electroporation increases the permeability of the cell membranes, allowing the RNA-guided nuclease to be introduced (or electrotransferred). Following this process, the cells are left to recover, during which the editing occurs. After some time, the cells are then cryopreserved to facilitate manufacturing quality analysis before being thawed (Malech, 2021). It is these treated cells that constitute the product known as CTX001 (and, as of 2023, known as Exa-cel). Some bioethical issues, discussed briefly in the final section below, may be raised by the creation of this cellular product out of the patient's own biological materials. Then again, the safety advantages of using the patient's own cells cannot be readily dismissed. During this manufacturing process, the patient is treated with a pharmacokinetically adjusted dosage of the myeloablative drug busulfan. Then, after the cells have been evaluated for quality, they are reintroduced into the patient's body through a single intravenous infusion. Again, while current safety data have not yet been validated, emerging evidence suggests that ex vivo SCGE applications may have a similar safety profile to an autologous (not allogeneic) hematopoietic stem cell transplant and its myeloablative conditioning regimen.

Bioethical Decision-Making About Ex-Vivo Nuclease-Mediated SCGE

Given the similarity of SCGE-based treatments to existing therapies, several commentators have dismissed the notion that SCGE presents unique bioethical challenges. 'From an ethical standpoint,' writes Eissenberg, 'somatic cell genome editing is no more problematic than transgenic [or gene] therapies' (Eissenberg, 2021). Of course, this does not mean that SCGE is any *less* problematic than other innovative therapies—be they gene therapies or stem cell transplants—and the cogent dilemmas for them will similarly perturb the bioethics of SCGE.

Patient safety is unsurprisingly one of the most pronounced concerns in the ethical discussions of investigatory therapies, and the influence of historical tragedies

continues to animate the discourse. The case of Jesse Gelsinger, the 17-year-old boy who died in 1999 while participating in a safety trial for an investigational gene therapy (Carmen, 2001; Eissenberg, 2021), is a case in point. Gelsinger died in circumstances where multiple aspects of his participation in the trial were ethically dubious. For instance, although he had the targeted genetic disease, Gelsinger's participation would not provide him any lasting benefit; instead, it was hoped that his participation might pave the way for treatments to children in future. Moreover, Gelsinger and his father (who accompanied him at the point of signing the consent form) were not fully informed of all the results of previous animal studies, nor of the extent to which the trial's sponsor would benefit financially from the trial. Finally, Gelsinger was accepted into the trial despite having ammonia levels outside the protocol's safety limit (Wilson, 2010).

The incident is an appalling but salutary lesson for bioethical decision-making in the context investigational therapies, particularly as it illustrates the concept of patient vulnerability. In what follows, we set out the bioethical issues raised by nuclease-mediated SCGE with occasional reference to our case study of sickle-cell disease, in order to illustrate the specific issues presented by the intervention. As noted earlier, we adopt a terminology already established by Beauchamp and Childress (1979) and Evans (2021) when discussing these bioethical issues, classifying them into the principles of nonmaleficence, beneficence, autonomy and justice.

Nonmaleficence

The principle of nonmaleficence should be used to guide decisions to receive, administer, or approve SCGE made by patients, practitioners, regulators and others to avoid or minimise harm to patients and other stakeholders—both physically, psychologically, financially, or in other ways. In the case of sickle-cell disorder, the apparent safety of emerging nuclease-mediated SCGE therapy is indeed promising; however, with world-first clinical trials only reporting safety data very recently, it is too soon to determine whether SCGE is or will be safe and effective for clinical uses. If, as these initial data suggest, the safety profile of SCGE is comparable to an existing therapy, such as hematopoietic stem cell transplantation, then the relative benefit, if any, of SCGE must be considered by all parties in all decisions before it is trialled or administered.

Similarly, enrolment into clinical trials, including safety trials, must continue to be overseen strictly by independent ethics and governance committees, such as appears to have occurred in the CTX001 trial (Frangoul et al., 2021). Trial approval authorities, including therapeutic products regulators, must take steps to ensure that all trials are designed to avoid or minimise potential harms. Similarly, the principle of nonmaleficence should be adopted in the regulatory setting, where considerations of the potential dangers to public health implied by certain policy and legislative

approaches to SCGE—so-called public interest considerations—must be prioritised above other considerations.

For instance, the creation of regulatory exceptions permitting unapproved or less established therapies to be accessed in hospitals, where clinical oversight is presumed to exist, must be carefully controlled. Such regulatory exceptions are already observed in the regulation of stem cell therapies in Australia (Waldby et al., 2020); however, such exceptions or 'carve-outs' should be avoided or otherwise drafted very narrowly so as not to permit SCGE to be administered in small hospitals or day clinics ('rogue clinics'), where clinical oversight and private commercial interests may engender a culture of risk minimisation or financial gain (Ghinea et al., 2020). Moreover, the establishment or use of licensing authorities for the approval of treatments using SCGE (as has been recently prescribed in proposed mitochondrial donation legislation in Australia; see Newson & Rudge, 2021) should be strongly considered; and any such licensing regime should be maintained at least until the safety and efficacy of SCGE is well established in the clinic.

In its recently published recommendations for governing human genome editing, the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight on Genome Editing (the 'WHO GE Committee') summarised several bioethical concerns about SCGE, including 'rogue clinics, medical travel, as well as the reporting of illegal, unregistered, unethical or unsafe research … including the offer of unproven so-called therapeutic interventions' (World Health Organization, 2021b). This summary recalls one of the most prevalent bioethical challenges of the last decade: namely, widespread often unreported uses of unapproved stem cell-based interventions by rogue clinics, including in the context of 'stem cell tourism'—a phenomenon at least partly facilitated by uneven regulatory standards across global jurisdictions (Petersen et al., 2017).

Similar issues are likely to arise in the case of SCGE, including where investigators find opportunities for 'ethics dumping'—travelling to different jurisdictions with less vigilant oversight to carry out unethical research or provide unapproved interventions to patients who may be vulnerable, desperate, and uninformed (Schroeder et al., 2018; Dryzek et al., 2020). This is particularly concerning in the case of SCGE for sickle-cell disorders given the prevalence of the disease in developing jurisdictions (such as sub-Saharan Africa and India), where governance frameworks may be poorly resourced and the potential for misleading and predatory promotion of SCGE may be higher. Among other things, the WHO GE Committee recommends the strengthening of its global human genome registry, which is now in a pilot phase (World Health Organization, 2021b). Equally, non-maleficence would require that open-source registries and records in all jurisdictions could and should be maintained.

In short, the principle of nonmaleficence (and its concern for patient vulnerability) is supportive of bioethical policy that prevents monitors medical travel to prevent investigators or clinicians from carrying out SCGE outside their home jurisdictions (World Health Organization, 2021b). However, these policies must be weighed against concerns for patient autonomy, discussed below. These principles would similarly support the creation of strong reporting mechanisms for SCGE,

such as complaints bodies tasked with receiving, recording, and responding to confidential notifications about practitioner or investigator misconduct (World Health Organization, 2021b).

Beneficence

The principle of beneficence invites us to consider the real prospects of benefit, both individual and collective, in the event that SCGE is introduced (or accelerated) into clinical practice. In Beauchamp and Childress's biomedical ethics framework, beneficence involves acting kindly and charitably (2019) or acting with mercy for families in need (Getz & Dellaire, 2020). Clearly, for many whose lives are burdened by sickle-cell disease, it would seem merciful to administer a safe and effective cure.

In another way, the principle of beneficence might be understood as coextensive (or at least compatible) with health maximisation theories in the bioethics discourse (or sometimes 'value maximization') (Tsu, 2011). These are theories in which the aims of benefit sharing, medical advancement and of realising the highest and broadest level of public good and public health are emphasised (Wilson, 2017). Certainly, there are very strong bioethical arguments for pursuing SCGE for sickle-cell disorder along beneficence and health maximization lines.

Beyond the beneficence conveyed through the seemingly curative powers of the treatment, the reduced cost of treating and managing the disease could be transformative—for individuals, national and union-member state economies and for global society. This is especially promising where organisations, such as the SCGE Consortium (Saha et al., 2021) or the not-for-profit Addgene repository (Vandenberghe, 2019), seek to reduce the time and cost of developing SCGE therapies by sharing data and materials to the research community (Saha et al., 2021).

The costs to patients with sickle-cell disease varies substantially, dependent as it is on the frequency of vaso-occulsive crises, insurance status (a public or private payer) (Shah et al., 2020) and the relative local cost of preventive interventions (Oron et al., 2020). However, studies estimate the indirect cost of the disease for US patients as between USD 15,103 (Holdford et al., 2021) and USD 27,779 (Tsolakidis et al., 2021; Shah et al., 2019) per annum. Moreover, the overall annual economic burden of sickle-cell disease to the health system in Greece, for instance, is estimated to cost more than USD 25 million per annum (Tsolakidis et al., 2021). In the United States, the annual figure was estimated to be in the order of USD 2.98 billion in 2015 (Huo et al., 2018). It is also worth remembering that roughly 5% of the human population carries variants for hemoglobinopathies, and that, globally, around 400,00 children are born each year with sickle-cell diseases (Cornel et al., 2019).

Given the enormous prevalence of sickle-cell disorder globally, it is worth recalling that CRISPR-mediated nucleases are thought to be radically more cost-effective than other gene-editing technologies. For instance, kits for ZFNs cost some USD

5000, whereas, some five years ago, CRISPR kits could be bought for only USD 30 (Ledford, 2015). It has also been argued, given that both the CRISPR machinery and the laboratory equipment needed to create the nucleases are relatively inexpensive, that CRISPR-based SCGE will be adopted at a low cost by small biotech firms, non-profit organisations or public institutions, potentially reducing the economic burden of sickle-cell disease for both individuals and governments (Bartkowski et al., 2018). Then again, with ongoing intellectual property disputes over the CRISPR-Cas9 platform, it remains difficult to predict whether SCGE will be free or cheap to use (Contreras & Sherkow, 2017).

Beyond considerations of treatment costs, another problematic issue taken up in the bioethics literature on SCGE is its use for human enhancement rather than for treating or curing a pathology (Bubela et al., 2017). Indeed, it may be possible to argue that the aim of health maximisation, and indeed the principle of beneficence, might sometimes support enhancement-oriented uses of the treatment (Haga, 2018). In the case of sickle-cell disorder, questions about the traditional enhancement/treatment binary may be asked in cases where, first, patients experience no symptoms but are eligible for preventive treatment, or, second, have very few symptoms—so-called 'less-severe' expressions of the disease—but might benefit from SCGE. In such cases, providing these non-phenotypic patients with SCGE might be unnecessary or overcorrective—especially if there are less invasive or even less-enduring ways to treat the illness than SCGE.

In such circumstances, a detailed assessment should be made, preferably by a genetic counsellor (Cornel et al., 2019), of the risks and benefits across many criteria, including in terms of the patient's safety, financial, psychological and other health risks. Then again, it may be, as Coller notes, that this enhancement/treatment binary is too simplistic, and that the prevention of illness across a population already predisposed to sickle-cell disorder through the application of SCGE would greatly improve human life expectancy and almost certainly reduce the incidence of the illness (Coller, 2019). As Coller (2019) writes, 'Preventing disease by modifying risk-associated variants thus occupies a middle ground between treatment and enhancement and bleeds into both of those categories' (2019).

In its recommendations, the WHO GE Committee contemplated both the positive and negative impacts of patents on access to SCGE (World Health Organization, 2021b). It is inescapable that patentees and their licensees can control who, if anyone, may use their patents legally (Nicol & Nielsen, 2021). While patentees could have a positive effect if they decided to license SCGE broadly, flexibly and cheaply to those conducting research or administering needed treatments, even the cheapest licences may restrict access to those who cannot afford them, particularly in developing countries (Baylis & de Vries, 2021). Patentees can also restrict uses of SCGE for ethical reasons, as in the case of the Broad Institute, which, through Editas Medicine Inc., are already using licences that exclude ethically questionable uses, such as gene drives and germline editing (Broad Institute, 2014). While this mode of self-regulation is interesting, with many real-world models emerging (Nicol & Nielsen, 2021), the principle of beneficence would require that patents are not used to restrict access or prevent the delivery of a cure to a patient in need. After all, the

prospect that an SCGE treatment for sickle-cell disorder is likely to require only one administration may mean that patentees will wish to set a high price to maximise profits beyond the costs of production (Sherkow, 2017).

Additionally, where SCGE therapies for sickle-cell disease depend on the patient's own cells, as well as the genomes in those cells (such as in the case of CTX001)—materials that cannot ordinarily be patented—the ability to scale up production will be inherently limited, at least in the short term. This may in turn encourage patent holders to set higher prices. Moreover, where legislation already excludes HHGE from patentability (Schneider, 2019), SCGE may be the only route for patent holders to make a profit from their research, and this may further induce artificial price inflation. If such conflicts of interest relating to financial profit are to be controlled, a clearer jurisdictional consensus may need to be reached about how to best define and limit the exercise of patent rights (Nicol and Nielsen, 2021).

Autonomy

Bioethical considerations of autonomy may be understood along several lines. One line relates to bodily autonomy and would require all medical interventions to be consistent with a patient's right against intentional or negligent trespasses on their bodies, such as those wrongs long recognised in tort law (Szalados, 2021). A parallel line relates to 'personhood' and 'free will,' and recognises a person's right to make uncoerced (autonomous) decisions relating their personhood. Recognising this right would require all relevant information about a medical intervention to be transparently shared with the patient through a comprehensive informed consent process consistent with existing legal and bioethical decision-making models (Lu & Adams, 2015). Failure to share such information may amount to negligence or, again, a legal trespass in the tort of battery (Feng, 1987). In the case of SCGE, the difficulty of explaining the technology may present issues for the accurate description of the treatment, potentially rendering practitioners liable but also detracting from the principle of patient autonomy. Indeed, the complexity of the treatment is underlined by the historical experience of those who have received autologous stem cell-based interventions in the regenerative medicine context and later taken civil action for injuries (Horner et al., 2018).

In one way, current SCGE therapies may be understood as building on the existing framework of the autologous stem cell transplant, but creating that essential additional step by which the harvested cells are editing before being reinfused. In this way, SCGE may be considered a bundle or group of treatments (autologous SCBI, myeloablative conditioning, the nuclease-mediated editing), each of which has its own potential risks and benefits. Accordingly, it will be paramount that 'robust and rigorous' education initiatives, as the WHO GE Committee has recommended (World Health Organization, 2021b), are undertaken to ensure that sufficient and accurate information is imparted to all those subject to SCGE.

Justice

The last and most all-encompassing principle of bioethics we will address is justice. In their discussion of justice in biomedical ethics, Beauchamp and Childress identified the principles of fairness, desert and entitlement as flowing through the many detailed theoretical conceptions of justice, from utilitarianism, to egalitarianism, through to communitarianism and 'wellbeing theories' (2019). Many of the issues already implied or discussed above relating to access to treatment, non-discrimination, health maximization, vulnerability, exploitation, undue profit and the right to health care, are central to justiciable approaches to SCGE.

In the case of sickle-cell disease, the unmistakable prevalence of the disorder in low- and middle-income countries presents a treacherous structural barrier to the delivery of clinical care in those places. In its *Framework for Governance* report (World Health Organization, 2021b), the WHO GE Committee acknowledged the urgent need to build both infrastructure and expertise in these places where it is most needed—a recommendation that recognises the challenges of distributing benefits and allocating resources in the pursuit of global health justice in a postcolonial public health context. Beyond redressing this overarching problem of accessibility, distribution and need, the principle of justice will require a recognition of patient health rights. As the WHO Framework acknowledges, those involved in the development and clinical application of SCGE ought to adopt a view that all patients have equal moral worth, are entitled to live without a genetic disease for which there is a cure, and deserve solidarity and support in pursuing and attaining positive health (World Health Organization, 2021b).

Conclusion

This chapter has provided an overview of the nature of somatic cells, their relationship with disease etiology and human genomes, and the different types of genetic diseases that might call for intervention through somatic cell genome editing. It has also offered a brief outline of the historical development of SCGE and focused on sickle-cell disease as a case study. Indeed, as a likely candidate for one of the first commercialised SCGE interventions in the near future, sickle-cell disease generates pressing bioethical questions.

To address those questions, we have considered the current best treatment for sickle cell disorder, including its bioethical implications, before considering the prospect of clinical uses of SCGE for the disease. The latter half of the chapter took up the bioethical questions of SCGE in a more concerted manner, organising several of the most problematic concerns under the four principles originally enunciated by Beauchamp and Childress: nonmaleficence, beneficence, autonomy and justice.

While this chapter is not an exhaustive treatment of the bioethical questions (or decisions) engendered by the clinical translation of SCGE, it is hoped that it may

prompt further analysis of the formidable challenges we are likely to face as soon as this decade, when various applications of SCGE will begin to enter the clinic and as many more undergo investigation in human clinical trials.

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Chapter 6
Gene Therapy and Germline Cells Research

Ferdinando A. Insanguine Mingarro

Abstract This chapter is aimed at providing the reader with an overview of the phenomenological complexity created by Gene Therapy and Germline Cell Research that has revolutionized bioethical and biojuridical debate. To achieve this goal, this chapter opens with a brief introduction to the technical highlights of Gene Therapy and Germline Cell Research and the different applications that are possible today, especially considering the innovations arising from CRISPR/Cas9 tool. The chapter continues with some reflections on the very concept of therapy, questioning the classic dichotomy between therapeutic and non-therapeutic purposes, and with an analysis of the most common bioethical and biojuridical arguments. Having established certain technical-scientific and epistemological bases, this work is intended to illustrate the complexity of ethical and social implications of Gene Therapy and Germline Cell Research and the many values involved, leading the reader to meditate on how not only diseases imply risks for humankind, but also new health's devices.

Keywords Germline Cells Research · Gene therapy · CRISPR/Cas9 tool · Germinal interventions · Ethics of germline gene therapy

Introduction

Biomedical innovations open new frontiers and therapeutic possibilities by creating, at the same time, spaces of uncertainty and risk (Tosini, 2006: 380) that cause a transformation in the concept of life (Resta, 2009: 43) and, above all, in the dynamics of control of this which, from being traditionally dominated by natural laws, becomes subject to the human domain (Ballesteros Llompart, 2016: 178). This scenario is even more visible in relation to genetic editing techniques, perfected by CRISPR/Cas9 system, which today constitute the basic mechanism in the

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functioning of germline gene therapy. The emergence of these techniques, which have, among other things, revolutionized the classic dichotomies between therapeutic and non-therapeutic purposes and between risk and safety, requires a detailed analysis of the values brought up and their underlying risks and benefits, in individual and collective terms.

Indeed, the purpose of this chapter is to give the reader a detailed overview of the phenomenological complexity created by germline gene therapy that has ended up revolutionizing bioethical and biolegal debate.

How Is Germline Gene Therapy Technically Possible? Advancing Germline Genomic Editing Techniques Through CRISPR/Cas9, a Nobel Prize Winning Combination

Following the mainstream doctrine, we could define gene therapy as a relatively young science that consists of genetic modification of a patient's cells, in order to prevent or correct a pathological condition caused by the presence of a defective gene (Lacadena, 2001: 8; Ferrari & Romeo, 2011: 497–507). Such a definition can and should be problematized in light of the liquid boundaries of the very concepts of therapy, health and disease. However, it is undeniable that genomic editing techniques are underlying the functioning of any type of gene therapy. It is for this reason that before describing the peculiarities of gene therapy and its main differentiation between somatic and germinal ones, we must deepen the set of techniques that make it possible to practice or think about practicing this type of therapy.

Genome editing, usually carried over to the field of genetic engineering, consists of a sum of techniques that, offering the possibility of separating and recombining fundamental elements of an organism's DNA, have an impact on both technological and purely medical aspects (Nicholl, 2008: 3–4). Specifically, all operations involving subtraction, substitution or aggregation of DNA in the human genome using nuclease-type enzymes are included in the notion of genomic editing. These enzymes, better known as molecular scissors,[1] allow double-stranded breaks to be performed in specific DNA locations that can be repaired by binding mechanisms – homologous or nonhomologous – thus producing controlled genetic modifications (Lacadena, 2017: 1; Deutsche Ethikrat, 2019: 8).

Scientific community began to question itself about technical and ethical problems of this type of operation already in the seventies of the last century, during the famous conferences of Asilomar. However, these discussions did not contemplate, even hypothetically, a possible application of genomic editing to humans, due to the

[1] Although in this work our field of reflection is limited to the applications of genetic engineering in humans, it must be emphasized that these techniques are also used in non-human organisms. Moreover, the main field of application of these is agriculture, specifically in the production of genetically modified organisms (GMOs) using recombinant DNA techniques (Fukuyama, 2002: 72).

lack of knowledge about the structure of genes that make up our genomes. It is for this reason that, unanimously, the specialized literature considers the *Human Genome Project* as the first and inescapable step towards the viability of genomic editing techniques on human beings: in fact, with the aforementioned study, developed by *the Human Genome Sequencing Consortium* (HGSC) and *Celera Genomics* under the direction of the *National Institutes of Health* (NIH), our species' genome has been completely sequenced (Balistreri, 2020: 15) and reverse the axiom by which each gene can encode a single protein, by proving that, on the contrary, a gene is capable of encoding different proteins, even with antithetical functions.

Although the success of the aforementioned project constitutes an essential starting point for the development of genetic editing, what has put such technique at the center of the global biomedical agenda has been the innovation given by CRISPR/Cas9 system, a molecular association capable of encoding enzymes that, in turn, provide the possibility of cutting and retrieving DNA in a predetermined position (Marfany, 2019: 19). This system, perfected by scientists Jennifer Doudna and Emmanuelle Charpentier in 2014, consists of an RNA molecule (CRISPR) and an enzyme (Cas9) that deal, respectively, with the transmission of genetic information, and to cut DNA into the exact part indicated by CRISPR (Doudna & Charpentier, 2014: 1077–1088; Zetsche et al., 2015: 759–771).[2]

Although the first significant studies[3] on CRISPR sequences were developed by Francisco Martínez Mojica (Mojica Martínez et al., 1993), it is the combination of the two elements that gives efficiency to the system. In fact, the literature has emphasized four fundamental characteristics that differentiate CRISPR/Cas9 from other pre-existing genetic modification techniques: (a) specificity, understood as the ability to induce modifications in very specific points of the genome, which in turn provides a high level of (b) efficiency, which is reflected in the high final percentage of effectively modified genetic sequences, in addition to (c) accessibility, for its ease of application, and (d) versatility, for different uses that can occur at the investigative level and, above all, for different forms of manipulation that can be operated (Santalò & Casado, 2016: 26). The set of these features and their enormous therapeutic potentialities crystallized in 2015, when *Science* named CRISPR/Cas9 innovation Breakthrough of the Year (McNutt, 2015: 1445) and above all encouraged the Royal Swedish Academy of Sciences to award Jennifer Doudna and Emmanuelle Charpentier the 2020 Nobel Prize in Chemistry for their work in developing the technique, defined as a revolutionary method of genetic editing that contributes to

[2] More specifically, CRISPR individualizes the area of DNA to be cut, interposes between the two helixes and separates them: this is when Cas9 comes into action by cutting both layers in the exact position indicated by the RNA molecule. This DNA rupture triggers the activation of cellular repair mechanisms that scientists can use to modify the desired DNA zone by deactivating the defective gene that is achieved by aggregation or subtraction of genetic material (Baylis, 2019: 51, 52).

[3] The use of the adjective "significant" is not casual: as highlighted by the Royal Swedish Academy of Sciences in its historical reconstruction (2020: 1), the first studies (although merely descriptive) on CRISPR in the genome of bacteria are due to a group of Japanese scientists (Ishino et al., 1987: 5429–5433).

the development of new cancer therapies and can also materialize the dream of curing hereditary diseases (The Royal Swedish Academy of Sciences, 2020).

At the same time,[4] it should be noted that in the light of the first empirical results and the observations of expert geneticists and qualified working groups, the "cut" in the DNA operated by CRISPR/Cas9 is not completely risk-free. As can be read in the prepared dossier of the Nuffield Council of Bioethics 2018, although there is little chance that the *tool* does not cut the area indicated by CRISPR, the risk of uncontrolled fissures capable of causing off-target *genomic modifications*[5] (Nuffield Council of Bioethics, 2018: 37) that could even become cases of *mosaicism* (De Montalvo Jääskeläinen, 2020: 49) cannot be underestimated.

Even so, continuous advances in terms of efficiency and safety of the technique and the features of specificity, accessibility and versatility mentioned above have generated great expectations in public opinion about the possible therapeutic use of genetic editing: gene therapy.

Gene Therapy: Definitions, Differentiations and Applications

As we have already emphasized, gene therapy consists of genetic modification of a patient's cells in order to prevent or correct a pathological condition due to the presence of one or more defective *genes* (Lacadena, 2001: 8; Ferrari & Romeo, 2011: 497). Going into more detail, gene therapy bases its function on the use of innocuous viral vectors that manage to infect cells and integrate new DNA sequences into the cell genome, thus being able to recover a physiological phenotype in patients or embryos with rare genetic diseases, with special reference to monogenic ones (Balistreri, 2020: 17).

In biomedical practice we can separate gene therapy into two typologies according to the area in which they operate: in fact, one takes the name of germinal because it acts on the germline of the zygote or human embryo, whereas the second is known as somatic because it operates only on somatic cells of fully formed individuals. Therefore, if somatic therapy modifies only the DNA of cells of certain tissues and its effects are limited to the individual recipient of the operation, its germinal epigon, modifying cells also in gametes, causes the transmission of genomic alteration

[4] Until the operation carried out in November 2018 by the Chinese geneticist He Jiankui, which will be discussed below, all the experiments had been performed without implanting in utero the embryos whose genetic heritage had been modified. The two most relevant studies of germ genomic editing in embryos are that of the working group led by the Chinese geneticist Zhang, whose results have been only discrete (Zhang et al., 2014: 40–46; Liang et al., 2015: 363–372) and the most recent, and with better results, carried out by the Oregon Health and Science University working group that has attempted to correct a genetic predisposition to contracting an inherited heart disease (Ma et al., 2017: 413–419).

[5] Off-target modification means an unwanted and unpredictable mutation of the genome of the individual or the embryo to which the technique is addressed (Baylis, 2019: 22).

to offspring.[6] As Françoise Baylis shows, if the somatic technique allows to modify individuals, the germinal gives the possibility to modify humanity (Baylis, 2019: 34), extending human power in the kingdom previously ruled only by chance (Stock & Campbell, 2000: 4).

This trait, which is unique to germline gene therapy, generates a lot of hope and, at the same time, a lot of fear in the scientific community and in public opinion because it would be able to permanently eradicate some diseases of genetic origin, but, at the same time, there is a very wide range of risks due to the fact that an illegitimate use of the technique could cause dysfunctions that would be transmitted to future generations (Birnbacher, 2018: 63) and, in the current state of the art, would remain irreversibly (Deutsche Ethikrat, 2019: 10).[7] The risks mentioned above lead to important doctrine and expert groups to consider germline therapeutic interventions as an extreme ratio that should be used only in case the somatic alternative and genetic diagnosis preimplantation (DGP) were not effective (Mertes & Pennings, 2015: 52–53; The National Academy of Sciences, 2017: 103).

While somatic gene therapy proves to be successful for most genetic dysfunctions, as highlighted, among other components of the German Bioethics Committee in a recent report, there are pathological predispositions resistant to modifications in somatic cells, in which only germinal interventions can be effective: we refer to multiorganic disorders, to pathologies that occur systematically (such as cystic fibrosis) or developing in tissues that are too wide (muscular dystrophy) or difficult to access (Huntington's disease) (Evitt et al., 2015: 25–29; Porteus & Dann, 2015: 980; Deutsche Ethikrat, 2019: 11). In cases where one parent is homozygous dominant from a genetic alteration that causes a monogenic disease, not even PGD and the subsequent *screening* could provide the possibility of selecting a healthy embryo, because all would present such alteration (Nuffield Council of Bioethics, 2018: 44–45; Ranisch, 2020: 63). In addition, PGD provides only the possibility for the couple to discard embryos with serious genetic diseases; however, by combining screening with germline gene therapy, these embryos would not be discarded but modified to suppress predisposed genetic disease and thus cured (Insanguine Mingarro, 2018: 71; Wells et al., 2019: 345).[8]

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[6] It is worth qualifying a circumstance that, although it may seem obvious, is often lost in the reconstructions of specialized literature. In order for a genomic modification carried out in the germline of an embryo to be effectively transmitted to future generations, it is necessary for the embryo to be implanted in utero (De Miguel Beriain et al., 2019: 109).

[7] As the members of the German Bioethics Committee stated in their recent report on genomic editing, the current state of the art does not allow the reversibility of the germ modification directly in its recipient, but, theoretically, if in its future generations: For this, it would be "enough" to modify the embryo again in its early stages of development to "undo" the modification made in its progenitor during its embryonic development (Deutsche Ethikrat, 2019: 10).

[8] In addition to the ability to cure monogenic diseases, referring in terms of prevention and not strictly therapeutic, it is essential to stress that germline editing also provides the possibility of modifying the human genome so that it is presented as less predisposed to contracting certain polygenic pathologies, including some form of cancer and diabetes (Ranisch, 2020: 64). As important doctrine emphasizes, this goal is unattainable for PGD techniques for several reasons: in addi-

To its characteristic of being the only valid therapeutic tool for some genetic malformations, germline gene therapy adds the aforementioned mechanism of heritability of the intervention that allows pursuing the objective, with an individual and collective dimension, to eradicate diseases permanently, without the need to renew the therapeutic cycle in each generational component. On the other hand, it is pointed out – with particular reference to the argument of the slippery slope to which reference will be made below – that a first legal legitimization towards the therapeutic use of the germinal technique would lead humanity towards eugenics, because it would end up legitimizing in the future any kind of genetic modification: from the selection of eye color and sex to the empowerment of abilities. Thus, bioethical and biolegal debate on germinal genetic editing has moved in recent years between rhetorical scenarios of a utopian future, without diseases, and a dystopian one, dominated by eugenic logics.

However, what has shaken public opinion, taking the phenomenon of germline gene therapy beyond academic settings, has been the news of last November 27, 2018, date in which, for the first time in history, the germline technique was used in human embryos implanted in utero. During the ceremony of the Second International Summit on Human Genome Editing, promoted by the National Academy of Sciences and the National Academy of Medicine of the United States, in collaboration with the British Royal Society and the Hong Kong Academy of Sciences, a Chinese geneticist, He Jiankui, despite the existence of a broad self-regulatory agreement in the scientific community for a moratorium on germline gene editing, announced the birth of Lulu and Nana, two girls whose embryonic germline had been modified with the aim of immunizing their genetic heritages from contracting AIDS. Specifically, Jiankui claimed to have deactivated the CCR5 gene, a protein encoder that opens the possibility for the virus that causes AIDS to penetrate the body's cells.[9] Although this is not, in absolute terms, the first application of the germline technique on human embryos, it is the first time that they have been implanted in utero. Therefore, the absolute novelty, which has had such a great impact on public opinion causing a general disapproval in the scientific and academic community,[10] consists in the fact that for the first time – two twin girls have

tion to being limited to the number of embryos produced and the genetic characteristics of the parents, embryo selection does not exclude the possibility that genetic weakness in the face of some pathologies will be transmitted to future generations (Savulescu et al., 2015: 476).

[9] It should be noted that, as highlighted more than 10 years ago by the renowned Italian immunologist Lucia Lopalco, not all HIV variants penetrate the body through the protein encoded by CCR5 (Lopalco, 2010: 547–600).

[10] In fact, the spread of the news of the genomic edition made by He Jiankui has provoked a new shift in the scientific community that, if with the dossier of the Nuffield Council of Bioethics (2018) seemed ever closer to liberal positions, He returns with force to much more cautious positions. One example is the recent publication of a series of calls to strengthen, including legally, an international moratorium on the use of these techniques. Among the most relevant, those published in Nature in 2019 (Lander et al., 2019: 165–168; Wolinetz & Collins, 2019: 175) and the Geneva Declaration, a document prepared following an important scientific congress on the subject (Andorno et al., 2020: 351–354).

been born, two fully formed individuals, with a modified genetic heritage in the germline.

The edition operated by He Jiankui seriously doubts two key dichotomies in the ethical debate and in legal praxis about these techniques: the possibility of differentiate between safe and risky public policies, and between interventions for therapeutic and non-therapeutic purposes. For example, with regard to the latter, it is impossible to subsume Jiankui's intervention in one of these two categories, at least without some clarifications and sub-differentiations. In fact, at the time of the operation, the genetic heritage of Lulu and Nana, in their embryonic state, did not present any pathology: likely, even without germline genomic editing, the twins would have been born free of all genetic diseases. Therefore, the deactivation of the CCR5 gene operated by Jiankui has not cured a pathological condition, constituting – however – a form of immune system enhancement aimed at preventing the contraction of one of the most fearsome diseases of our society. In short, it is a kind of genetic vaccine, with a therapeutic intention, but it does not act directly against a pathology. Can this be considered a therapy or for there to be a therapy is necessary to have manifested, previously, a disease and, therefore, it belongs to non-therapy threshold any type of enhancement, either intellectual, muscular or immune? With the ambition of trying to separate the therapeutic germline genomic edition from editions with other purposes, I will address this and other questions in the next section, in which I will question the dichotomy between therapeutic and non-therapeutic purposes proposing a more detailed plan of differentiation between the potential uses of germline genomic editing.

When Do We Really Talk About Germline Gene Therapy? One Step Beyond the Dichotomy Between Therapeutic and Non-Therapeutic

As Diego Gracia emphasizes, the more complicated an action scenario is presented, the more human beings' tendency to reduce all phenomenal reality and its possible developments emerges in only two extremes, one facing the other, generating dichotomies and falling into what he defines as "dilemma bias" (Gracia, 2019: 104, 105).

It is not by chance that, in the specialized literature, when discussing what type of germinal intervention can be considered as ethical or legally lawful, the dichotomy between therapeutic and non-therapeutic purpose of genomic alteration is generally used. As we have already anticipated, in the light of He Jiankui's daring experiment, this hermeneutic key – in addition to needing a determination of the content of the notion of therapy – is no longer sufficient to read the phenomenological reality of germline genomic editing. Therefore, we consider it opportune to address the question from four potential macrofinalities: one (a) stricto sensu therapeutic, another (b) preventative, one with purpose of (c) potency and, finally, one

that we could identify as "voluptuous." Still, we will see how the peculiarities of germ genomic editing will highlight the weakness of the boundaries between these notions.

(a) Traditionally, the concept of therapy is proposed as indissolubly linked to the notion of disease: For example, the Royal Spanish Academy defines therapy as a treatment of the disease and the Italian Treccani Encyclopedia as the study and concrete action of means and methods to combat diseases. Hence it seems to us entirely plausible that in order to qualify a set of studies, means and medical methods as therapeutic it is necessary that there be a disease and that it is convenient to analyze the two concepts simultaneously and, moreover, with a focus also on the correlative of the notion of disease, namely, health.

Attention to sociological literature on the basis of the distinction between health and disease, between normal and pathological situations, it has roots in the last part of the nineteenth century and specifically in the texts *The Division of Social Work* and *The Rules of the Sociological Method* by Èmile Durkheim whose first editions were released, respectively, in 1893 and 1895. In his attempt to give a new base of values to French society in his secular process of remodelling, the French sociologist charges the concept of health of an axiomatic value (Ardigò, 2003: 118–119), radicalizing the distinction between this and the disease and stating that "for both societies and individuals, health is good and desirable; disease, on the contrary, is the evil and what must be avoided" (Durkheim [1895]2001: 93). The construction of the antithesis between health and disease is developed, according to the French sociologist, only in the social section not taking into account the contribution that the patient's life experience can provide in the individuation of the pathological state. In fact, for Durkheim a state can be defined as pathological only if a significant difference is manifested, in statistical terms, between the average type of trend in an organism of a given species, in a given social context and within a certain age threshold (Durkheim [1895]2001: 102). Hence, for the Durkheimian reconstruction, the concepts of health and disease need the support of the numerical sciences and statistics and not the subjective contribution of the sick (Ardigò, 2003: 121). However, Georges Canguilhem argues that for a more precise elaboration of the content of these concepts it is essential to start from the doctor-patient relationship, considering the patient as a judge of the transformations in his state of health (Canguilhem [1966]1971: 138). Thus, the recognized philosopher of science manages to differentiate the notions of pathology and anomaly: although the latter, when understood as variation, morphological-functional and congenital, with respect to a specific type, can be measured in statistical terms, However, disease or pathology would be a measurable notion only through the environment and never in absolute terms. In fact, the disease provokes a norm of life incapable of adapting to the environment, in the sense that it does not tolerate any distancing from the conditions in which it is valid. Therefore, the abnormal living can be considered sick only if, penetrated in the environment, it proves not to have an adequate stabilizing capacity

(Canguilhem [1966]1971: 138–140). Thus, with the contribution of Canguilhem, disease becomes conceived as an organizational-functional deviation that, to be individualized and defined, needs to study the relationship between the individual and the environment.

If we embrace the concept of disease just mentioned, an embryo could not be identified as sick, at any stage of its development: in fact, it is only from the moment of birth that we can verify whether the embryo, by becoming an individual and having contact with the environment, it presents a standard of living unable to tolerate some situations.

Therefore, if an embryo cannot in any case be considered sick and if an intervention can be defined as therapeutic only if it is aimed at eradicating a disease, we can never define germ genomic editing as strictly therapeutic because it is not possible, by definition, affect the germline after birth. However, as Arthur Caplan has emphasized, among others, genetic technology has produced a secondary code in the relationship between disease and health: the one that develops between the genetically "normal" and the genetically "suspicious." In fact, as a result of genetic screening it is possible to identify in the embryo a tendency to disease that, as evidenced in the previous section, may only be avoided by means of a germ genomic edition. Well, in this case, could we qualify the intervention as therapeutic? As we have already anticipated, if we embrace the concept of disease that we have developed, the answer is no: the disease, in an embryo, does not yet exist, so it is a tendency, a predisposition that, consequently, at the conceptual level it is much closer to the notion of prevention than to that of therapy.

(b) As a result of all the arguments made in the previous section, all the activities of germline genomic editing aimed directly at avoiding the contraction of a disease caused by a pathological genetic predisposition fall on the threshold of prevention.

However, the concept of prevention is broader and deserves an ex professo analysis: in fact, to this type of intervention, which we could define as "direct prevention", are added others that, in antithesis to these, we could label as "indirect prevention." Specifically, these interventions are those that, instead of being carried out with the intention of modifying the gene or the group of genes that causes the pathological predisposition, are aimed at enhancing the immune system so that this, reinforced (or enhanced?) being more efficient in preventing the contraction of certain diseases. It is precisely this specific decline of the preventive purpose that has used the Chinese geneticist He Jiankui to boost the immune system of Lulu and Nana, affecting their germlines.

Besides separating between direct and indirect prevention, indirect prevention needs to be subdivided by highlighting the difference between immune system enhancement operations to reduce the chance of contracting a contagious disease and one – however – focused on the prevention of a non-communicable pathology. It is clear that between these two types of intervention there is a substantial

difference in terms of social effects: reducing the contraction of contagious diseases is undoubtedly a benefit for society, bringing this type of germinal intervention closer to a kind of genetic vaccine.

(c) The reflections on the category of indirect prevention constitute a useful *trait d'union* with the concept of genetic enhancement to which, often even in the Spanish language literature, we refer with the English term genetic enhancement. More than *trait d'union*, for a certain decline of empowerment we could speak only of union with the concept of indirect prevention. We refer, obviously, to all those activities of empowerment defined by the literature as "medical" that, following the rebuff of the transition of the doctor from healer of sick to promoter of health, are oriented to improve the state of health of the individual (De Wert et al., 2018: 465).

This type of enhancement, inspired by medical purposes, has little to do with enhancement in a stricter sense because it is led to a direct improvement of the intellectual or muscular abilities of the future person who, as will be seen below, open to different and even more complex problems. In fact, empowerment aimed solely at improving the benefits of the human being in society is totally divorced from the concept of health, even in its broad meaning elaborated by the World Health Organization, which as is known, in addition to the absence of diseases, includes psychological, physical and social well-being (World Health Organization, 1998: 1). As Bert Gordjin and Ruth Chadwick stress, such practices would be the fruit of a change in the paradigm of medical science: if for many years the polar star of medicine has undoubtedly been the regulative idea of a restitutio ad integrum of the patient, whose body needed to be returned to its normal functioning, today you notice a transition towards the idea of a *transformatio ad optimum* (Gordijn & Chadwick, 2009: 1).

(d) Finally, germinal interventions can be guided by completely "voluptuous" purposes, that is to say, aimed at fulfilling desires that – without being related to medical requirements, prevention or improvement – concern different aspects such as the color of the eyes, skin or sex selection. Indeed, even in this type of purpose it seems sensible to reflect on the different degrees of "voluptuousness": if, probably, the predetermination of eyes color does not produce any social consequence, the issue changes radically in the selection of sex or color which, especially in certain societies, can lead to the creation of obstacles or social benefits and are therefore capable of changing a person's aspirations in the future.

Therefore, the "voluptuous" purpose is presented, like all the others, with blurred boundaries, in particular with the category of empowerment and, to a certain extent, it is perhaps a greater danger in relation to a possible eugenic drift from which we shall analyse in detail in the following section.

Fear of a Eugenic Drift and the Controversial Violation of Human Dignity: Two Major Bioethical Objections to Germline Gene Therapy

Against the use of germline genomic editing techniques, even in their therapeutic dimension, there are two major objections that, as we will see, usually come to intersect: the fear that genomic alterations may give life to a eugenic society and that they may constitute a violation of human dignity.

As regards the first objection, it is based on the fear that an authorisation to intervene in the germline, even if it is to prevent a disease directly, could lead society towards a eugenic drift, that is to say a regression in a dystopian future in which our techniques would end up being applied indifferently, transforming into a technology of permanent discrimination with which to program any character of embryos and promote social inequalities (Pollack, 2015: 871).

The term eugenics, coined by Francis Galton in 1883, began to be used to indicate a certain scientific branch oriented to investigate how to grant to the more suitable race or strains of blood a better chance of prevailing speedily over the less suitable than they otherwise would have had (Galton [1883]1907: 17). Pushing eugenics from a scientific to an ideological dimension was dedicated to the hateful social and political movement that developed in the first half of the twentieth century in Germany in order to study strategies to reproduce only Aryan individuals (positive eugenics) and prevent the birth of individuals other than the Aryan race (negative eugenics), who were considered dysgenic specimens (Esposito, 2004: 136). However, according to Susan Root, eugenic studies, in their origin, had a much more restricted and less odious scope because it was limited to the attempt to increase the chances of a child being born healthy (Root, 2000: 873). While it is undeniable that ideological shift has led eugenics towards unpredictable destinies, we find it difficult to think of a concept of eugenics completely lacking a negative component, even in the time of Francis Galton; in fact, as Roberto Esposito states, a concept oriented to the improvement of the species is indissolubly linked to a negative component, with the function of preventing the spread of dysgenic specimens: only in the vacuum of the elimination of the worst opens the space for the increase of the best (Esposito, 2004: 136).

According to Allen Buchanan, new techniques of genetic engineering cannot be described as eugenic instruments, even in a Galtonian sense. However, these would give life to a new genetic: the fundamental difference would rest on the inclusive and universalistic character of the current genomic editing instruments oriented to the cure of diseases and on the exclusionary and particularistic character of classical eugenics which, from the middle of the twentieth century, is obsessed with the dogma of the superiority of the Aryan race (Buchanan et al., 2000). Instead, the long shadow of the Nazi project and the fear of living again this terrible experience pushes the public opinion and the doctrine to identify the new practices of genetic

engineering with the notion of eugenics that developed in the Hitlerite era and, therefore, with something to avoid at any cost (Segers & Mertes, 2020: 35).[11]

The identification of any authorization to intervene in the human germline, even if it is limited to the prevention of specific medical problems, such as the spark for an inevitable drift towards a eugenic society brings its origin in the conviction that, once germline genomic operations are allowed, no regulation would be able to avoid social pressure towards empowerment practices (Lanphier et al., 2015: 411). This position, classifiable among the objections of consequentialism, is based on the argumentative technique of the slippery slope that Eugene Volokh defines as a form of predictive sociology that develops by interlacing an ethical premise and an empirical forecast (Volokh, 2003: 1028). In our case, the first would be to consider highly probable that, admitting now a therapeutic use of the germ modification (decision A). In the future, a solid social acceptance would be generated towards practices of genetic enhancement or merely aesthetic changes, which have nothing to do with the protection of health (decision B). Therefore, on the basis of this empirical forecast, although decision A is considered ethically acceptable, the fear that it may lead humanity to accept decision B, which is ethically despised, leads to the renunciation of decision A. Thus, as Lydia Feito Grande stressed more than twenty years ago, distressed by the fear of slipping on the slope, supporters of this argument consider it preferable to renounce the possibility of eradicating odious monogenic diseases (Feito Grande, 1999: 298, 380). Underlying this thesis, we find a feeling of distrust not only towards the human being- who is considered unable to limit himself, victim of the paradoxical Promethean unevenness (Anders, 2011: 30 ff.) – but also towards law that could not avoid to slip on the slope of eugenics.

To this end, a clear contradiction cannot be avoided. As has been observed, those who argue the need for an absolute prohibition do so on the basis of the argument that there is no form of regulation that frees us from start us down a path towards non-therapeutic genetic enhancement (Lanphier et al., 2015: 411). Well, but if the Law has no hope of saving us from the slip on the slope, what is the point of banning the technique altogether, thus renouncing the therapeutic benefits? (De Miguel Beriain & Armaza Armaza, 2018: 195).

It is not surprising, however, that such a dystopian scenario is a source of overriding concern for society and the political system although it is, today, absolutely unlikely; indeed, as Luhmann states, if individuals usually worry about future events of medium or high probability, in biotechnology sectors it seems that everything

[11] However, it is necessary to emphasize how there are illustrious examples that have clearly differentiated genetic engineering and eugenics. Among them, Jürgen Habermas who, while expressing all his concerns towards the developments of these techniques, fruit of a liberal genetics, the differences of Nazi eugenics which, however, was the product of an authoritarian model (Habermas, 2002). Along the same lines, we also find the International Bioethics Committee, which, in its 2015 report on the tension between genetics and human rights, while taking a stance against any kind of genetic intervention for non-therapeutic purposes, stresses that the objective of empowering human beings cannot be confused with Nazi eugenic projects which, however, were aimed at eliminating certain groups of individuals (International Bioethics Committee, 2015: 27).

that is very likely is completely normalized, while the improbable and catastrophic gain interest (Luhmann, 1991).

To this criticism, fruit of an internal reasoning to consequentialism, another is linked with a deontological nature: the fear that interventions in the germline, in addition to causing a transition to a more unequal society, they end up altering the human genome as a whole, putting at risk the purity of human nature sublimated in the genetic heritage, common to the entire species. This argument is based on a scientifically erroneous conviction: that there is only one genetic heritage for the human species and that it also has a static nature and is therefore potentially immutable. However, as the geneticist Lluís Montoliu emphasizes, there is no connection between human identity and the inalterability of the genome: on the contrary, there are as many genomes as human beings (Montoliu, 2019: 342, 343). Also, as the experts of the American National Academy of Science, among others, claim, no human being is destined to die with the same genetic makeup that he presented at the time of his birth, due to continued exposure to various enviromental impacts, such as radiation, which cause uncontrolled and unforeseen genetic mutations (The National Academy of Sciences, 2017: 94, 95; Raposo, 2019: 257).

Despite scientific evidence, this need to preserve human nature in its current condition leads to subordinate, in relation to these demands, the welfare of future generations (Foht, 2016: 8). In approaching this thesis with attention, although it may seem paradoxical, it can be said that the argument used to try to stop the future existence of a eugenic society is configured, by itself, as a eugenic argument. Insisting that human embryos undergoing germline gene therapy cannot be implanted to prevent their edited genes from contaminating the germline leads to the same short circuit of eugenics, that is, to value the abstraction of the 'germline' and the purity of human nature over the lives and medical interests of current human beings. In fact, as Roberto Esposito states, eugenic discourse is not antithetical to the conservation of human nature: as is known, eugenics does not aim at the correction of nature, rather at the correctness of procedures – artificial, obviously – they have negatively influenced their course (Esposito, 2004: 135).

Underlying all theses oriented to the preservation of human nature – and, as we have seen, paradoxically eugenics are also – there is the conviction that the expression of the natural is "wiser," citing a fortunate expression of Leon Kass (1985: 72). In any case, better than artificial, whose manifestation would be technology. In contrast, Lee Silver states that it is not possible to identify, always and in any case, the natural order with the good (Silver, 1998: 256): in truth, nature has produced viruses, natural catastrophes – perverse effects, in the semantics of Thomas Khun (1963) – that the artificial, by means of technology, has overcome without, therefore, humanity losing its nature. Similarly, as Raposo says, genetic dysfunctions are part of human nature, as well as the need to cure them: modifying the human genome to eradicate them would not change our nature, but, on the contrary, would reaffirm it (Raposo, 2019: 255). In addition to reaffirming it, according to the extreme position of Russell Powell, it would save it: humanity, over the years, has always been more dependent on *ex post* therapeutic intervention which, in a scenario of political and economic collapse, may not be guaranteed. For this reason, Powell believes that

taking the opportunity to eradicate diseases *ex ante* could lead humanity to loosen that link of dependence with medicine that, in its reconstruction, could lead to catastrophe (Powell, 2015: 669–695).

On the other hand, some supporters of the thesis of the preservation of human nature, radicalizing the dichotomy between nature-good/technical-evil, give such normative force to human nature that they conclude that it is necessary to accept it as it is. Linking this argument with the consideration by which the human genome would be an expression – or even expression – of human nature, defends the intangibility of this in any case (Kass, 2002).

This thesis is usually accompanied by a very persuasive argument, to the point that it has been defined as an "argument-ending trump card" (Cutas, 2005: 312) and that, since 1997, has been corroborated by the Universal Declaration of the Human Genome of UNESCO: the need to safeguard the dignity of the human species. As is known, the Declaration mentioned in its art. 1 affirms that the universal recognition of human dignity materializes through the human genome. This being common to all human beings, would have the function of guaranteeing the unity of the human species, becoming the justifying element of the universal attribution of human rights. Although the concept of human dignity outlined by the Declaration would play an identity function of the human species, this does not imply that this concept is presented in a de-individualized form: on the contrary, precisely because dignity belongs to the whole family of human beings it also belongs to each of its components in its individual dimension.

Although at the theoretical level there is no discontinuity between the typical notion of dignity and that proposed by UNESCO, we do find an important difference in the prism of practical reasoning and human rights praxis. In fact, the Declaration uses the concept of dignity very differently from the post-war constitutionalism and the 1948 Universal Declaration of Human Rights whose texts use dignity for the purpose of empowering the individual. As Beyleveld and Brownsword affirm, this functional paradigm consists in constructing, around the individual, a sphere of non-interference towards the State, the fruit of an increase in individual autonomy (Beyleveld & Brownsword, 2001: 11). In contrast, in the Universal Declaration of the Human Genome, dignity plays a role of constraint of individual autonomy, making room for what Giorgio Resta defines as a metasubjective idea of dignity, that transcends the individual dimension to embrace the entire community of those who belong to the human species (Resta, 2014: 9). Likewise, referring to human dignity becomes the basis on which to build limitations to the holders of the same, with the aim of protecting them: one of these limitations would concern precisely the germinal genomic editions defined, in art. 24 of the Universal Declaration of the Human Genome, as practices potentially harmful to human dignity.

Therefore, according to the operating paradigm that is interpreted as prevalent, the protection of human dignity can be an argument for or against the application of germ genomic editing for a therapeutic purpose. For example, in principle, Jürgen Habermas considers that any practice aimed at modifying the natural modalities with which the person incarnates in the body is contrary to human dignity. This

author affirms that only by qualifying as legally unavailable the chance of birth can guarantee equal access to life and, therefore, preserve the ethical self-understanding of humanity, which is the necessary condition for mutual respect, which is also the indispensable presupposition for respect for the dignity of others (Habermas, 2002: 44–45). According to their reconstruction, this would be the only way to guarantee equality between human beings at birth. Habermas's argument has been criticized as it does not take into proper consideration that human nature, at the time of birth and especially in the composition of genetic heritage, does not align all individuals in a position of equality, but assigns them a certain position that varies according to the composition of the genome: in terms of health, who, incidentally, inherits a genetic dysfunction is not in a condition of equality with who, always by chance, does not inherit it. Therefore, advocating the conservation of human nature, even in the presence of health demands, in order to avoid an injury to the ethical self-understanding of the human gender ends up obtaining the paradoxical result of maintaining social inequalities, rather than mitigating them.

Instead, supporters of a functional model of dignity inspired by empowerment reach antithetical conclusions: for example, Caplan and Sykora show how, besides not being diminished by germ genomic editing, human dignity would even be reinforced by the effect of a regulation that admits these techniques, as long as they are proven safe and efficient and are applied only for a therapeutic purpose (Caplan & Sykora, 2017: 1871–1872). In this same line, Segers and Mertes (2020: 38) argue that this type of intervention constitutes a maximization of the autonomy of the individual that, in this way, could avoid contracting serious diseases that cause severe personal limitations. In addition, it could be argued that by providing germ gene therapies human dignity would also be reinforced in a collective dimension: the possibility of eradicating several monogenic diseases, in the medium and long term, can be interpreted as a way of reinforcing the dignity of the human species. And, on the contrary, deciding to ban them, despite the fact that the technique has achieved acceptable safety standards and with the consequence that hundreds of children will continue to be born with odious diseases, could constitute a violation of human dignity.

Does Eradicating Disease Mean Eradicating the Sick? Disabilites Rights Critique and Germline Gene Therapy

Although the therapeutic purpose is undoubtedly presented as the practical application that raises fewer objections, in the specialized literature we find additional criticism to those already mentioned in the previous section.

One of the most serious objections concerns the fear that germline genomic editing could become a social tool for correcting the disease, considered an expression of a deviation. Certainly, the structure disease-deviation is not unprecedented in the sociological literature: in fact, Parsons (1991) defines the disease as a state of

disturbance of the normal functioning of the human individual, and he classifies sick subjects as incapable of performing their social functions effectively and therefore as deviant.

The possibility that diseases can be eradicated through germline genomic editing has generated many fears within associations representing the rights of persons with disabilities, concerned that the elimination of diseases entails a social suppression of carriers of those diseases (De Paor & Blanck, 2016: 5). Paradoxically, the opponents of the genomic revolution in general, and of germline gene therapy in particular, would include precisely those who could have avoided contracting a disease. In fact, most representatives of people with disabilities consider innovations in the field of genetic engineering as a tool to exclude individuals carrying "bad genes" from enjoying the most relevant common goods (Buchanan et al., 2000: 262).

Within this position, known as "Disabilities Rights Critique," this type of argument is defined as an expressive objection and is generally used to oppose the use of genomic interventions to prevent disabilities (Edwards, 2004: 418). The supporters of this objection, which has a dogmatic character, consider that the decision to intervene in the genetic heritage of the embryo (or even to enhance the basic research system on the techniques that allow it) to suppress a defective gene causing a disability implies a negative judgment on the person with a disability, with the consequent risk of undervaluing his dignity or moral value (The International League of Societies for person with mental handicap, 1994; Morris, 1992: 16). Following this line, they argue that the decision to legalize germline gene therapy would imply a change in the perception of disability (De Paor & Blanck, 2016: 5) It can even generate the conviction in society that only the lives of human beings who have a "perfect" genetic heritage deserve to be lived. This scenario would not only be in violation of ethical principles, but would also not respect the fundamental right of persons with disabilities to be treated as persons of equal value (Buchanan et al., 2000: 272).

As has already been anticipated, generally this criticism is uses to stop any type of funding towards scientific projects that aim to improve the techniques of germline genomic editing by the fact that they generate in society the conviction that people with disabilities are not nothing but "genetic accidents" or even "waste products" to be eliminated with a eugenic-firendly program (Ware, 2004). In fact, as De Montalvo Jääskeläinen (2020: 154) points out, the diffusion of these techniques could lead to a human regression towards that odious medical paradigm, now outdated, in force of which the reproduction of persons with disabilities was concerned, considered carriers of an evil to be avoided.

Such a consideration of persons with disabilities would be the first step towards a return to social policies based on the model of expendability, which, citing the long-standing argument of Colombian Constitutional Court judgment C-066/2013, would be based on the assumption that: "a person with disabilities has nothing to

contribute to society, nor can he live a life of sufficient dignity" and, therefore, constitutes "a burden both for his close relatives and for the community".[12]

The objection we have just discussed suffers from a kind of theoretical reductionism based on the absence of a distinction between the disabled and disability per se. There can be no doubt that persons with disabilities have the same ontological relevance and dignity as persons without disabilities, but precisely for this reason the tendency to cure disability should be read in a positive and not negative hermeneutic key. I share Buchanan's position in emphasizing that undervaluing disability is solely the result of evaluating the opportunities that the welfare state has to provide to those who suffer from it (Buchanan et al., 2000: 278). Applying this reasoning to a lower level of abstraction, we can affirm that, by deactivating the deafness gene in an embryo, the value of the life of a disabled person is not questioned, but the possibility of not having to deal with the suffering caused by deafness is being offered to future generations (Valdés, 2018: 180).

I think it is timely to analyze another argument that, although it can be redirected to the "disabilities rights critique," has a different nature as it belongs to the family of consequentialism: it is the "Loss of Support Argument." This is based on the consideration that, by reducing, through gene therapy, the number of people with disabilities, the support of public opinion and, above all, of institutions is destined to diminish in a sensitive way. Even if we carefully analyze the weighting of interests underlying this reasoning, it is difficult for us to think of a conflict between the interest to be born healthy and the interest of the components of the community of persons with disabilities to not be forgotten. Rather, becoming paradoxically exclusive, the application of the interest to not be forgotten can be translated into the desire that children with disabilities continue to be born for fear of losing social support. Once again, the phenomenon of fear is presented as a decisive and conditioning element, not only for social and legal policies, but also for public opinion and certain centres of interest. In this case fear can be interpreted as a distrust of the social system, due to the continuous "cuts" to the welfare state that politics has operated, systematically, in the last 10 years.

It should be stressed that a reduction in the number of people affected by a disease does not eliminate or reduce the duty of the State to maintain an adequate social support system and that, On the other hand, it is much more complicated to argue that the State has a duty to ensure that the number of persons with disabilities is not reduced. Moreover, it cannot be overlooked that, trivially, the decline in persons with disabilities would mean an increase in resources available to support and sustain persons who, however, still present a disability.

Therefore, taking as a starting point the same theoretical framework of the two aforementioned objections, it is possible to reach an antithetical conclusion: germline gene therapy would not be exclusive, but inclusive: precisely because persons with disabilities have equal dignity, it would be a duty of the State to fund both

[12] Colombian Constitutional Court, Judgment C-066/2013 on "conditional exequibility" of Art. 3 of Law 361/1997, point 9.1.

biotechnology research, useful, among others, in combating disability, such as facilities and instruments providing the necessary medical and social support.

In any case, it is crucial to enhance the presence of associations of persons with disabilities in the debate on germline genomic editing techniques, giving effective action to the International Convention on the Rights of Persons with Disabilities (2006) and especially its art. 3 which highlights the need to ensure the social participation of these people (Comité de Bioética de España, 2017: 5). In fact, an active participation of this group in decision-making procedures would imply an important advance in the protection of their rights, leaving behind a model that conceived of persons with disabilities only as an object of social protection rather than as active subjects (from De Montalvo Jääskeläinen, 2020: 153; Castellanos Claramunt, 2020: 43–46).

Conclusions

The analysis developed has shown the complexity of ethical and social implications of germline gene therapy and the numerous values involved. Precisely because of this complexity, it does not seem like timely to label as correct or incorrect none of the lines of argument enumerated that has led us to reflect on how in addition to disease, health also carries risks. In any case, deciding to ban any kind of germline genomic editing, even if it is aimed at directly preventing a disease, undoubtedly entails the risk of giving up curing and eradicating pathologies: in short, it implies a sacrifice in terms of health that, according to the most extremist views, it could even cost the destruction of human species (Powell, 2015). However, as we have seen, betting on health can also be risky: allowing germline gene therapies could generate a desire in society to use the technique for other purposes that could cause a slip in the eugenic slope – and could endanger social perception towards people with a disability. Our scenario is so peculiar that even with the same theoretical tools we can construct different argumentative lines that lead us to antithetical conclusions: it is the example of human dignity that, as we have shown, can play for or against the admissibility of germline gene therapy.

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Chapter 7
Bioethical Quandaries in Preimplantation Genetic Diagnosis

Erick Valdés

Abstract Generally, Preimplantation Genetic Diagnosis (PGD) is understood as a tool for embryonic selection involving therapy, enhancement or sex selection, yet other doors opened up by the technique, which entails far-reaching and controversial bioethical quandaries, are neglected. As a matter of fact, for some disabled parents, the best child possible may be a disabled one, and according to some arguments there might be good reasons to select for disability. Moreover, PGD encompasses polemical nuances related to producing saviour siblings, which also needs to be addressed and delimited. In this chapter I will analyze and discuss such paradigmatic contentious scenarios by displaying competitive arguments and visions so that the readers are able to get a better idea of the debate and take their own position about these issues. The approach as usual in these settings is not pacific although it is eloquent and illustrative of the historical and current discussion on PGD' scopes.

Keywords Preimplantation Genetic Diagnosis · Procreative beneficence · Procreative autonomy · Disability · Transhumanism

Introduction

Preimplantation genetic diagnosis (hereinafter, PGD) consists in studying human embryos' DNA in order to (i) select those that meet certain features, according to previously chosen stereotypes, or (ii) eliminate those carrying some kind of congenital defect. However, two concepts must be distinguished in this technique: first, *PGD*, which allows the early detection of serious genetic diseases, which can be transmitted to offspring if the parents are carriers or sick (in general, these are monogenic hereditary diseases such as Fragile X Syndrome, Huntington's disease and muscular

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dystrophy); second, *Preimplantation Genetic Screening or PGS*, also called aneuploidy screening (De Rycke & Berckmoes, 2020: 2). In this case, alterations in the number or structure of chromosomes are identified (the best-known chromosomal disease is Down Syndrome). Depending on whether genetic or chromosomal alterations are to be detected, techniques for analyzing the embryos' DNA will be different.

As PGD implies performing an embryo's cells biopsy before implantation, it can avoid transferring aberrant embryos by detecting diseases and conditions caused by genetic and chromosomic alterations (De Rycke & Berckmoes, 2020: 2). Thus, while it localizes and prevents diseases from happening, PGD can also stop transmission of diseases into offspring reaching that way a healthy progeny, so that it improves IVF cycles' aftermaths and it dwindles multiple pregnancy rate (as multiple transfer is also reduced). Likewise, PGD allows the best embryo selection as it is aimed at detecting genetically healthy embryos (Ly et al., 2011). Therefore, those carrying mutations or aneuploidies potentially implanted into the mother's womb, which could lead to implantation failure, miscarriage or birth of a sick child, can now be immediately discarded. In this fashion, using PGD implies a lower risk of miscarriages as it prevents spontaneous abortions from happening by avoiding damaged embryos to be transferred.

Most of parents undergoing FIV processes use PGD to select their children and make sure to have healthy ones. Yet, other reasons may be involved. Usually, PGD is recommended in the following cases:

(i) When the parents, or at least one of them, are carriers of some inherited genetic disease.
(ii) When the parents, or at least one of them, have an altered karyotype (chromosomal study). For example, they may be carriers of chromosomal inversions or translocations.
(iii) When the parents already have a sick child due to a disease that requires a blood cell transplant and they decide to have another healthy and compatible child, namely a savior sibling.
(iv) After several repeated failures in IVF cycles.
(v) After several embryo implantation failures.
(vi) When there are recurrent abortions.
(vii) When the woman is of advanced maternal age (it is recommended for women over 38–40 years of age).
(viii) If there is a history of an aneuploidy pregnancy (wrong number of chromosomes).
(ix) In specific cases of male infertility (e.g. when it is necessary to obtain sperm from the epididymis or the testis).

Yet, PGD also encompasses some drawbacks. As the embryo biopsy is an invasive procedure it involves punching out the pellucid zone by allowing it to spend longer outside the incubator. Some embryos do not make it and stop their development. In addition, using PGD implies discarding a number of embryos when anomalous. So, if the couple did not have many embryos after fertilization, the risk of having to cancel the transfer is greater (Klitzman, 2016).

PGD is ethically controversial because it involves screening and eventually destructing embryos, as well as offspring's selection based on the choice of specific traits, among others. As selecting embryos implies discarding many of them, this straightaway discloses a vast constellation of bioethical quandaries. Still, discarding damaged embryos avoids early abortion and improves the number of evolutive pregnancies. But, at the same time, it prevents impaired embryos from being implanted, which reduces the odds of disabled people's births. While stop producing handicapped babies may sound plausible and desirable to most of parents, it encompasses disturbing implications for conservative surroundings. Conservatives argue against the use of PGD to select and discard embryos as such use might undermine and erode human dignity. Instead, there is a liberal camp fostering to use PGD to select the best embryos possible and discard those with diseases and abnormalities.

For liberals this practice should be made widely available as the parents are free to choose the best embryos and discard the imperfect ones. Accordingly, any policy or governance framework created to rule this terrain should be made under broad discretion. Liberals hold that embryos are a cluster of cells whereas conservatives assert that they have dignity and are prevented from being treated as mere things. Hence, whilst those who object PGD when applied on situations other than therapy and sustain that the right to life encompasses a lexically preeminent value at any stage of biological development, those who think that an embryo represents a very rudimentary moment in the existence of a human being to be a rights holder, do not see major problems in this technique. There exists, therefore, significant disagreement about whether PGD is a promising dawn for humanity or it rather epitomizes the possibility of tendentiously fracturing the logic of life.

Generally, PGD is understood as a tool for embryonic selection involving therapy, enhancement or selection of sex, yet other doors opened up by the technique, which entails far-reaching and controversial bioethical quandaries, are neglected. As a matter of fact, for some disabled parents, the best child possible may be a disabled one, and according to some robust arguments there might be good reasons for selecting handicapped embryos (Savulescu, 2001).

These pros and cons point out several bioethical controversies in DGP. Some people, because of their belief or religion, consider that life begins at the very moment of fertilization. Therefore, they are not in favor of discarding embryos that could give rise to a life, as are the people against abortion. On the other hand, they also do not consider it ethical to reject embryos that could give rise to children with Down syndrome, Turner syndrome or other genetic diseases. Either way, PGD comprises significant nuances and swathes that need to be addressed and clarified. All of them can be translated into questions:

Is It Ethical Using PGD to Select Healthy Embryos and Discard Those Carrying a Disease or Disability?
Is Using PGD to Create a Savior Sibling Ethical?
Is It Ethical using PGD for Sex Selection?
Is it ethical that disabled parents select for disabilities?
Is it ethical using PGD to enhance human species?

I will address such questions by displaying competitive arguments and visions so that the readers are able to get a better idea of the debate and take their own position on such issues.

Is It Ethical Using PGD to Select Healthy Embryos and Discard Those Carrying a Disease or Disability?

Using PGD to screen embryos for aneuploidy and genetic disease as well as for susceptibility to cancer and for late-onset diseases is an extended practice nowadays. What seems to underlie parents' desires to know the genetic condition of the embryos they produce is to avoid giving born a sick or handicapped child. Facing a choice between a damaged embryo and a healthy one, most of parents would select the latter. This clearly encompasses a medical reason as bringing the healthiest people into world makes perfect sense both in the context of *Lex Artis* and that of bioethics (Beauchamp & Childress, 2019), as the principle of beneficence orders to do good, and the principle of nonmaleficence requires not to do harm, which highlights canonical professional obligations in medical practice. Likewise, this seems to be in perfect tuning with law, as "wrongful life" is a cause of action for a disabled child to sue his/her parents for failing to prevent his/her birth or having given him/her birth by knowing in advance his/her genetic condition. This can lead to think that parents undergoing an IVF process would have not only the right but the obligation to ask for the genetic analysis of every embryo before implantation. In other words, while couples have the right to exercise their autonomy when selecting an embryo (procreative autonomy) they also have the obligation to select the best embryo possible (procreative beneficence) (Savulescu, 2001). This ironic dichotomy has shaped most of the ethical and legal approaches to PGD over the last two decades (McGee, 2020; Asch, 2019; Barker & Wilson, 2019; Gyngell & Douglas, 2018; Bayefsky & Jennings, 2015; Boardman, 2014; Savulescu, 2001, 2002, 2007; Bleeker, 2013; Taylor-Sands, 2013; Hall, 2013; Klein, 2011; Krahn, 2011; Madeo et al., 2011; Shakespeare, 2011; Wilkinson, 2010; Robertson, 1994, 2003, 2010; Savulescu & Bostrom, 2009; Bostrom & Savulescu, 2009; Bostrom & Sandberg, 2009a, b; Bostrom & Roache, 2008; Scott, 2007; Shakespeare, 2006; Bostrom & Ord, 2006; Glover, 2006; Bostrom, 2005; Hampton, 2005; McMahan, 2005; Wolf et al., 2003; Parens & Asch, 2003; Boyle & Savulescu, 2001; Savulescu & Dahl, 2000; Buchanan, 2000).

According to the principle of procreative autonomy, parents have a wide range of freedom to exercise their reproductive rights, as they are entitled to make reproductive decisions with no external coercion and in tune with their life project. They can decide whether they want to have children or not, when procreate, by which means, and what kind of children they would like having (Buchanan, 2000: 206). In this order of ideas, as a clear signal of their reproductive autonomy, parents are able to impose their will to subject embryos to DGP and select the one they consider the

best. In the case they were prevented from undergoing PGD and selecting among the embryos they have produced, that might be understood as a severe and unacceptable restriction of such reproductive autonomy. Moreover, as reproductive autonomy encompasses the kind of child the parents are willing to have and the type of embryo they will select, the likely impact of having a disabled or severely sick child on their lives is an element that deserves to be considered in any family planning (Robertson, 1994, 2003).

Currently, PGD is a frequent target of parents who want to make sure to have a healthy child. Twenty years ago, when the technique had a relatively limited use, the potential selection and manipulation of offspring set off alarms bells in conservative circles (Fukuyama, 2002; Kass, 2002; Stock, 2002). However, a slow but persistent PGD colonization continued in reproductive practice. Even non-IVF patients look for PGD when they are under special risk for genetic disease, and want to have a child without exposing to an uneasy pregnancy or later abortion. In addition, as several indications for PGD single gene mutational analysis have been reported since early 2000s (Robertson, 2003), the demand for it has boosted especially among couples unwilling to use prenatal diagnosis and selective abortion. In this fashion, couples also request PGD to detect mutations for susceptibility to cancer and for late-onset diseases, such as Alzheimer.

However, the principle of procreative autonomy can lead parents to select a disabled embryo if they have some reason to do it (Savulescu, 2001: 418–419). If procreative autonomy claims that parents should be free to decide not only when and how to procreate but what kind of children to have, deaf parents could use DGP to produce, select and transfer a deaf embryo without any ethical or legal counterweight (I will return on this point later on). Before this potential scenario, the principle of procreative beneficence demands parents to select the best embryo possible among all the healthy embryos available, which automatically rejects those with genetic conditions. Also, parents might choose the embryo they consider to have the best potential welfare in the future, which might lead to counterintuitive scenarios in some cultural contexts, such as to select a male embryo instead a female one, or go producing white children rather than black ones. Alike, couples are often tempted to produce and then select embryos with well- defined features, such as, height, physical appearance, eye and hair color, intelligence and memory, among others. Intricate nuances and implications of theses possible uses of PGD have engendered profuse discussion on procreative autonomy and procreative beneficence' scopes and its likely aftermaths for designer babies (Savulescu, 2001, 2007; Savulescu & Dahl, 2000; Buchanan, 2000), and the ethics of enhancement (Clarke et al., 2016; Bostrom & Sandberg, 2009a, b; Savulescu & Bostrom, 2009; Bostrom & Roache, 2008).

Beyond this debate, and even though it seems to verge on reproductive discrimination, the principle of procreative beneficence has been relatively successful in informing decision-making in PGD' scenarios. It is known that some non-disease genes can impact the likelihood of people running the best life, which points to the need of using information available of such genes in reproductive decisions-making. Therefore, couples should be able to select embryos expected to have the best life

possible, based on available genetic information, including that of non-disease genes (Savulescu, 2001: 413).

Likewise, procreative beneficence entails that couples should request genetic test for non-disease traits in selecting embryos even if such action increases social inequality (Savulescu, 2001: 415). Despite the reluctance that selecting healthy embryos instead of impaired ones has caused in some settings, there seems to be strong reasons to not consider such averseness seriously as it based upon misunderstanding fact differences as moral ones. Indeed, the fact that disabled people are different in some respects should not made us see treating them differently as discriminatory. It is one thing to argue that people with some type of disability must be given the most optimal socio-structural conditions to carry out their life project, and quite another to assert that choosing a non-disabled child is a biased act. When disabled people turn to medicine to mitigate, solve or eliminate their disability, they themselves are showing that preferring a life without disability is not a mere capricious or discriminatory act. Some handicapped people might say that they do so because social conditions rather than physical or intellectual ones disable them. However, this statement misrepresents the more limited truth. Being able to walk, see, hear, and be free from pain are, under any social conditions, real advantages.

On the other hand, disability advocates affirm that preferring healthy people instead of disabled ones encompasses an undesirable form of discrimination as doing so implies that disabled's lives are less worth living than the lives of people who are not disabled (Singer, 2011: 165). Yet this assumption leads to counterintuitive arguments. Indeed, after Singer (2011), if we accept such belief we wouldn't have any problem with encouraging women to take pills during pregnancy that risk fetus and cause children to be born with no limbs. Taking for granted that there is no reason to think that a life of a disabled person is likely to be any worse of that of a non-disabled one seems to hide a confusion between fact differences and moral ones. Preferring having children with limbs instead of children without arms and legs is not showing disrespect or discrimination for handicapped people but simply recognizing an objective reality. In fact, the principle of equal consideration of interests (Singer, 2011: 165) rejects disregarding the interests of people grounded upon disability as many times dealing with and getting over such barriers is in itself a triumph.

This should be addressed from a simpler perspective, namely, identifying difficulties inherently associated with a given functional characteristic. In this case, when asking whether a blind or deaf person has the ability and possibility of enjoying the same goods of life a sighted or hearing person has access to, the right answer seems to be self-evident.

Is procreative beneficence eugenics then? Beyond controversy this question brings up, there is a robust argument to consider it rhetoric. Savulescu (2001: 424) clarifies that eugenics consist in selectively (and systematically) producing a better population, whereas procreative beneficence does not encompass such purpose as it does not interfere in reproduction at a public interest scale. While eugenics is essentially a public enterprise, procreative beneficence is not and remains as a private matter.

Therefore, at the end of the day, procreative beneficence and procreative autonomy are competitive principles even though both of them are grounded on self-interest. Often autonomy and private interests collide with social justice and public good. Still, procreative beneficence can become a self-interest principle as parents can determine what is the best child possible for them, even if such child is disabled. Whichever direction the discussion takes, there is no a pacific solution, especially in liberal, pluralistic and democratic societies where liberty is an assumption. Conservative positions will argue that parents do not have the right nor the autonomy enough to choose and select a child according to their desires, whereas liberals will assert that couples can select a disabled child if they have good reasons to do so insofar as such action allows the child to have a life worth living.

A couple may avoid having a disabled child for diverse reasons but none of them are necessarily discriminatory. Preferring a child without an illness or disability does not mean parents judge those people with such conditions. However, if ethics and law agree with avoiding to have disabled children by giving couples room enough to make such decisions, it seems plausible to give the same room for, under other circumstances, allowing them to select for disability (Elliston, 2013: 188).

Is Using PGD to Create a Savior Sibling Ethical?

Consider the following story. Kate Fitzgerald has acute promyelocytic leukemia. Since neither her parents, firefighter Brian and lawyer Sara, nor her older brother Jesse are genetically compatible, Dr. Chance, Kate's oncologist, suggests designer IVF and DGP to conceive and select a child to provide, among others, stem cells to Kate. Anna was born as a savior sister. Beginning with the removal of her umbilical cord at birth, over the next 11 years, Anna donates compatible organs, blood, stem cells, and tissue to Kate. Anna's life is one of hospitalizations, growth hormone injections, opioid painkillers, sleeping pills, bleeding, and infection. While Sara has no qualms about using Anna's body to treat Kate's, Brian is closer to Anna and has second thoughts about how they treat her.

At 15, Kate is suffering from kidney failure and Anna knows she will have to donate one of her own. He realizes that having only one kidney will limit his life; avoid playing sports, drinking alcohol, maybe even having children, and putting herself at risk in case her only remaining kidney has a problem. Anna sues her parents for medical emancipation and rights to her own body. Brian understands, though Sara is outraged. Attorney Campbell Alexander agrees to represent Anna as her guardian *ad litem*, demanding successfully partial termination of parental rights.

While this is not based on true events (it is taken from the novel – later turned into a movie – *My Sister's Keeper* by Jodi Picoult), it does point out an actual controversial use of PGD (together with tissue typing) to select an embryo to produce a donor-child for an existing person. Most of ethical analysis consider at least,

three potential problems: (i) savior siblings (Spriggs & Savulescu, 2002)[1] will be treated as commodities, (ii) this practice will lead to create designer babies; and (iii) savior siblings will be physically and psychologically harmed (Sheldon & Wilkinson, 2004).

(i) The famous second formulation of Kantian categorical imperative "So act that you use humanity, whether in your own person or in the person of any other, always at the same time as an end, never merely as a means" (Kant, 1997: 38) forbids instrumentalizing and reifying people. Those who reject using PGD to create and select savior siblings often refer to this Kantian dictum as doing so it would infringe human condition of end in itself, even accepting, from a lax perspective, that parents have a wide range of reasons and expectations when deciding having a child, which either way would instrumentalize them to a degree (Knoppers, 2006: 202, 212). In this fashion, the practice becomes acceptable as long as the donor child is valued for him/herself and parents are intended to look after and love him/her (Wolf et al., 2003). Whilst popular, this argument is naive, as it is just self-evident that a couple trying to help and save a severely sick child can at the same time be loving parents, which makes unlikely the savior child is treated as mere means to ends (Devolder, 2005; Sheldon & Wilkinson, 2004; Boyle & Savulescu, 2001).

The epistemological background of the Kantian imperative is that it would be wrong to bring children into the world moved by "conditional" interests. Yet, even it was desirable, a world where parents only have children "categorically" or "unconditionally" seems like a conceptual impossibility. Often couples have children for specific purposes, such as, to build a family, to help care of parents' business, and to give someone else the chance to enjoy the goods of life, among others. This does not seem to contradict Kantian imperative whatsoever as it says that "never uses people *merely* or *solely* as a means" (Boyle & Savulescu, 2001: 1241). If parents take care of and love the savior sibling there is no problem with that child benefiting (or being used to benefit) other. In the vast majority of cases, it is very likely that a child conceived as a donor will be truly valued as a person. Therefore, as far as it can be seen, potential psychological harms in the future being should also be discarded.

Nevertheless, opposite visions argue that the sole intention of creating a child to save another is ethically controversial (Sparrow & Cram, 2010; King, 2006; Sutton, 2004; McBride, 1990) as saying that the parents of a savior child will love it for its own sake hides a tendentious argument. While it is clear that the parents will love the savior sibling it is difficult to separate the action of creating it from the fact that they did so essentially motivated by the desire of saving another child's life. In this case, the parents would not likely have had a second child without the need of

[1] These authors coined the term to point to a "perfect match sibling" created to be a donor of life-saving tissue for an existing child.

saving the first one's life. Hence, it is possible to see such action as a paradigm of how treating a person as a means to an end (Sparrow & Cram, 2010: 671).

(ii) The second problem is that using PGD to produce savior siblings steps onto a slippery slope towards creating "designer babies" (Robertson et al., 2002) based, among others, on shallow grounds, such as choosing babies' hair or eyes color. As this common fallacy rests upon an unlikely conjecture and it does not lead to valid (conclusion is followed necessarily from the premise(s)) or solid (what is told is true) arguments it is easy to refute. This fallacy claims a proof of consistency or *reductio ad absurdum* as it is trying to show that creating savior siblings has bizarre repercussions (Sheldon & Wilkinson, 2004: 534). Yet, while slippery slope fallacies imply *reductio ad absurdum* arguments they are also built on analogy reasoning. Both types or arguments are quite resistible and difficult to sustain. If we consider the following analogy argument:

(i) It is immoral to create a savior child to save his sibling's life.
(ii) Creating designer babies is as wrong as creating savior siblings.
(iii) Therefore, it is immoral to create designer babies.

It is clear that (i) and (ii) imply begging the question and are nothing more than mere unproved statements. This overturns the conclusion and weakens its epistemological density at the same time. As slippery slope fallacies are grounded on these kinds of analogies, often enclosing bigotry and bias, they do not display compelling reasons to take them seriously.

Let us focus now on this argument based on Sheldon and Wilkinson (2004: 534):

(i) Allowing couples to create savior siblings is morally equivalent to allowing them to select "designer" features (hair or eye color).
(ii) Therefore (from (i)), banning or allowing one implies we should ban or allow the other.
(iii) Allowing people to choose designer features is morally wrong and should be forbidden.
(iv) Therefore (from (ii) and (iii)), allowing parents to select savior siblings is morally wrong and should be banned.

This second version of a slippery slope fallacy shows clearly an analogy argument behind. This should be a reason enough to reject it. However, if we analyze each premise separately, the lack of validity and solidity of the argument is even more evident. Indeed, (i) and (iii) demands begging the question, so that (ii) and (iv) are not implied in and cannot be inferred necessarily from (i) and (iii) respectively. After this, a plausible conclusion is that the problem of "designer" babies is not self-evident and is hard to prove as there are no reasons to think that even existing a slope there would also be an inevitable slide down associated. Moreover, analogies here do not work compellingly as there are undeniable differences between savior siblings and "designer" babies. Such divergences are overlooked by the slippery slope fallacy (Sheldon & Wilkinson, 2004: 535).

iii) Regarding this problem, those who dissent with the creation of savior siblings usually claim about the welfare of those children as they would have worse lives than children conceived naturally or other children created using PGD. Yet, some fissures in the argument underlying such assumption, especially in the latter scenario, have already been identified (Sheldon & Wilkinson, 2004: 536–538). Regarding the potential physical harm the savior sibling will be subjected to, there is evidence enough since over 20 years that PGD itself doesn't imply any damage either for the embryo or the future person resulting from it (Lancet, 2001: 1195). This leads to think that there are no compelling reasons to argue that savior siblings are any worse off than other children created using PGD. Well-based ethical positions defend the above as using this procedure should unlikely cause harm to anyone (including the savior sibling) and is likely be beneficial to some (Boyle & Savulescu, 2001). Some more moderated proposals argue that PGD for Human Leukocyte Antigens (HLA) matches to be plausible when the child born after PGD was himself at risk for the condition treated in the existing child (Robertson, 2003), which means that it would be acceptable to use PGD for HLA in cases such as Fanconi's Anemia but not in cases leading to the later child might inherit some genetic mutation.

In addition, Smith (2015) asserts that the only justification for limiting a family's reproductive liberty is when the exercise of reproductive decision-making leads to harming others. However, the harm principle is already the underlying feature of ethical and legislative action in Western democratic society, and as such, it delivers solid grounds some strong and dense arguments are based upon to fostering a less-restrictive regulatory framework for the savior siblings' case.

Likewise, Taylor-Sands (2013) argues that the welfare of the child to be born is concomitant with the welfare of his/her family. From this premise, she proposes a relational model for selective reproduction based on a broad conception of children's welfare by including both individual and collective family interests, and mapping out how law and policy might support such relational model for savior sibling selection. In this specific case, her conclusions can be analogically extended to bioethics surroundings.

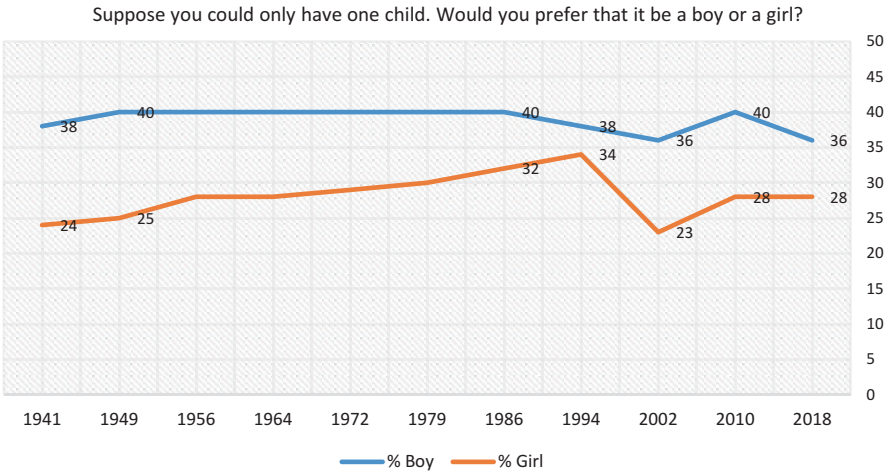
Is It Ethical Using PGD for Sex Selection?

As it involves cultural components, the case for sex selection brings up counterintuitive scenarios. Savulescu (2001: 423–424) talks about a society where women are severely discriminated against. Essentially, they serve as slaves to men. It is logical to think that couples will prefer to select male embryos instead of female ones. That way, their children might aspire to have better lives and flourish more easily. This action will clearly boost discrimination against women and, from a longtermist perspective will turn such a society into an intolerable place for male to live.

Although the solution does not lie in prohibiting sex selection but in restructuring society in such a way that discrimination against women disappears, it is difficult to free sex selection of the embryos from cultural patterns deeply rooted in

Western society. In the same fashion, it might be that, in certain xenophobic societies, black parents preferred to have white children to ensure them to live free from discrimination, stigmatization and social barriers to display their life project.

These potential scenarios, although coming from dystopic and semi-slippery slope arguments, at least show that sex selection needs sound policy for its governance. In a survey conducted in 2018, Gallup polling asked respondents in all 50 states and DC, "Suppose you could only have one child. Would you prefer that it be a boy or a girl?" The answers showed a preference for a male child, 36% to 28%. More specific indicators points to the preference for boys over girls has averaged 11-point margin since 1941, men are strong in their preference for a male child, 43% to 24%, and women have divided preferences: 31% want a girl; 30%, a boy (GALLUP 2018). Overall, the graphic is as follows:



Source: Slight preference for having boy children persists in U.S. (gallup.com)

In this atmosphere, the ethics of sex selection is binary. While there are permissive positions facing the practice other conservative visions are intended to prohibit it. Arguments supporting sex selection for non-medical reasons claim that parental autonomy implies reproductive liberty and as sex selection represents a material aspect of reproductive decision-making it should be permitted (Dondorp et al., 2013; Sharp et al., 2010; Macklin, 2010; Harris, 2005; Steinbock, 2002). New technologies giving individuals a broader catalogue of reproductive options support parental autonomy in such context, so that policing preferences for sex may violate not only autonomy but privacy in sex selection decision-making settings (Kalfoglou et al., 2013).

Other positions supporting sex selection for non-medical reasons argue that preferences for sex do not necessarily entail a discriminatory attitude. There is nothing wrong in parents whishing a specific sex if they think that there are reasonable differences in the experience of raising male or female offspring. Hence, such rearing

experiences cannot be imputed to be discriminatory as parents may have multiple reasons not related to gender bias to select progeny's sex (Macklin, 2010; Harris, 2005; Heyd, 2003).

Arguments against using PGD for sex selection for non-medical reason cover a range from harm to offspring and misuse of medical resources to risks of discrimination and perpetuation of social injustice (Kalfoglou et al., 2013). In this last case, framing sex selection as a neutral option for couples may boost its naturalization in countries with evident preferences for a particular sex (Ethics Committee of the American Society for Reproductive Medicine, 2022: 722).

There are also some critics claiming that sex selection fails in evincing categorical parental acceptance of their children independently from personal interests and preferences (Gilbar, 2009; Herissone-Kelly, 2007; McDougall, 2005; Baldwin, 2005). This attitude might trigger that the use of medical resources for non-medical reproductive purposes would fall into a slippery slope towards selection of other traits in offspring related to eugenics (Wilkinson, 2005: Seavilleklein & Sherwin, 2007; Wachbroit & Wasserman, 1995). Likewise, allowing sex selection may result in preventing children from exercising their right to an open future as parents might impose wrong gender norms on them, reinforcing undesirable biased patterns of what being male or female means (Wilkinson, 2005: Seavilleklein & Sherwin, 2007). Such imposition may be psychologically detrimental to children and disruptive of the parent-child relationship as well as it might also create gender prejudices against one sex or the other (Committee on Ethics, American College of Obstetricians and Gynecologists, 2007).

In its most recent statement, the Ethics Committee of the American Society for Reproductive Medicine (2022: 723) expresses some concerns about the practice, as it encompasses risks and burdens, related to gender bias, sex stereotyping and non-acceptance of offspring, among others. The Committee concludes that while the practice remains ethically controversial and needs clear policy for its governance, sex selection should not be encouraged for non-medical reasons. Also, carrying the procedure out with purposes other than therapeutic would divert medical resources from authentic medical needs. Yet, this argument is weak as the practice can be performed at private institutions and no one has strongly promoted that the state should subsidize sex selection for non-medical goals (Savulescu & Dahl, 2000: 1879).

Is It Ethical That Disabled Parents Select for Disabilities?

In the spring of 2002, lesbian couple, Sharon Duchesneau and Candy McCullough were looking for deaf sperm donors. Having been deaf themselves since birth, they wanted a deaf child to communicate with in sign language, and raise him in their own non-hearing culture. As screening out all sperm with genetic diseases and disabilities was a common procedure in sperm banks, they sought out a deaf friend with five generations of deafness in his family who later on donated his sperm to help the women make their dream comes true. Having found a sperm with the deaf

gene, the couple used PGD to ensure producing and selecting a deaf embryo. About a year later, the couple's son, Gauvin, was born deaf. However, as few months went by, doctors discovered that Gauvin had residual hearing in his right ear. With the use of a hearing aid, Gauvin would be able to learn some spoken English, and maybe even learn how to lip-reading. Doctors told the couple that it was crucial to benefit of that as early as possible in Gauvin's life. Normally, hearing parents with a deaf child take advantage of this small glimmer of hope, and see it as an opportunity to boost their children's odds to communicate more efficiently. However, Duchesneau and McCullough, declined the use of a hearing aid, but said that they will let him use it if he wanted to when he is older (Valdés, 2021: 119–120).

Although using PGD for conceiving children with disabilities is rather infrequent, there is evidence that it has occurred other times. In fact, in a survey applied in American clinics offering PGD, 3% of respondents reported having intentionally used PGD to select an embryo with a kind of disability (Baruch et al., 2008a, 2008b). Certainly, using PGD to create deliberatively a deaf child poses the question if doing so is ethical. The issue has several edges and nuances, as since the case was known the debate was profuse and numerous claims, opinions and arguments have been raised thus far.

Within the non-hearing community, deafness is a strength rather than a weakness as it permits to cooperate with and be part of their own culture (Valdés, 2019: 290). Deaf people belong to a closed community, yet that does not mean being disabled but it encompasses a big chance to develop and enhance communication skills and social interaction. In this atmosphere Gauvin's mothers matured their passion for such culture by working as therapists for non-hearing people. It was not rare that they wanted to have a deaf child able to enjoy all the benefits associated with growing up in that environment. The couple thought that wanting a deaf child instead of a hearing one was not different from wanting to have a girl rather than a boy.

Deaf people assert that assuming that they are intended to live with particular complications is a fake premise hearing people live with. As these are used to living inside their own normality and are not able to picture their lives with no sound, they believe such a life is difficult. However, deaf people are born without the ability to hear, so deafness symbolizes what is normal in their lifestyle. In this fashion, Duchesneau and McCullough's supporters said that people with five senses have no more value than those with only four and, consequently, there was nothing ethically wrong in wanting to have a deaf child. That way, Gauvin was not going to be prevented from enjoying the goods of life any other hearing child does.

However, once the *Washington Post* published the story, Gauvin mothers' decision was on several criticisms. Jeanette Winterson said that "it is a simple and irrefutable fact that it is better to live with five senses than with four," and compared Gauvin's mothers with those fanatical parents who follow cults or fundamentalist religions and brainwash their children (Valdés, 2019: 291). Nancy Rarus, of the National Association of Deafness asserted: "I cannot understand why anyone would give birth to a disabled child having the opportunity to do just the opposite," adding that "deaf people do not, in fact, have many options in life." (Mundy 2002). In addition, Alta Charo, a professor of law at the University of Wisconsin, said the couple

was limiting and reducing Gauvin's capabilities to have a fuller life, and asked whether the parents had violated the duty of parenthood, namely to maximize to some reasonable degree the advantages available to their son. "I'm loath to say it, but I think it's a shame to set limits on a child's potential." She concluded. (Teather 2002).

By applying principlism (Beauchamp & Childress, 2019), what the couple did seems to be against some rules of nonmaleficence, such as "do not incapacitate" or "do not deprive others of the goods of life." Moreover, Gauvin's mothers did not meet a basic rule of beneficence every parent should observe: to maximize, until a reasonable degree, the advantages available for a child to unfold his existence in the best way possible. Likewise, Gauvin's individual autonomy was restricted, as he was prevented from counting on an important tool to carry his life project out. In addition, conceiving and selecting children with disabilities is, at best, arbitrary and opposite to justice, as some benefits and goods of life any person has the right to, were in advance unilaterally taken away from him.

A liberal position that advocates for couples' autonomy to select and have the child they want to is grounded on the premise that "deafness is not that bad" (Savulescu, 2002: 772) as a deaf child only is harmed if his/her life is so bad it is not worth living. Therefore, a reproductive choice intended to produce and select a deaf child does not harm the child so couples should be allowed to do it "even though they may be having a child with worse life prospects" (Savulescu, 2002: 772). In fact, before difficulties and intricacies that defining what the best life prospect is – for a couple of dwarves the best child possible might be a dwarf one (Davis, 2001) -, according to this position, trying to impose a one and only 'best life possible' meaning would be "at best overconfidence – at worst, arrogance" (Savulescu, 2002: 773). Therefore, as 'best life possible' is an open concept that tolerates multiple connotations and quite subjective approaches, producing and selecting a child with ALS (Amyotrophic Lateral Sclerosis) might be perfectly acceptable as living with that condition would not be "that bad" and many people live with it giving their lives diverse meaningful purposes.

In these kinds of scenarios, procreative beneficence means that we can do wrong (discard an embryo with a disease or select a deaf baby) without harming no one, so the underlying argument (grounded on a Parfitian defense of procreative beneficence) is that there is no harm unless our lives are so bad they are worse than death (Savulescu, 2001: 417–418). Therefore, a couple can select for disability as even they might be doing something wrong nobody will be harmed. Extending this argument to medical settings can leads us to a strange conclusion. A doctor lying a patient may be doing wrong but if it does not harm the patient there would not be anything morally reproachable in the act. Consider for example the following case: a doctor who promises his patient that he will perform a surgery but after the patient falls asleep goes to play golf and leave a resident doing the surgery. Nothing bad happens, everything goes well, and the patient never finds out that the doctor did not perform the surgery. The lie has been innocuous; therefore, it is morally irrelevant.

By referring to the best interest of the child, Savulescu (2001: 419) says that a couple could choose an embryo with a disease (Asthma) and still be doing

everything possible in the interest of the future child. This argument also seems to be weak as caring of the best interest of the child does not only mean to do everything we can do for the child's welfare, but it also may entail not to predetermine his life. In fact, the best interest of the child is a legal guarantee that children have consisting in that parents should adopt and display actions to promote and protect their rights, instead of performing deeds that may violate them.

Other perspective is founded upon the so-called "social model of disability" (Abberley, 1993, 1987; Barnes & Mercer, 2003), which states that disability cannot be based on alleged individual anomalies, but rather on excluding social, economic, political and cultural conditions. In opposition to the idea that certain disabilities represent inherent individuals' conditions, the social model argues that incapacities are not only boosted but caused by the social environment. Following this position, it is perfectly deductible that facing the selection of disabled embryos there would not be any ethical issue to be worried about.

In this sense, disability would be grounded on society, an often hostile and unsuitable surrounding to disabled people's needs. While disability would not be a condition *per se*, but rather a result of social sphere's ineptitude to adapt itself to functionally diverse people, it would turn into a subjective setting characterized by discrimination and stigmatization. In other words, dysgenic DGP to produce and select disabled embryos does not encompass any ethical concern as none personal interest of the future person is violated because neither deafness nor dwarfism are, according to the social model, disabilities *per se.* Therefore, dysgenic PGD could be massively extended without any moral scrupulous if we structure society so that disabled people can display their life project without facing societal barriers.

If disability is not only in the body but also in the social environment most of deaf people would argue that "there is little disability in an all-signing environment" (Bauman 2002: 314). Hence, disability appears once there is no access to communication and the dichotomy "hearing/deaf" emerges as in such "contact zone," where social system is not suitable to non-hearing individuals, (Bauman 2002: 314) hearing people enjoy advantages with regard to deaf ones. Yet, following this argumentative line leads to a counterintuitive conclusion: by selecting and breeding a deaf child, a family would have less contact with disability conditions than by choosing a hearing child. This means that being deaf is not necessarily worse off than being hearing.

Beyleveld & Brownsword (2000: 40) state that while human dignity may be attacked by discriminating or stigmatizing functionally diverse people, it may also be threatened by introducing or selecting morbid conditions to produce disabled individuals, whose circumstance is not uniquely provoked by society. Rendtorff and Kemp (2000: 69) argue that violence on the human body has increased in the bioscientific era, by opening up a new catalogue of harms menacing human vulnerability. In this context, they affirm that disabled ones are even more susceptible to be harmed because of their special weakness. Singer (2011: 68–70) addresses the relationship between equality and disability, concluding that fostering collaboration and support for disabled people and seeking to eliminate social barriers that intensify discrimination, is quite different from sustaining that disability is the consequence of social hostility instead of being an individual particularity.

Also, as international instruments do not consider new forms of discrimination, stigmatization, marginalization and human exploitation that may emerge by virtue of biogenetic empowerment, human vulnerability adopts another ontological facet only evident when human life collides with bioscientific practices able to subject it to a permanent risk of intergenerational scope. Indeed, as dysgenic practices represent a controversial face of genetics, they point out to penetrating dilemmas for governance and policy as well as they challenge bioethics to understand vulnerability far beyond the traditional meaning of human rights (Valdés & Rendtorff, 2022: 184).

Selection of Embryos and Transhumanism: Is It Ethical Using PGD to Enhance Human Species?

The actual possibility of our current humanity transitioning into a transhumanity is an idea that has hanged around bioethical discussions over the past three decades. Specifically, the case for enhancing the species through embryo selection has raised interesting debate. Referring biological brains, Bostrom (2014: 36) affirms that a primary form of improving their functioning is through selective breeding. By accepting that biomedical enhancement could reach bigger and faster results in improving human capacities or in achieving physical and intellectual stereotypes, which would render futile any human breeding policy, the only fact that humanity is improvable through embryo selection should deserve some attention.

Selecting for eugenics mostly points out hypothetical scenarios. Yet, even conjectural those scenarios are likely, and strictly speaking, couples who choose the best embryo possible when undergoing an IFV process are, imperceptibly but systematically, making humanity better (in a broad sense) than it currently is. Bostrom (2014: 37) suggests to consider the idea of genetic selection. Selecting at the level of embryos or gametes would be a more useful and effective process than any eugenics program to control mating patterns. As PGD has been used to map out embryos produced for monogenic disorders such as Huntington's disease and some late-onset diseases as well as it has been displayed for sex selection and creating savior siblings, the range of traits potentially selected for or against is broad and promising. In fact, theoretically, any trait is susceptible to selection.

Bostrom (2005: 204–212) casts aspersion on conspicuous voices expressing fears about improving humankind through biotechnologies. Such reluctances stemmed from conservative positions, ideologically opposite to transhumanism. The underlying argument grounded (and it still does) on that selecting for eugenics, or enhancing humanity by using technology would erode human dignity (Habermas, 2003; Kass, 2002, 2003; Annas et al., 2022; Fukuyama, 2002; Jonas, 1985).

Kass (2003) sustains that using technology to enhance ourselves debases our human condition and belittles the bestowals of nature. However, Bostrom (2005: 205) responds that some nature's gifts "are poisoned and should not always be accepted." Indeed, some nature's conferrals do not excel like others do and

underpinning such naturalistic argument may forestall ourselves of seeing the whole landscape. Catastrophic diseases, starvation, unnecessary suffering, genocide, rape, among others, show horrors of nature, which dwindles the position relying on nature as it was the archetype to establish what is desirable or morally right.

Annas et al. (2022: 162) affirm that any inheritable genetic modification is a "crime against humanity" as it implies that a hypothetical posthuman species will threat the existence of the current one. According to these authors, posthumans[2] will likely slave humans for considering them inferior, savages and fit for slaughter. Bostrom rejects this position as he sees some rhetoric behind. While bioterrorism and artificial intelligence do comprise existential risk for humanity, they can be governed through effective policy no one reasonable individual would be against. However, assuming that inheritable genetic modification or selection for eugenics (if we expand the argument) would lead to two different and separate species seems to be an unlikely guess. Bostrom (2005: 207) advocates for a continuum of differently enhanced individuals, "which would overlap with the continuum of as-yet unenhanced humans." Yet, whereas extermination is not the most likely outcome in this scenario, it is advisable to pay attention to new forms of discrimination and stigmatization that might arise in the future. When thinking of such scenario people should not be dystopic or alarmist, we rather should start to tackle the enterprise of working on configuring a better social environment for everyone whether equal or different.

As others in history, Fukuyama (2002: 160) states that there is something called dignity that makes us unique and morally superior in the world. Denying such a human condition could make us fell down into a dangerous track inexorably leading to disaster. In this fashion, selecting for eugenics and introducing transhumans into the existence might cause humans, in general, and some special persons (disabled, for example), in particular, lose their moral status. This way, the principle of equal dignity would be shattered. Facing this argument, Bostrom (2005: 209) asserts that dignity is not incompatible with eugenics as there is no reason to think that transhumans will lack the ability to display high levels of morality only because they will be more technologically advanced. Using technology should not cripple morality, rather it should happen exactly the opposite. New technologies (eugenic PGD, among them, for example) could even enhance morality and make humans better than they currently are (Bostrom, 2005: 206).

Jonas (1985) argues that parental broad discretion to make decisions on children design would be a kind of tyranny that would weaken the child's dignity and ability for self-determination. This author is afraid of technological advances as if they necessarily imply inescapable abuses for future generations, which will certainly be themselves more technologically advanced and powerful. His argument, besides asymmetrical seems like counterintuitive. Bostrom (2005: 211) shows its failure as even choosing to be less intelligent or less healthy than us, transhumans would always count on means to prevent us from enjoying the goods of life.

[2] I use the terms 'posthumans' and ´transhumans' as synonyms after Bostrom (2005).

Habermas (2003: 23) also participates in the debate by stating that the mere fact that a child gets to know he was created for an intended purpose by his parents, could derive into disastrous aftermaths as such circumstance not only prevents an individual life from choosing freely but it also undermines "the essentially symmetrical relations between free and equal human beings." Bostrom (2005: 211) takes care of this by affirming that there is no plausible reason to believe that a person has no choice over her own life just because someone else selected her genes. As a matter of fact, such person has the same options as other whose genes were selected by chance. Even, being smarter or more talented are abilities that open life options rather than obstruct them.

Other compelling reasons to select the best child possible have been around for some time. One of them is that it is self-evident that selecting for the best is better than selecting for the worst (Savulescu, 2007: 286), otherwise, selection of embryos would become a setting leading to self-defeating positions.

Surrendering a life's fate to random or to the will of a purported supernatural entity could be distortive for decision-making in embryos selection surroundings, as every person can now judge on his own about what the best life is. Although intricate, the concept of the best child possible offers some room for objectivity, as it is not that hard to determine what a capacity, a power or a talent are (Savulescu, 2007: 288). This fact should lead as to select for abilities instead of disabilities. Although some parents would consider to choose a disabled child, good reasons and arguments to select the best one still exist. Indeed, no rational person would think of inflicting pain or causing calamity on others to help them have better lives (Savulescu, 2007: 286).

Final Remarks

PGD encompasses a significant collection of bioethical quandaries. While it may be used for therapeutic purposes, it also might be intended to eugenic and dysgenic goals. I have reviewed some of PGD's moral intricacies by presenting both conservative and liberal positions for the reader to get an objective reception of ethical discussion on its scopes. Let us remember that often this practice is requested by parents who want a healthy child. This may overlap with eugenics as most of couples also whish the best child possible, attitude that for some visions leads to a potential transhumanist scenario. In addition, the case for sex selection is also controversial as reproductive options comprise gender preferences, specifically tending to select males in some cultural contexts. As to using PGD to conceive a savior child, this is a convoluted scenario too as it might imply to use people as means to other people's ends. Likewise, using PGD to choose disabled children raises puzzling questions that challenge bioethicists to ponder competitive arguments and assess whether a belligerent position about worsening humankind through biotechnologies is justified. Whatever the position taken on these matters, clear policy, compelling reasons and further discussion seem to be needed.

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Chapter 8
Rare Disease Research

Francesc Palau and Carmen Ayuso

Abstract We address ethical issues in the field of rare diseases (RDs) focusing on four aspects that are relevant for research and translation into clinical practice. First, the reuse of personal, health and genomic data, for research purposes, beyond the main purpose for which they were collected. Later, three aspects related to fundamental parts of clinical medicine such as diagnosis, treatment and prevention in relation to RDs. In this context, we address ethical aspects of research and its practical application that have to do with the diagnostic effort in patients with undiagnosed diseases. A third topic is research programs in rare disease therapy and its translation into the treatment of patients. Finally, some points are discussed regarding the incorporation of genomic analysis in newborn screening, having the analysis of genetic variants as a complementary biomarker to biochemical tests that allows expanding the number of RDs in which to act preventively.

Keywords Rare diseases (RDs) · Ethics · Data · Undiagnosed diseases · Treatment of RDs

Introduction

The medical art is expressed, mainly, in the relationship between the physician and the patient, which is recognized as an interaction between the doctor and the person who comes seeking help from the health professional when he feels ill health. This interaction can be seen as a process in time that includes three fundamental aspects:

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diagnosis, prognosis and treatment. The proactive model on individual health brings us closer to medical action in the field of public health, targeting not only the individual but the general population. This is where one last aspect of health care lies, prevention.

Rare diseases (RDs) are those which affect a small number of people. The primary criterion is prevalence, which is variable in different countries and geographical regions. In the European Union, a disease is considered rare when it affects less than five persons per 10,000, whereas in the United States the criterion is less than 200,000 affected people. RDs are also recognized because most of them are severe, chronic, progressive, and produce handicaps in patients (Council recommendation, 2009; Orphanet, 2021). Over 6000 different RDs have been identified to date (6171 rare disorders with Orpha code as unique identifiers), and although individually infrequent, they currently affect 3.5–5.9% of the worldwide population, and more than 70% are genetic (EURORDIS, 2021, Nguengang Wakap et al., 2020).

In this chapter we are going to focus on ethical aspects on RD research topics. We will address the issues underlying the secondary uses of patient data, that is, reuse of personal, health and genomic data, for research purposes, beyond the primary aim for that they were collected, and some questions on three areas related to aspects of medicine that we have mentioned previously, such as the diagnostic effort in patients affected by rare and undiagnosed diseases, the research programs in the therapy of RDs and its translation to the treatment of patients, and the genomic analysis in neonatal screening incorporating genetic variants as a complementary biomarker to biochemical tests that allows expanding the number of RDs in which to act preventively.

The Secondary Research Use of Rare Diseases Patients' Data. Definition

In a primary use, the patient's -demographic, personal, clinical and/or genomic- data are collected by the clinicians or researchers and used for a specific aim. By contrast, in the secondary use, the data are processed and used for different purposes to those that originally were pursued, at the time that information was gathered. Thus, it could involve different data processor or researchers, other than those who were primary involved in collecting those data (primary data collectors) (Schlegel & Ficheur, 2017).

Here, the definition of secondary use is adapted from the described in the Beyond One Million Genomes (B1MG, 2020) project recommendations documents, which is "*the processing of* –rare diseases patients/families– (personal, clinical, and genomic) *data by users for* different purposes to those that originally were pursued, including *research, healthcare and policy development. The assumption is that data has been collected in a healthcare or research context or is part of a genomic initiative in the country*".

Ethical Aspects to be Considered (see Table 8.1)

In a global and digitalized world, the access to personal and health data by third parties must be carefully regulated, to avoid the vulnerating of individual rights (Alfonso Farnós & Alcalde Bezhold, 2020). In Europe, the legal general context of them has been addressed by the General Data Protection Regulation (GDPR), with several national implementations. Therefore, the requirements regarding the legal basis for processing health and genetic data for primary and secondary uses vary from country to country in Europe, as well as out of Europe, as Health Insurance Portability and Accountability Act in United States of America (HIPAA), and others. Several of the basis for its legitimation are also supported by ethical principles (Beauchamp & Childress, 1979), *as consent, public interest, and legitimate interest.* Here we only will refer to the ethical aspects as a complementary view to the essential legal issues, that although should be considered, are out of the scope of this chapter.

RDs involve vulnerable and sometimes easily identifiable people, but at the same time, their rarity makes it imperative to collect data from around the world, for research and to find a diagnosis and therapeutic solutions for them. Thus, what framework is ethically appropriate to allow the secondary use of your data in future research (SUfR)? What are the bases for it? What kind of safeguards or measures should be taken to this end? Some of the moral issues to consider in relation to the SUfR on rare diseases are described below.

Table 8.1 Secondary use of data for rare disease research. Values to consider

Patient needs	Improve the diagnosis and general treatment of these conditions
	Improve individual clinical care
	Establish collaborative networks for educational and social purposes
Scientific research	Reduce costs and research time
	Promote the acquisition of new scientific information and its validation (identification of new genes and mechanisms that cause diseases, comorbidities, healthcare needs, natural history, new drugs and therapies)
	Facilitate patient recruitment (eg, clinical trials) and cohort collections
Public interest, public health, social needs	Reduce healthcare costs (speed up diagnosis and improve prevention)
	Implement more adequate health policies (more precise and personalized clinical care)
	Facilitate detection and prevention programs tailored to the exact needs of patients
	Carry out clinical and public health research
	Facilitate educational and social programs
	Promote social values such as altruism, solidarity and citizenship
The rights of the participants and their families	Autonomy
	Privacy
	Proper balance between risks and benefits

Patients' Needs

Patients with RDs suffer from the delay in diagnosis, which is "unacceptably long in many cases and susceptible to improvement", as has recently been shown (Chazal & Aymé, 2021). Therefore, organizational changes in health care must be implemented, along with specific investigation programs for undiagnosed cases, to shorten this odyssey of diagnosis and the long journey currently. In addition, it has been estimated that treatments are currently available for less than 6% of DR diseases, and regulatory agencies around the world approve fewer than 50 new therapies per year. This scenario is far from meeting the needs of these patients (Hivert et al., 2021).

Therefore, in 2017, the International Rare Diseases Research Consortium (IRDiRC) established three main research goals, for the research of RD within the 10 following years (Table 8.2), to improve diagnosis and treatment of the RD patients and to develop tools for monitoring the impact of those measures (The IRDiRC 2021, https://irdirc.org/about-us/vision-goals/). To those ends, some efforts have to be made, first, from basic research field, to identify new molecular pathways related with etiopathogenic mechanisms, and drug repurposing and searching; and second, from epidemiological and clinical research, by establishing well-studied cohorts of patients for prospective and retrospective observational studies –on natural history and genotype-phenotype correlations–, as well as to conduct clinical trials.

Given the low frequency of these conditions, the creation of cohorts of RD cases and the establishment of well-coordinated scientific and clinical collaborations are crucial for the success of this type of research; therefore, sharing clinical and genomic data among the scientific community is a cornerstone of this research. In fact, this was specifically addressed by the Scientific Therapies Committee (TSC) of the IRDiRC, in a recent analysis of strategies to accelerate the achievement of Goal 2 (availability of treatments for patients with RDs). In its Strategic Theme 3: Data collection in health practice, TSC emphasizes the needs of (namely) "*data sharing, and use and reuse of data, in particular in healthcare practice for real-world evidence generation in RDs*" (Hivert et al., 2021).

The low intrinsic prevalence of RDs makes the SUfR of patient's data necessary to allow research aimed at improving the diagnosis and treatment of these

Table 8.2 IRDiRC goals for the 2017–2027

Goal 1	All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline
Goal 2	1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options
Goal 3	Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients

conditions. On the other hand, in individual cases of RD, being able to access pseudonymised data from other cases that have the same RD could improve the clinical care of this case by exchanging information with other clinicians, patients and relatives, and establishing collaborative networks for educational and social purposes.

Scientific Research

Many fields of scientific knowledge about RD will be enhanced by accessing more data and mega-data. Although it could be achieved through individual experimental effort, performing secondary analyzes on the same data reduces research costs and time (Safran et al., 2007; Geissbuhler et al., 2013). On the contrary, data collection and analysis would become longer and more expensive (The Danish Council of Ethics, 2015), as new data sets would have to be created each time a new goal emerges.

SUfR also encourages the acquisition of new scientific information and its validation, such as the identification of new disease-causing genes and the characterization of new pathways and circuits. On the other hand, artificial intelligence applied to these data could eventually discover other new relevant aspects of rare diseases such as comorbidities, care needs, natural history, new drugs, and therapies (Decherchi et al., 2021). Ultimately, SUfR will make the convening of patients (e.g., clinical trials) and cohort collections feasible (Tartaglia & Dallapiccola on behalf of the WG8 Experts, 2021).

Public Interest

Through SUfR, the clinical and genomic data of patients with RD will speed up diagnosis and improve prevention, with appropriate genetic counseling, reducing healthcare costs. Several aspects related to a more precise and personalized clinical care (patient stratification), such as studies on genotype-phenotype correlations and the natural history of RD, are also relevant to save costs and implement more appropriate health policies.

Large epidemiological studies on prevalence and incidence will be possible in the real world, thus facilitating screening and prevention programs tailored to the exact needs of patients, and to carry out clinical and public health research (Martani et al., 2019).

The same study results could eventually be used for educational and social programs to cover other relevant aspects in the lives of patients with RDs. On the other hand, it must allow the DR SUfR data to promote social values such as altruism, solidarity and citizenship (Nuffield Council on Bioethics, 2015).

The Rights of the Participants and Their Relatives

Although this point is developed last, when giving access to their SUfR, the rights of patients affected by RDs should be considered first. These are the aspects of autonomy, privacy, and risk/benefit balance of the participants.

Regarding autonomy, consent is not either a mandatory legal basis (since there are others) nor an appropriate one, to legitimate secondary use in Europe (The General Data Protection Regulation GDPR, Art. 6, 2016); 1+Millon Genomes Initiative (1MG) and, according to a recent World Health Organization (WHO) publication (2015), in the case of data processing for public health and research, certain limitations on the rights of data subjects may apply. However, any ethical legitimation must contemplate a process of information to the participants, including publicity and transparency. Therefore, the informed consent (IC) process, as far as possible or convenient, could also be considered from an ethical perspective, although not a legal one. According to the European Data Protection Supervisor (EDPS, Preliminary Opinion 8/2020), consent serves not only as a possible legal basis for the activity but as "*an additional safeguard, giving more control and options to the research participants, thus maintaining the society's confidence in science*". The policy of including information on possible SUfRs later, at the beginning of any type of research or genomic diagnostic process, and requesting consent to do so, could be a consistent measure, in this sense, to reinforce ethics.

In addition, privacy must be protected. Given the nature of genomic data, privacy could affect not only the participants but also their family members. The relevant aspects related to privacy in SUfR of the RD patients are the purpose of access to the data, the identity of the people or organizations that will access the data, what data and how it will be reused (minimum, aggregated, etc.) and re-analyzed (federated), and what will be (if any) the barriers to data exchange. Therefore, it is necessary to strike the right balance between the potential benefits of SUfR and efficient safeguards to protect personal health data, both genetic and non-genetic (Jensen et al., 2012).

According to WHO (2015), "*if possible, personal data should be aggregated or anonymized at source and be kept separate, ideally in physically separated IT systems*. In this context, this separation could include codification, pseudonymization, a complete or irreversible anonymization. There are different measures to protect privacy on data sharing. Pseudonymization has been defined (The General Data Protection Regulation (GDPR); art 3, 2016) as '*the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person*". Consequently, pseudonymization allows the SUfR of data, without access to the identity of the participants by new users or data controllers, but, contrary to anonymization, it allows to return to the individual data subject, in

case it may be necessary, for their benefit. Using or not using this particular measure, all responsible persons involved in data protection (researchers, research ethics committees, regulators and authorities) must ensure that all the necessary technical and organizational measures are implemented to protect the privacy of data. participants.

Finally, the appropriate risk/benefit balance for SUfR participants must be ensured. It is important to analyze the risks and benefits associated with the primary use of data from those related to SUfR. Furthermore, they must be carefully explained to the participants. A summary of the possible benefits and risks, modified from the B1MG project, is shown in Table 8.3.

The Ethically Relevant Aspects. Suggestions on How to Address Them

Although this analysis is not exclusive or complete, we have identified at least three relevant aspects such as data confidentiality/privacy, voluntary participation in research, and information to participants about the research and its results. Throughout this part of the chapter, we suggest some solutions to approach them ethically, such as some privacy safeguards and measures.

IC has also been considered a relevant tool, if not the only one, for the exercise of the autonomy of the participants. The characteristics of the IC, in the context of SUfR, must be freely given, informed, unambiguous and specific, and be possible to withdraw it by the interested party, unless it is not technically possible (total anonymization) or there is another established basis that requires continuous processing. While maintaining specificity, broader consent (for the purposes of research areas) and other innovative forms of consent for research, such as dynamic and tiered consent, are considered new approaches to apply for SUfR of RDs.

Finally, it is necessary to develop robust governance frameworks and a transparency policy that includes public information about the different research projects in RDs that are subsequently carried out with the data, and how the participants could eventually know their global results and (if any) individual. In the latter context, it is very appropriate to facilitate the exchange between the clinical and research framework, since a long follow-up of these RDs participants is expected in this context.

As a general conclusion of this section, the new scenario of availability of a large amount of personal, demographic, health, and genomic data, together with the use of artificial intelligence, is an opportunity to develop efficient and accurate research in the field of RDs. However, secondary uses of these data for new research also pose new ethical challenges. Justice, beneficence, transparency, and respect for people are crucial for a responsible approach to persons.

Undiagnosed Disease: Between Medical Effort, Research And Clinical Ethics

The diagnostic process is one of the most important tasks of the physician (Oski, 1990; Rozman & Cardellach López, 2020). Diagnosis is essential not only to face the clinical and biological management of the disease and its vital process in the patient, but also for those ethical problems that may arise in the course of such a process (Gracia Guillén, 2020). In the process of diagnosis, the doctor performs a cognitive act (Laín Entralgo, 1986) in which, as a human being, he can be right, wrong or not reach a definitive solution despite the efforts made. One of the reasons why a patient is undiagnosed may be due to an error or lack of perseverance in the search for it. The Institute of Medicine of the United States has recognized that there is a need to reorient diagnostic error as a "moral, professional and public health imperative" (Institute of Medicine, 2015), which requires an additional effort to improve our capacities to diagnose and offer greater patient safety (Singh & Graber, 2015). However, a diagnostic error should not be confused with an undiagnosed disease. This medical category is considered when the diagnosis is not reached after a reasonable, relatively exhaustive effort, taking into account the state of the art of medical knowledge. Both situations are similar in that both require active change to achieve the patient's diagnosis. Transforming a diagnostic error into a diagnosis of certainty is a professional and moral duty that corrects an anomalous situation. The diagnosis of an undiagnosed patient is a cognitive act associated with a scientific and technological effort that often requires teamwork. In this case, the professional and moral duty does not lie in correcting an error that could have been avoidable, but in considering the additional diagnostic effort as a health value in itself.

Classifying or considering a disease as undiagnosed is challenging (Gahl et al., 2012, 2016). What criteria can we have in applying such a consideration? The temporal criterion is imperfect because the symptoms can be maintained over time without major changes that can be indicative. The perpetuation of a nonspecific semiology can lead to an evaluation process that is too long with the cost of proper management and delay in treatment. To this must be added the emotional cost of the patient and the family. It is therefore important to speed up the diagnostic evaluation and reduce the times of action. Complexity is also an imperfect criterion, because many undiagnosed diseases can be restricted to one or a few symptoms or to the affectation of an organ, at a certain moment of the evolutionary process, while others show a multisystemic affectation and require an approach from different medical specialties. Each patient has their own vital development and how they suffer from a disease is an individual process: the diagnosis of undiagnosed disease requires the application of more than one criterion and the rational indication of diagnostic procedures, from assessing the passage of time well and the natural evolution of the disease to the progressive use of complementary methods, ranging from the most basic to the most aggressive, even invasive when considered appropriate. The diagnostic effort must extend beyond the immediate, but it must be done in clinical terms and within reasonable time limits.

Many patients go through a long process to reach the diagnosis of the disease they suffer, that is, a diagnostic odyssey. Throughout the process, patients are assisted by many doctors, specialists and even subspecialists in referral centers, sometimes for years. For the odyssey to end, one must understand the path taken. The factors that influence the evaluation and management of an undiagnosed disease concern the idiosyncrasy of the disease itself in pathophysiological terms, its variability in its clinical expression and natural history, its chronobiology, and ultimately the primary cause; these would be objective factors. Nevertheless, it is necessary to take into account subjective factors, those that concern the individuals who participate in the process of knowing what is happening to the sick person; we return to the patient and the doctor and the interaction they establish. The delay in diagnosis has a multifactorial genesis. Kliegman et al. (Kliegman et al., 2017) address this delay in two broad categories, one inherent to the disease process itself, and the other related to the difficulties of the assessment process itself. These latter difficulties can be broken down into three basic elements, those specific to the patient, those specific to the physician, and those related to the various modalities and diagnostic tests. In this sense, it is important to determine what the primary problem is in order to be able to influence effectively within the framework of the healthcare structures of the health system.

Faced with a situation of non-diagnosis, it is important to take into account the ethical need in medical practice to seek and offer the patient a diagnosis that allows progress in the correct clinical and therapeutic management of the disease, in its both organic and mental aspects and social. The correct, definitive diagnosis affects the person's way of life and her family environment. On the contrary, the absence of such a diagnosis generates uncertainty, which has consequences that affect the person's life project and entail a psychological, social and economic cost. Before the patient we are in a situation in which decisions must be made. Is it possible, then, that a patient does not have a diagnosis of his/her disorder? How far to take the 'diagnostic effort' when pertinent evaluations have been carried out based on established medical knowledge and technological availability, such as, for example, genome analysis? Is research on new biomarkers and biological or image analysis techniques part of the diagnostic process?

It would seem that, in terms of beneficence, non-maleficence and justice, giving continuity to the diagnostic effort is a moral value and an ethical attitude, always respecting the principle of autonomy of the patient or their guardians. However, when faced with a patient with a clinical picture for which there is no scientific knowledge, not even due to similarity with other known entities, what can the doctor do? And, above all, what can be done from the health system? In the absence of evidence, the system cannot offer a structured answer, and, in this case, the physician would not be obliged to persist. In this situation, the lack of diagnosis would not generate an 'ethically bad act'. However, we think that there is an option, which requires an organized response. The structure of the health system can be oriented towards offering a solution that gives continuity to the diagnostic effort, taking into account not only human, moral and social criteria, but also economic ones (Palau, 2017).

From a practical point of view, it is possible that "we cannot go any further" and we are facing an apparent diagnostic impasse. However, it is also possible to consider the attitude of scientific and multidisciplinary to approach the diagnosis of a specific patient without diagnosis. Although using a negative formula, this is where the situation of not having a diagnosis can be elevated to the category of clinical process of 'undiagnosed disease' in the framework of modern medicine based on two well-established points: (i) the scientific approach to the knowledge of the disease and its pathophysiology in biological terms, and (ii) the availability of a structure and human and material resources in the health system. The conjunction of both aspects, the scientific-technical and the structural, offers the opportunity to improve our diagnostic capacity and focus on the care level, both clinical and ethical, the patient without diagnosis or, in other words, undiagnosed diseases. From the point of view that the diagnosis in a decision-making process based on established knowledge, the scientific approach in each patient would not be part of the diagnostic effort. However, in a translational model, approaching science to clinical practice, it could be considered to take into account the incorporation of experimental and functional studies in the laboratory as part of the diagnostic process (Pijuan et al., 2021). On the other hand, in the effort to reach the diagnosis at the end of the odyssey and focus on the medical problem raised, counseling is necessary that facilitates informed decision-making and clearly establishes realistic expectations for the possible consequences (Basel & McCarrier, 2017).

Be that as it may, the implementation of a program on undiagnosed diseases in an institutional framework, such as a university medical center of reference, is an effort at all levels of health care (and social), but also a necessity and a moral duty. In modern medicine, diagnosis continues to be a fundamental act in the future of clinical practice that affects the doctor and the entire healthcare staff, but it is also a process in which the patient, their parents or guardians, their family, participate, in an integrated, proactive and responsible way. The diagnostic effort then becomes a moral, ethically good act, which can be given scientific, technological and social support so that the sick person benefits from it. Even more relevant is when behind there is someone who suffers from a rare disease (or an atypical or rare form of a common disease) that cannot be left in the category of undiagnosed disease.

Therapies, Between Policies and Therapeutic Research

In the field of research aimed at treating patients with RD, two essential aspects can be distinguished for the individual with a certain disease and for the group of patients affected by such a disease and their relatives. In the first place, the reasons for researching and developing new therapies based on whether they are going to be financed by health systems and health insurance. Second, what is the applied scientific knowledge that academic scientists, and the pharmaceutical and biotechnology industry are interested in?

It is very important to define the point of view from which the question of research and investment in treatments and new therapies is viewed. RDs give us a name for a very broad set of disorders that condition people's lives. These diseases are recognized as such due to their low prevalence, but this criterion, although necessary for their recognition, may not be sufficient to consider that they have legislative benefits in relation to therapies and treatments that common diseases do not have, especially in developed countries. These legislative developments are aimed at the special recognition of drugs heading for treating RDs, which we know as orphan drugs.

Policies and Regulations of RD Treatments

In Europe, the United States, and other countries, RDs benefit from orphan drug policies. The regulations of these countries indicate that the fundamental factors used to designate orphan drugs are the prevalence, severity and the existence of alternative therapies (Gammie et al., 2015). However, from an ethical perspective, rarity is being questioned as a moral reason to actively promote the financing of RD treatment and research on therapies directed at these diseases, proposing that moral principles can confirm that this is fair or not (Juth, 2017).

In a recent article, Magalhaes discusses the moral reasons that support prevalence as a criterion for investment and development of therapies (Magalhaes, 2021). To the low prevalence, this author contrasts the severity of the disease as a criterion for making decisions about where to guide policies and investment in health. In her argumentation, she discards potential moral reasons to value rarity, such as the rescue rule (Rosselli et al., 2012; Rodriguez-Monguío et al., 2017), the priority of the identified victims, and personal responsibility. The rescue rule assumes that it is imperative to save those people who are in immediate danger or harm. However, if this is the reason for applying the rule to a case, it is not a valid criterion as it does not differentiate between rare and common diseases. The fact that we feel identified with victims or people affected by a rare disease and that doctors and health professionals must act in the best interest of their patients is not a sufficient criterion either. This attitude contrasts with the obligations of population-level policymakers who must be oriented to treat each citizen or member of the population in an equal way. On the other hand, the argument that patients are not responsible for the disease they suffer as a criterion for making rare diseases an exception to the equal claims view (Magalhaes, 2021) would not be a sufficient reason to take into account in policies about financing of treatments. Also, according to Magalhaes, personal responsibility, by itself, does not distinguish between rare diseases and common diseases since both types of disorders depend on factors independent of the people who suffer from them. In terms of recommendations and actions on prioritization policies, Magalhaes proposes that the health-loss criterion issued by the third Norwegian Committee on Priority Setting in the Health Sector (Ottersen et al., 2016) as equivalent to the severity criterion, be a greater criterion for assign greater

priority to diseases that cause greater loss of heathy life-years compared with a life expectancy of 80 healthy life-years (Table 8.3).

Faced with the view about the moral value of prevalence versus severity, it is possible to oppose the medical criterion, understood as one that takes into account the factors that influence the way of falling ill and offering a response of cure or improvement to the patient. These factors include causality, lifetime and the biography of the individual, and the natural history of the disease, often chronic in nature, but with moments of exacerbation, and often affect several organs and physiological systems (Berman, 2014). Although prevalence is the first criterion to take into account, the definition of RD includes other aspects that affect the life and way of falling ill of affected people (Palau, 2010, 2012). RD is also characterized by chronicity, disability, and the feeling of being alone (believing that there are no other people with the same problem, and it will take time after accepting the diagnosis to interact with patient associations). Furthermore, the high probability that the primary cause is genetic (Nguengang Wakap et al., 2020) carries a risk of recurrence and that it may appear in another member of the family.

Prevalence is not only an epidemiological data, which differentiates RD from common diseases -although as an arbitrary criterion-, but a factor that combines under the concept of rarity a high number of diseases in which underlying causes and several pathophysiological processes. In a significant number of patients, we can consider the triad of rarity, age of onset and severity. It must be taken into account that the majority of RD are ultra-rare, with a prevalence below 1 in 50,000 inhabitants, which makes the affected people, who are dispersed in geography, feel helpless in society and in the face of health services. It is also relevant to take into account the fact that many of them begin in childhood, at some point in human

Table 8.3 Possible benefits and risks of secondary uses of data for research on rare diseases

Benefits	1. Scientific progress
	(a) General knowledge, advance in RD understanding
	(b) Specific: prevention, diagnosis and/or treatment of people with a similar RD condition
	2. Commercial products such as drugs or algorithms (no participants monetary rights in these products)
Risks	3. Psychological harm (type and amount of personal data processed and shared)
	4. Safety risks if data are misused or misinterpreted
	5. Handling of results and incidental findings that have implications for the health of participants and/or their families, including capacity limits of health care systems to provide adequate follow-up care
	6. Risk of privacy breaches
	(a) Sharing data with researchers from other institutions
	(b) Risk of being re-identified from genomic and related health information, (although technically difficult today, it still remains)
	7. Unanticipated forms of research on genomic data that may turn out to be controversial

Modified from B1MG project

development during the pediatric age, from birth to adolescence and young adulthood. This leads to the person suffering from the disease throughout a very long period of his/her life, which may affect the entire biography, regardless of the prognosis he/she may have. These two factors, on the other hand, are usually associated with the fact that they are severe, chronic diseases and with periods of exacerbation in many cases. It is not so much to contrast rarity versus severity, but to contemplate how the low prevalence mostly represents a group of people who need specific actions so as not to be isolated and diluted in the much broader set of common diseases, although these can also be serious. From a principles-based ethics approach, it can be considered that RDs can be devoted to special treatment, since the principle of justice and equal claims view are not affected. On the contrary, the high coincidence between rarity and severity means that patients affected by a RD can have benefits in terms of health systems policies without compromising the equity of citizens and the principle of justice. Nor would the health-loss criterion be affected in a striking way since many of the patients with RD begin in childhood and have a vital prognosis that is below the healthy-life considered of 80 years. Progress towards that age, still distant, is given for some diseases due to the promotion of research in new treatments, such as those that have been approved in recent years for cystic fibrosis (Middleton et al., 2019), which together with lung transplantation, have modified the life-expectancy of these patients.

Research in the Treatment of RDs

In the moral assessment of treatment in RDs, equity and opportunity cost must be compared. It is important to seek a balance between approaches that can be opposed such as the utilitarian approach, equity in access to treatment, the imperative of treating patients without taking into account the economic cost and the desire to advance knowledge as a basis for new therapies (Taylor et al., 2018). From a utilitarian perspective, the allocation of resources to research in the field of therapeutics can lead to contradictory ethical conclusions. The costs of developing a new drug vary widely and investing funds in orphan drug research can be considered unfair and unethical with respect to investing in diseases that are more prevalent in the population (Gericke et al., 2005; Hews-Girard et al., 2020). However, this utilitarian approach contrasts with the moral principles of justice and beneficence for each person, regardless of the frequency of the illness they suffer.

It has been estimated that only around 6% of RDs have treatment (World Health Organization, 2015; Zamora et al., 2019), which contrasts with the situation of common diseases. As individuals and autonomous citizens, RD sufferers have the same right to effective treatment (EURORDIS, 2017). This raises whether it is moral to promote and facilitate special actions in the field of RD therapeutics compared to the needs of new therapies for unresolved problems of common diseases, emerging diseases, such as the SARS-CoV2 pandemic and COVID-19 (World Health Organization, 2021) and mRNA vaccines (Centers for Disease Control and

Prevention, 2021) or neglected diseases that are common in developing countries (Barrenho et al., 2019), such as malaria in sub-Saharan Africa and other geographic areas. Specific efforts must be oriented towards two scenarios, basic research and clinical trials, which allow the development of safe and effective drugs. Recent examples of fundamental therapeutic research are the new pharmacological therapies for cystic fibrosis (Middleton et al., 2019), molecular (eg, antisense oligonucleotides) (Finkel et al., 2017; Mercuri et al., 2018) and gene therapies (Mendell et al., 2017) for spinal muscular atrophy or CAR-T cell-based immunotherapy for drug-resistant leukemias and lymphomas (NIH National Cancer Institute, 2021). The translation of the discovery of a new orphan drug -those designated for the treatment of RD- to clinical practice requires rigorous clinical research that demonstrates its safety and efficacy (Dal-Ré, 2016). At this point, on many occasions a conflict arises between patients, who claim to have drugs as soon as possible and the need to evaluate them with scientific criteria. In the interests of their support, medicines agencies are more flexible with orphan drugs. However, this does not mean that there are no specific requirements, such as that the drug is indicated for an unmet need and that, in addition, efficacy has been demonstrated against the main variable of the clinical trial design and that it is clinically relevant (Putzeist et al., 2012). But, on the other hand, in the case of RDs the number of target patients (and available after informed and correct acceptance) is small, and, nevertheless, the requirement for a rigorous scientific evaluation should be the same as for controlled and randomized clinical trials in parallel groups that make it possible to measure the efficacy of the treatment and the indication or not to incorporate the orphan drug into clinical practice. This is where the ethical dilemma arises about how to act in the therapeutic research of RDs. Two aspects can be distinguished, the scientific approach and the funding of research.

In relation to research projects, is it possible to accept greater flexibility in accepting the results of a therapeutic trial or is it necessary to develop alternatives to controlled and randomized clinical trials? In order to achieve proven results that can serve the majority of patients with the same rare disease (principle of beneficence), the efficacy of the drug must be investigated under scientific criteria. In recent years, some alternative solutions adapted to a low number of participants have been proposed (Gagne et al., 2014; Dal-Ré, 2016). The objectives of the experimental designs are to either (i) minimize the number of trial participants, but obtain a sufficient number of data, or (ii) maximize the number of cases treated, ensuring that all participants receive the experimental orphan drug, and using the crossover trial in which the participant receives the experimental therapy and the control therapy (eg, placebo) or no treatment in an alternating way. One of the designs that is demanding attention for ultra-rare disease research is the n-of-1 clinical trial (Lillie et al., 2011). Recently, approaches have been published aimed at investigating, developing a new drug and treating a patient affected by a rare genetic disease (Kim et al., 2019). These investigations and n-of-1 situations raise questions of a scientific nature such as the scientific evidence that needs to be determined before exposing a person -often a child (Kreeftmeijer-Vegter et al., 2014)- to a new drug, such as the safety of the drug, dose, route of administration and treatment regimen, or the

urgency of the patient's clinical condition (Woodcock & Marks, 2019). But this new drug-discovery paradigm also raises many ethical and societal issues. As these are therapies designed for a patient, it will be necessary for them and their families to become collaborators of the project and aspects such as "stopping criteria" should be considered before the start of treatment, if possible with the help of an ethicist. Another question that needs to be considered is how to proceed if the intervention appears to be useful and can be applied to other patients affected by the same gene, and if a new clinical trial has to be designed for this purpose (Woodcock & Marks, 2019). In the event that such personalized treatments increase, some with good results, regulatory aspects will also be relevant, as well as their sustainability and financing (Artsma-Rus, 2021).

One concern, which again raises ethical questions, is the financing of clinical trials in rare diseases, especially in ultra-rare disorders with few patients and dispersed in geography. Sustained funding from the industry cannot be expected for many of them, nor is it easy to develop projects with academic and non-commercial funding. One approach that has also been developing in recent times is that of participant-funded clinical trials. There are several models of self-funded clinical research (Dal-Ré et al., 2020; King & Ballantyne, 2019), such as 'pay to try' and 'pay to play/participate', and the 'plutocratic proposal', still a theoretical model, which has been recently proposed and is based on the donor is offered the possibility –although not a guarantee– of participating in a clinical trial, a possibility that can be transferred to a third party (Masters & Nutt, 2017). Many of these models are financed through crowdfunding projects, which raises the immediate question of whether it is ethically acceptable for research and therapeutic advancement of ultra-rare diseases, including n-of-1 therapies, to be based on the effort of patients and families and of the researchers involved.

Genome Analysis in Newborn Screening

The screening of newborns constitutes a public health action of the first magnitude in the field of secondary prevention of diseases of onset in the neonatal or infancy period of life. Newborn screening (NBS) programs allow early identification in asymptomatic newborns of various diseases, most of them genetically based. The diseases included are those that can be avoided, cured or improved since it is feasible to intervene to modify the course of the disease in a positive and significant way. Depending on the countries, states or regions, current neonatal screening programs vary in the number of diseases that are investigated. These disorders fall into the category of inherited metabolic (e.g., phenylketonuria), endocrinologic (e.g., congenital hypothyroidism), and hematologic (e.g., sickle cell disease) diseases in which the biomarker used for screening is a gene product, either a metabolite, a hormone, or a protein. The inclusion of diseases takes into account the classic principles of Wilson and Jungner (1968) who first introduced decision criteria and good practices in neonatal screening (Table 8.4). These principles have been considered

Table 8.4 Revision of the Wison and Jungner criteria

Synthesis of emerging screening criteria proposed over the past 40 years (1968–2008)
The screening program should respond to a recognized need.
The objectives of screening should be defined at the outset.
There should be a defined target population.
There should be scientific evidence of screening program effectiveness.
The program should integrate education, testing, clinical services, and program management.
There should be quality assurance, with mechanisms to minimize potential risks of screening.
The program should ensure informed choice, confidentiality, and respect for autonomy.
The program should promote equity and access to screening for the entire target population.
Program evaluation should be planned from the outset.
The overall benefits of screening should outweigh the harm.

the gold standard but there have been adaptations (Andermann et al., 2008). However, many of the rare genetic diseases do not have a specific biomarker that can be used in a screening program. On the other hand, the number of 'actionable' diseases, that is, in which an early intervention at birth or early childhood can modify the prognosis and therapeutic action, is increasing (Palau, 2021).

Genetic analysis of specific disorders is already being investigated for its implementation as a biomarker in NBS programs due to the availability of new treatments that can modify the course of the disease. This is the case of spinal muscular atrophy because of the new molecular treatments based on antisense oligonuleotides (Vill et al., 2021). On the other hand, exome or genome analysis by next-generation sequencing technologies allows defining biomarkers based on recognition of genetic variants for a large number of disease-causing genes (Berg et al., 2017). In this sense, a series of projects have been started, among which the BabySeq project stands out (Holm et al., 2018). There are already results that inform about the interpretation of genomic findings (Ceyhan-Birsoy et al., 2019), about the benefits, risks and usefulness of genomic sequencing in newborns (Pereira et al., 2019), the interest of parents in participating in these projects (Genetti et al., 2019) or the feedback of the findings (Holm et al., 2019).

In a progressive way, the methodology applied in screening is including genetic or genomic techniques, but these approaches raise ethical-legal reflections (Johnston et al., 2018). Among the areas to take into account and on which to reflect are selection of genes and diseases to be studied, overdiagnosis or overtreatment, information management and informed consent, data confidentiality and protection, justice and legal regulation (Esquerda et al., 2021). Other issues are the process of delivery of the results to parents, the aspects derived from its implementation in the healthcare systems, and the general and specific ethical framework that contemplates the moral principles to be preserved (Ayuso, 2021).

Among the ethical challenges, the possibility of making predictive diagnoses of late-onset diseases (in adulthood) stands out. Only those diseases whose prevention or treatment depends on early intervention in childhood should be included in the

Table 8.5 Factors to be considered in newborn genetic screening

Adequate study design	Establishment of technical and human resources	Clinical aspects	Review over time
Selection of patients Informed consent Criteria for reporting: – Type of variants – Genotypes and genetic status (affected, predictive, carrier) – Definition of pathologies/ genes (severe, actionable, age of onset)	Process quality analysis and interpretation (centers and professionals): Confirmation of results Deadlines for reporting	Genetic counseling and reporting Clinical monitoring and access to data by clinicians and relatives	Access to data in the mature age of the minor New genes, new diseases (according to the possibility of being actionable)

screening, avoiding violating the autonomy of minors when making predictive diagnoses without benefit for the newborn and with the consequent damage on their future freedom to choose know them or not. Another risk is the detection of genetic variants whose clinical impact is doubtful or unknown. Thus, screening should avoid as far as possible identifying or reporting doubtful results. Finally, it is convenient to foresee the possibility that the child, once reached maturity, can have access and receive the genetic information that concerns him. Table 8.5 shows proposed factors to consider implementing neonatal genetic screening (Goldenberg et al., 2019).

To conclude, it is currently feasible and somewhat advisable to include the genome analysis as a set of biomarkers and NGS techniques in NBS as they can provide higher quality information and benefit the health of the participants by being able to intervene early and effectively on certain diseases. For this, it is necessary to comply with certain ethical premises that affect both the design and protocol of the study, as well as the informed consent, the clinical processes and the monitoring and evaluation of the results (Ayuso, 2021).

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Chapter 9
Limits of Debate: Governance of Human Embryo Research and the Making of the Fourteen-Day Rule

J. Benjamin Hurlbut

Abstract This chapter focuses on a limit that was defined in the early days of IVF and which for nearly four decades was widely affirmed and adopted. This is the so called fourteen-day rule. It designates that human embryos should not be cultured in vitro beyond fourteen days of development. The fourteen-day rule has long been offered as an assurance that scientific horizons are subject to ethical limits. Over the course of several decades, it has also become a matter for relatively widespread consensus. Although there remains significant disagreement about whether instrumental use of human embryos for research can ever be acceptable and about what sort of limits, temporal or otherwise, it ought to be subject to, the fourteen-day rule has long formed a centerpiece of policies in numerous countries that affirm ethical concerns while also allowing room for research by marking fourteen days as a definitive limit.

Keywords Fourteen-day rule · In vitro fertilization (IVF) · Research on human embryos · Fourteen-day rule · Governance of scientific research

Introduction

Forty-four years ago in the spring of 1978, embryologist Robert Edwards and obstetrician Patrick Steptoe were closely watching a developing pregnancy in the United Kingdom. They were anticipating a birth that they knew would make headlines worldwide. When Louis Brown, the first "test tube baby" finally arrived, it felt simultaneously like a radical break with the natural order of human procreation and of a continuity with it. The scene of the babe in her mother's arms broadcast the world over was as familiarly and universally human as they come. Yet this birth also

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heralded a profound transformation in human life, a technological displacement of conception out the dark interior of the body onto the illuminated surface of the laboratory bench.

More than forty years have passed, and the procedure that Edwards and Steptoe pioneered has been the means for millions more moments of this sort, making parents of many. It has also allowed unprecedented access to a previously hidden phase of life, rendering human embryos accessible for manipulation and, in some jurisdictions, routinely available as an experimental resource for studying the earliest stages of development.

From its inception, in vitro fertilization (IVF) was accompanied by ethical and policy uncertainties about whether and under what circumstances human embryos could be used experimentally. This question has long been—and remains—a subject of significant ethical and political controversy. To be sure, it touches upon deep and challenging questions: of how society should relate to developing human life in the laboratory, of what potential to advance scientific knowledge or human health warrant its instrumental use, and of what limits to research must be set in the name of respecting and protecting human integrity and dignity.

More than forty years later, these questions remain live as ever, even as limits have been established in many countries. In recent years they have re-emerged in novel forms as new techniques have led researchers to want to use human embryos in new ways. They were at the center of the debates over embryonic stem cell research in the 2000's (Hurlbut, 2017), and they are intensifying today with developments like the creation of human embryos for research on germline genome editing (Hurlbut, 2020), with techniques that allow embryos to be cultured *ex vivo* longer than ever before, and with the advent of synthetically produced embryo-like entities and embryonic human-animal chimera (Jasanoff, 2019; Lovell-Badge et al., 2021).

From the inception of IVF, there were significant ethical disagreements about the permissibility of research on human embryos. Yet there was also almost universal agreement that there had to be limits, and that, for purposes of policy and governance, those limits had to be well-defined. The question was where those limits should be drawn, and how. In many jurisdictions those limits came to be codified in law, ranging from complete prohibition of experimental use of human embryos to allowing certain forms of research up to fourteen days of development. Four and a half decades after Edwards and Steptoe's headline-grabbing achievement, scientific research is bumping up against long-established limits and pushing for their dissolution.

This chapter focuses on a limit that was defined in the early days of IVF and which for nearly four decades was widely affirmed and adopted. This is the so called fourteen-day rule. It designates that human embryos should not be cultured in vitro beyond fourteen days of development. The fourteen-day rule has long been offered as an assurance that scientific horizons are subject to ethical limits. Over the course of several decades, it has also become a matter for relatively widespread consensus. Although there remains significant disagreement about whether instrumental use of human embryos for research can ever be acceptable and about what sort of limits, temporal or otherwise, it ought to be subject to, the fourteen-day rule

has long formed a centerpiece of policies in numerous countries that affirm ethical concerns while also allowing room for research by marking fourteen days as a definitive limit.

Despite the fact that there is significant variation internationally in the policies and politics surrounding human embryo research, the fourteen-day rule has been remarkable widely adopted. It is codified as law in over a dozen countries, and for decades was a centerpiece of the recommendations and rules of various professional societies and scientific organizations like the American Society for Reproductive Medicine (ASRM), the International Society for Stem Cell Research (ISSCR), and the US National Academy of Sciences (NAS) (American Fertility Society, 1986; Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council, 2005; International Society for Stem Cell Research (ISSCR), 2016). In the United States, there is no formal, federal law that governs human embryo research, only law that prohibits federal funding for it. Therefore, the ASRM, ISSCR and NAS guidelines have played an influential role in governance of non-federally funded research (Hurlbut, 2017).

In recent years, however, a shadow of doubt has been cast over this bright line. In the mid 2010s, Magdalena Zoenicka-Goetz, a developmental biologist then at Cambridge University developed a technique for culturing embryos significantly longer than had been possible before. In her first attempt to culture a human embryo using this technique, she ended the experiment only because she had reached day thirteen, roughly four days longer than had had previously be achieved, and disconcertingly close to the fourteen-day limit (Zernicka-Goetz & Highfield, 2020).

A chorus of scientists and ethicists responded to this newfound ability to potentially transgress the fourteen-day rule—the most consistently and widely adopted and well established limit to human embryo research in the world—with immediate calls to revise it (Hurlbut et al., 2017; Hyun et al., 2016; Reardon, 2016; Rossant, 2016). Subsequent advances in embryo culture techniques suggest that human embryos can be sustained in vitro beyond the fourteen-day mark—and potentially well beyond (Aguilera-Castrejon et al., 2021). In 2021, these technical advances led the International Society for Stem Cell Research to abandon the fourteen-day rule.

Importantly, this research on extended embryo culture marks the first time since the inception of IVF that the fourteen-day rule has materially restrained scientific practice. Prior to this point, the ethical limit had been enforced by the limits of culture techniques, which could only sustain a human embryo in vitro to about eight days of development. Thus, although the fourteen-day rule was foundational to the development of a whole field of scientific research because it allowed research to proceed by providing assurance to society that ethical limits would be respected, once science had caught up with the ethical (and, in numerous jurisdictions, black-letter legal) rule, prominent members of the scientific community declared the rule to be obsolete and inimical to scientific progress.

It is a remarkable notion that a rule should be abandoned simply because it becomes possible to transgress it. Yet this is the essence of the position that prominent scientific figures and organizations have taken on the fourteen-day rule. Regardless of what one thinks of the ethical merits of the rule itself, it has for

decades been one of the most explicit, definitive and widely-adopted ethical limits to a highly controversial area of scientific research. It was—and remains—a key pillar of the regulatory regime surrounding human embryo research in the UK, a regime that many UK citizens cite as an example of particularly effective and trustworthy governance (Jasanoff & Metzler, 2020).

Thus, what is at stake in abandoning the rule is not merely whether certain lines of research will be permitted, but also the prior commitments made by science to society to accept limits on research in deference to widespread ethical concerns, and further, the importance of establishing limits themselves in the democratic governance of science. As I argue below, the fourteen-day limit was significant not only because of the temporal marker, but because it was a limit—a bounding off of freedom of scientific inquiry in acknowledgement of and deference to public ethical concern.

My purpose in this chapter is not primarily to ask whether the rule is ethically well-justified, but to explore how that question has been asked and addressed—by whom, in what terms, and grounded in what forms of reasoning, certitude and authority. The history of the fourteen-day rule reveals some of these patterns and the ways they are re-emerging in the context of efforts to unwind it. In addition, most of the calls for abandoning the rule have been grounded in accounts of its development that purport to show that it was an unprincipled and provisional compromise intended to have a limited lifespan. Those accounts, designed to justify a partisan desire by recruiting voices from the past, have been repeated as if their story is beyond question. One of my aims here is to challenge those accounts (since they are incomplete and incorrect.)

But an additional aim is to surface certain key patterns in approaches to the governance of biotechnology that are evident in the development of the fourteen-day rule and in the efforts to dismantle it. I focus on the distinct (though somewhat intersecting) pathways of development of the fourteen-day rule in the U.S. and the U.K. Because the processes on both sides of the Atlantic arrived at the same place—a fourteen-day limit on in vitro embryo culture— they are usually lumped together. But the reasoning and processes that led to the rule differ in important respects (Hurlbut, 2017; Jasanoff, 2005). Those differences in process and reasoning are important because they reflect different background conceptions of appropriate bases for establishing ethical limits on science, and on the role of limits in settling (if not resolving) public ethical disagreement by drawing a bright line beyond where science pledges not to go while simultaneously acknowledging persistent ethical concerns.

A Natural(ized) Limit

The fourteen-day rule was first articulated in 1979 by the Ethics Advisory Board (EAB), a bioethics body that had been convened by the U.S. Department of Health, Education and Welfare (DHEW), which housed the National Institutes of Health.

(Department of Health, Education, and Welfare Ethics Advisory Board, 1979). The EAB was the first national bioethics body in the world to evaluate IVF. The EAB's report suggested a policy that "No embryo will be sustained in vitro beyond the stage normally associated with the completion of implantation (fourteen days after fertilization)." This relatively late addition to the report was added to provide an unambiguous limit. The Board chose fourteen days in deference to existing US federal regulations on fetal research that had been put on the books before the advent of IVF (Hurlbut, 2017).

In 1975, the National Commission issued recommendations for governance of "research on the fetus" (United States, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1975). The commission made no differentiation of ethical entitlements based on stage of development. However, when the DHEW promulgated regulations based on the Commission's recommendations, it defined the fetus as the conceptus from the time of *implantation* forward. When objections were raised, DHEW explained that the policy needed to be practicable. To protect the fetus against ethical violations in research it be possible to detect its presence. And because a pregnancy could only be detected from the time when implantation was complete, about fourteen days post-fertilization, the Department had adjusted the regulatory definition of "fetus" accordingly.[1]

Thus, when facing the need to draw a line, the board chose fourteen days in deference to the committee's view that research during the first several days of development was permissible. The board simply adopted fourteen days to cohere with the fetal research policy, intending to return to the question at a later time. The EAB's presumed that it was to be a standing committee and therefore would repeatedly revisit its own case-by-case judgements. However, it was disbanded about a year later and never reconstituted.

In 1984, the American Fertility Society (AFS, now the American Society for Reproductive Medicine) established an ethics committee to define ethical rules for the emerging (and essentially unregulated) IVF industry. The AFS committee took the ethics of human embryo research as one of main areas of focus. Like the EAB, it recommended that research use of human embryos should be limited to fourteen days (American Fertility Society, 1986). However, according to the committee, the EAB had set the right limit for the wrong reasons. The limit made sense, the committee argued, not primarily for ethical reasons, but for scientific ones.

The committee grounded its recommendations in an evaluation of what it referred to as the "biologic status" of the human embryo. It argued that a scientific recognition of a fundamental change in the nature of the embryo at fourteen days would necessarily lead to the ethical discernment that fourteen days was the right place to draw the line. For instance, the embryo will sometimes split into two, producing monozygotic twins. Thus, the committee argued, the embryo is not a true biological

[1] For the definitions of fetus and pregnancy in the regulations promulgated in response to the national commission recommendations, see 40 Fed Reg. 33,529 (August 8, 1975), 33,529. For a discussion of comments on the definitions, see 39 Fed. Reg 30,651 (August 23, 1974), 30,651 and 42 Fed Reg. 2792 (January 13, 1977), 2792.

individual until twinning is no longer possible after the formation of the primitive streak at fourteen days of development. Because persons are always necessarily individuals, the *philosophical* question of personhood (and, thus, the ethical question of what entitlements a person is due) simply *cannot* reasonably be raised before gastrulation, at least not in an ethical approach that that takes scientific facts into account (American Fertility Society, 1986).

The author of these sections of the AFS report was Clifford Gorbstein, a developmental biologist with an interest in science policy. Testifying before Congress in 1981, Grobstein offered what has become a familiar and common refrain about how public bioethical judgments should be made. Because facts are necessarily "common to all parties in a dispute," biological facts of the matter that preclude certain philosophical conclusions should be drawn upon to delimit ethical disagreement and circumscribe public debate. Where ethical notions are built on presumptions contradicted by science, those presumptions must give way. They may not satisfy "individuals committed to a religious view of the matter," but that, Grobstein observed, is not the purpose of policymaking (Quoted in Hurlbut, 2017, p. 84) In other words, public facts must be separated from private values, and the former should describe the limits of debate in processes of public bioethical judgment.

The AFS committee adopted this approach, arguing that gastrulation—the developmental marker that coincides with the completion of implantation at about fourteen days post-fertilization—was an objectively transformative developmental moment and, therefore a morally significant, biological bright line. In rendering this judgment, the committee was not seeking to balance or compromise between competing ethical perspectives. Rather, it was asserting that the biological grounding of their ethical judgment allowed them to simply cut through disagreement. The ethical rule was built not on the foundation of consensus or compromise, but on (a representation of) nature itself. Here the committee was working on a presumption that has become familiar—even normative—in American bioethics: ethical judgment should be preceded by and grounded in robust scientific knowledge (Hurlbut, 2015b). In practice, this means that the scientific experts are authorized to make discernments that reveal and clarify matters of bioethical concern (or lack thereof). Put differently, the parameters of (reasonable) ethical disagreement and deliberation—including even the terms of debate—are defined in advance by scientific experts.

Indeed, the AFS committee went so far as to codify the natural (ethical) line it had discerned by altering the technical terminology of embryology itself. The committee coined a new scientific term to distinguish the pre- from the post-gastrulation embryo-- the "preembryo." The committee explained that this scientific neologism was meant to clarify, not prejudice public discourse. It was designed to ensure linguistic precision in ethical deliberation by drawing language into alignment with the natural facts (as discerned by the scientific experts on the committee). It was "not intended to imply a moral evaluation" (American Fertility Society, 1986, p. vii)

Yet the term served the function of reshaping (or, rather, defusing) ethical disagreement. The change in language was meant to insert a (scientifically authorized) distinction into the discourse of ethical deliberation itself, regardless of whether

those who used the language understood (let alone critically examined) the rationale for the distinction. The committee maintained that the public had ethical misgivings about IVF because it was confusing the preembryo with later developmental stages. By segregating debate about embryo research from preembryo research, the committee hoped objections to (pre)embryo research would evaporate.

Thus, the fourteen-day rule in its earliest principled instantiation was rooted not only in a biological distinction between the pre and post implantation embryo, but also in a corollary demarcation between reasonable and unreasonable ethical concerns—between secular, scientifically grounded judgments and religious commitments, and thus between appropriately public reason and matters of private belief (Hurlbut, 2015a). On this view, science's value-neutral, ontological discernments precede and guide public, ethical judgment. Science speaks first and defines the values-questions that are (and are not) in play.

Note that this idea is built on a tacit theory of deliberative democracy: in a properly-functioning democracy, facts provide the incontestable common ground for addressing disagreement over values-questions. Therefore, ethical and policy judgments must be tethered to scientific discernments about the nature of the object of ethical concern. Science provides the correct classifications and democracy sorts out their moral significance, if any. Thus, the fourteen rule as it developed in the US was more than a limit on research. It also codified a conception of the right role of expert's biological discernments in public bioethical deliberation. In effect, the fourteen-day rule embodied a democratic theory of the right relationship between scientific expertise and public ethical judgment.

From Facts to Reason

The AFS committee was not a publicly authorized body. But in the absence of public regulation of IVF in the US, the AFS committee recommendations (and, therefore, the fourteen-day rule) governed in fertility clinics and laboratories that wanted AFS accreditation. However, about a decade later, a federal bioethics body, the Human Embryo Research Panel, further solidified the fourteen-day limit.

The Human Embryo Research Panel was convened in 1994 to recommend rules and limits on human embryo research. It was created in response to a regulatory change made early in the Clinton administration that eliminated an element of review that had precluded federal funding for human embryo research since 1980.

The Panel affirmed the fourteen-day rule, but elaborated on the AFS committee's reasoning by supplying an explicit (rather than merely tacit) theory of how public ethical judgments should be made in the face of democratic disagreement. "a variety of distinct, intersecting, and mutually supporting considerations" (Human Embryo Research Panel (U. S.) & National Institutes of Health (U.S.), 1994, p. 38) The panel asserted that it was not a proper role for a public ethics body to decide which views are correct since "public policy represents an effort to arrive at a reasonable accommodation of diverse interests" (Human Embryo Research Panel (U. S.) &

National Institutes of Health (U.S.), 1994, p. 39). The panel therefore refrained from judging the correctness of ethical arguments held by members of the public. Instead, it subjected them to a test of reasonableness. If the Panel thought reasonable people would find an argument convincing, it was given greater weight. (These judgements were based on the Panel's imagination of the reasonable person—not on anything like public opinion surveys.)

Thus, the Panel positioned itself as a surrogate for a democratic polity engaged in robust public reasoning (i.e. reasoning the actual democratic public may not itself be capable of engaging in). In fact, the Panel actively ignored the actual input they received from members of the public: it received a significant amount of mail that directly contradicted the position they ultimately took. (Most of it categorically opposed human embryo research, and a significant portion came American citizens who either explicitly identified themselves as pro-life, or seemed to the Panel to be speaking from pro-life perspectives). The Panel chose to ignore this input, and actually took active steps to prevent public input in their deliberations on the presumption that the public's actual views should be excluded because they were necessarily scientifically uninformed and therefore would be unreasonable. The Panel maintained that because the embryology was complex, cutting-edge and understood only by select scientific experts, the actual views of non-expert citizens could (and should) be disregarded. Instead, the Panel made a judgment about what kinds of reasons people *ought* to agree upon. And here they agreed with the AFS committee: ethical deliberation must be delimited and disciplined by giving priority to scientific reasons, because scientific reasons are common to everyone, at least to everyone who is both informed and acting in accordance with the norms of deliberative democracy—accepting the facts (i.e. deferring to scientific experts) and engaging with each other in a common language of secular reason. Treating the ethical arguments that were more deferential to expert discernments as higher on the reasonableness scale and thus as carrying more weight, the Panel used the same biological arguments as the AFS committee (about twinning, early embryo loss, etc.) to declare that fourteen days was the right limit.

Most of the bioethics bodies in the US that have addressed issues of human embryo research have affirmed the fourteen-day rule by referring to the Human Embryo Research Panel's recommendation and those of other bodies that have reaffirmed it. The reasoning behind it came to be treated in mainstream scientific and bioethical circles as a matter of wide consensus that needed no further elaboration or justification.

What I want to highlight is how, in the US context, this consensus was not grounded in anything remotely resembling inclusive democratic deliberation. Nor was it reflective of a pragmatic compromise. To the contrary, it was a product of a particular idea of the role of expert scientific discernment in the process of public bioethical judgment, one that authorized imposing limits on the scope of public

ethical disagreement in the name of scientific authority, even to the point of defining the authorized terms of debate.[2]

I want to draw attention to how the approach to public bioethical decision-making evident in these moves entails particular conceptions of reasonableness and unreasonableness that are not themselves subject to deliberation. This was the approach to bioethical judgment that yielded the fourteen-day rule in the U.S. Thus, the primary justification for that rule was not that it achieved a workable compromise between competing viewpoints, but rather that the nature of the embryo itself (as elaborated by scientific experts) revealed where the line should be drawn. This approach allowed the (American) authors of the fourteen-day rule to sidestep meaningful public deliberation. And yet, as noted above, the rule nevertheless become a durable element in human embryo research governance in the United States. That is not to say that it was not controversial. Indeed, U.S. Congress responded to the recommendations of the Human Embryo Research Panel by enacting law that banned federal funding for all human embryo research. (That law remains in place nearly 30 years later). The enormous political controversy over human embryonic stem cell research in the 2000s focused on the research use of in vitro human embryos at five to six days of development, well before the fourteen-day limit.

But for the many Americans who supported some forms of human embryo research, the fourteen-day rule was a given: a bright-line, universally affirmed among embryo-research advocates, that was grounded in science, and therefore was unchanging and unchangeable. That firm upper limit made it unnecessary to worry about how far things might go, thereby strengthening public support for allowing latitude for experimentation prior to fourteen days. It is worth noting how important it was that the fourteen-day rule appeared to be beyond question. The rationale for the rule signaled that there was nothing tentative or temporary about it. Because the nature of the embryo was unchanging, so too would be the rule. Indeed, this natural permanence was precisely what the US ethics bodies that advocated for the rule pointed to as justification. It is safe to say that had they presented that line as a political compromise between competing perspective, the process through which they arrived at it (which included suppressing dissenting perspectives) would have been self-evidently illegitimate and the rule would have seemed far less secure.

[2] It is worth noting that the moments detailed above are not isolated incidents. They reflect a larger pattern that has shaped deliberation in around human embryo research in the US since the early 1980s. Similar moves were made to intervene in public discourse and reform terminology in the name of enhancing the quality and, thus, the legitimacy of democratic deliberation. For instance, at the height of public controversy over embryonic stem cell research in the mid-2000s, leading figures in the scientific community sought to cleanse public discourse of the term "cloning" when used describe the creation of a cloned human embryo for research use, replacing it with "somatic cell transfer for the procurement of pluripotent stem cells" (International Society for Stem Cell Research (ISSCR), 2004; National Research Council, 2002; Silver, 2001) They even went so far as to file law suits seeking to constrain the use of the term in political debate related to ballot measures to authorize or directly fund human embryo research. (There were several, e.g. Berg v. Shelley, CA Sup. Court, Sac. County, Case No. 04CS01015, and Missourians Against Human Cloning v. Carnahan Cole Count. Cir., MO. Case No. 05 AC-CC01108.)

This observation is particularly important in light of recent developments in cell and developmental biology and the corollary moves to discard the fourteen-day rule. Before turning to that issue, however, I briefly discuss the parallel but separate formation of the fourteen-day rule in the UK.

Politics of the Limit

The fourteen-day rule has another, largely separate origin in the UK. It was a central element of the recommendations of the UK committee of inquiry popularly known as the Warnock Committee which was convened to advise Parliament on how to govern IVF (Committee of Inquiry into Human Fertilisation and Embryology, 1984). In 1990 it was codified in law by the Human Fertilization and Embryology Act.

The development of the fourteen-day rule in the US and UK is a study in contrasts. Unlike in the US, the Warnock report did not primarily ground its ethical discernments in scientific discernments of biological markers. Noting that "biologically there is no one single identifiable stage in the development of the embryo beyond which the in vitro embryo should not be kept alive," the committee felt that a definitive limit was nevertheless required "in order to allay public anxiety" and instill public confidence that science would proceed only within publicly designated constraints (Committee of Inquiry into Human Fertilisation and Embryology, 1984, p. 65).

The committee explicitly refused to define when morally significant human life begins as a prerequisite for establishing the rule, noting that such problems are "complex amalgams of factual and moral judgments" (Committee of Inquiry into Human Fertilisation and Embryology, 1984, p. 60) In adopting fourteen days, the committee took into account many of the same embryological factors as the AFS Committee and the Human Embryo Research Panel. But, in contrast to those committees, it did not elevate scientific reasoning to the position of arbiter of public reasoning. Instead, it incorporated these elements alongside others, like the notion that a bright-line limit was essential, and that it had to be straightforward, unambiguous and clear. Warnock later noted that fourteen days not only seemed reasonable in light of changes in the embryo at gastrulation, but because two weeks was a recognizable and easy-to-remember interval, and thus one which was therefore likely to seem reasonable and command the assent of the British Parliament and public.

The Warnock Committee report initiated more than a half-decade of debate in the UK Parliament. The details of that debate, though fascinating, are beyond the scope of the present analysis. Suffice it to say that regulation of IVF in general and the fourteen-day rule in particular received national public attention, producing a regime that has been widely seen as successful by the British public (Jasanoff & Metzler, 2020). The important takeaway from the UK story is that the fourteen-day rule was widely taken as an expression of a collective, political recognition that science must be subject to definitive limits, and that setting those limits was a matter

for the commonsense judgment of the democratic polity and their representatives. This was the explicit rationale of the Warnock Committee, and it became a centerpiece of the legislation in the UK the created space for scientific inquiry within democratically defined constraints.

Sheila Jasanoff has shown how this mode of reasoning cohered with British civic epistemology—the mode of producing publicly-legitimate discernments about questions of science and science policy peculiar to UK politics (Jasanoff, 2005). The key point that I want to draw out here is how the legitimacy of the limit was grounded in radically different claims to authority in the UK than in the US, and how the former therefore necessarily went through a process of public evaluation and deliberation, whereas the former side-stepped it.

Yet, in both cases the clarity and definitiveness of the limit was fundamental to its persuasiveness. In the US, the ethical limit was elevated essentially to the position of a natural fact: solid, unchanging and beyond disagreement (at least amongst secular perspectives deferential to scientific knowledge). In the UK, it was the centerpiece of a kind of public moral discernment that grew out of a duty to bear "witness to the existence of a moral ideal of our society..." in which, ethical disagreement notwithstanding, the designation in law of universally binding limits "is the embodiment of a common moral position" (Committee of Inquiry into Human Fertilisation and Embryology, 1984, pp. 2–3) Quite apart from where exactly the limits were fixed, for the Warnock Committee, the fourteen-day limit reflected a commitment to a common morality: "There must be some barriers that are not to be crossed, some limits fixed, beyond which people must not be allowed to go.… The very existence of morality depends on it" (Committee of Inquiry into Human Fertilisation and Embryology, 1984, p. 2).

Thus, the US and UK origin stories are a study in contrasts. The processes through which the rule was arrived at differed profoundly, as did the sort of reasoning that grounded it. Yet what was shared between them was a commitment to rendering scientific research rule-bound. In both countries, the process of setting limits was driven by the recognition that research must be subjected to limits that ensure that the moral stakes of this domain of research are acknowledged, affirmed and respected. In both jurisdictions, this took the form of defining a definitive rule that would apply uniformly and unambiguously to everyone, regardless of whether or one agreed with the reasoning behind it. This is more than a symbolic gesture. It represented a rejection of the notion that what is scientifically possible is presumptively permitted: that the fact that if an experiment can be done mean that it should be done, unless there are compelling reasons to the contrary.

Unlimiting Science

Four decades after the fourteen-day rule was first articulated, the forms of scientific research that it made possible have probed human development progressively closer to the limit. This is in keeping with the expressed intentions of that limit: the rule

imposed an unambiguous constraint on practice, thereby eliminating the interpretive flexibility and potential slippage associated with discretionary applications of a more abstract principle or norm. By providing reassurance that science would not pass beyond it, the threat of ethical transgression was likewise delimited, quieting public concerns even as research progressed. Judged in terms of the original purpose of the rule, the fact that experiments have reached but not transgressed the fourteen-day limit represent a success story.

Yet prominent figures in the scientific community see things differently. They have argued that the advent of techniques for culturing embryos beyond fourteen days means that the fourteen-day limit is obsolete, and it is time to "extend or even abolish this limit" (Lovell-Badge et al., 2021). According to Janet Rossant, an eminent development biologist, the techniques for culturing human embryos through gastrulation "again raise the question of where to place the ethical limits on human embryo development in vitro" (Rossant, 2016) One pair of prominent bioethicists extoll the fourteen-day rule as "a shining example of how science policy and regulation can be developed with interdisciplinary consensus and applied across a number of countries" but go on to assert that technical advances in embryo culture have rendered it "no longer fit for purpose" (Appleby & Bredenoord, 2018). Others put it more bluntly: "these advances… put human developmental biology on a collision course with the fourteen-day rule" (Hyun et al., 2016).

These are perplexing claims. Why would the science's ability to transgress an ethical limit mean that that limit should be pushed back or abandoned? One reason the advocates for abandoning the limit have asserted is that the rule is subject to revision because it is "arbitrary" (Clark et al., 2021; Robin Lovell-Badge, quoted in Stein, 2021). It was merely a "public policy tool designed to carve out a space for scientific inquiry…" that was "never intended to be a bright line denoting the onset of moral status in human embryos." (Hyun et al., 2016). Rather, it was a "workable compromise"(Lovell-Badge, 2021) that allayed public concerns without inhibiting research. "It shouldn't be thought of as a hard and fast moral pronouncement" (Insoo Hyun, quoted in Monahan, 2016), and thus has runs its course and can and should be revisited and revised.

The history of the fourteen-day rule recounted above belies the notion that the limit was explicitly arbitrary, temporary and provisional. Indeed, in the US the justification for removing the question from the political sphere and placing it in the hands of experts was precisely that this was a limit grounded in the unchanging facts of nature to which scientific experts had special access. The idea was that unreasoned democratic deliberation could be legitimately displaced by reasoned expert discernment because experts were not making an arbitrary judgment or constructing a compromise, but arriving at a correct judgment. The British rationale was different, but it was no less definitive or permanent. The fixity of the line, a barrier "not to be crossed" was a commitment to elevating morality above expediency or desire. As the Warnock Committee said, "the very existence of morality depends on" society imposing such limits upon itself. (Committee of Inquiry into Human Fertilisation and Embryology, 1984, p. 2).

Yet this notion that the rule must adapt and evolve is not merely rooted in a revisionist history designed suit the scientific desiderata of the moment. Rather, it is grounded in a more entrenched, if more subtle, conception of the relationship between social norms and scientific advancement. The notion that the fourteen-day limit is on shaky ground because "we have arrived at the edge of the horizon that the Warnock committee foresaw, and current research is running headlong into prohibitions established" long before science had advanced to its present state construes the limit as dependent upon the state of the science, rather than the reverse (Pera, 2017). Scientific advances "again raise the question of where to place the ethical limits" (Rossant, 2016) and make a limit "no longer fit for purpose" (Appleby & Bredenoord, 2018, p. 28) only if one presumes that limits ought not hold back science and become suspect or even illegitimate the moment that they do.

This way of thinking follows a logic that presumes that governance of science must be calibrated to—and thus must follow from and react to—the "state of the science." Progress in science demands revision of the norms and rules that govern it. Ethical commitments to limits imposed before those limits could be transgressed are marked as empty, void of durable ethical significance because the limits meant nothing in the absence of the capacity to transgress them. And because they meant nothing, they can therefore be challenged and revised once that technological capacity comes into being. Back of this is the notion that ethics and law inevitably lag behind science, just as science inevitably and inexorably progresses.

I want to note that, as with the AFS committee's arrogation of ethical authority by claiming to see the right moral order through its privileged view of the natural order, this too is an arrogation of authority, but one grounded in a claim not merely to privileged knowledge, but also to progress. The arguments for abandoning the fourteen-day limit are a mixture of calls for escaping the darkness of ignorance into enlightened self-knowledge and promises of the benefits that this knowledge will hold for intervening in and enhancing human life.

This construction of limits—as temporarily necessary to allay public concern, but discardable as soon as science considers them no longer "fit for purpose" entails a bioethics that is always subsidiary to—and responsive to—the capacities, desires and aspirations of the science of the moment.

Indeed, limits that until only recently were widely considered beyond question (e.g. that it would be unthinkable to create and gestate human-monkey chimera) are being displaced with regimes that are deferential to scientific desiderata (Hyun et al., 2021; Stein, 2021). They are taking a form that is very different from establishing clear limits. Rather, there is a push to relocated bioethical judgments into processes of oversight that remain flexible and constantly re-calibrated to shifting science. The rationale is that ethics will be more precise and up-to-date if judgments are always made in relation to particular proposed experiments. The International Society for Stem Cell Research, which in 2021 called for abandoning the fourteen-day rule, has advocated for this reorientation. Rather than propose an alternative limit, the ISSCR suggested that research should be reviewed on a case-by-case basis with no predetermined developmental limit.

This shift from explicit limits to procedures of oversight locates discretionary authority in the apparatus of scientific research. At stake is not merely the risk of regulatory capture, but of displacement of democratic judgment by a regime that authorizes itself by asserting that "the very existence of morality depends upon it" constantly recalibrating its ethical discernments to developments in science and technology. Ethics lags behind by design. This regime treats moral limits as contingent and bound to change when confronted with the awesome promise of scientific control over life and the benefits presumed to flow therefrom. In effect, it delegates to science (and its in-house apparatuses of bioethical decision-making) the remit and responsibility to define progress—moral as well as scientific, and thus to set limits on setting limits. "Blanket bans enshrined in law appeal in their simplicity, yet leave the public worse off, and are more vulnerable to dogma or instinct rather than evidence. Guidelines from international scientific societies can offer leadership in reassuring scientists and the public" (Lovell-Badge, 2021, p. 479). This is an arrogation of public authority, made in the name of the benefits that will accrue to society but which society, with its preference for the simplicity of "blanket bans," is incapable of anticipating and adjusting its own ethical commitments to accommodate.

This move to abandon limits in favor of (opaque) case-by-case judgments comes just as the arena of human embryo research is becoming significantly more complicated. The clarity of the fourteen-day rule lends itself less well to rapidly advancing capacities for constructing synthetic embryos or embryo-like entities, for producing human animal chimera, and other forms of bioengineering with the potential to leap-frog over early embryogenesis (Aach et al., 2017; Jasanoff, 2019). Yet it reminds us that this field with its extraordinary—and, sooner or later, transgressive—capacities for control over human development itself developed in a space that was opened up by setting a limit. The purpose of the fourteen-day rule, like many limits society imposes upon its members, was intended to hold back science in deference to public values, even when scientists believe there is good reason for pushing past those limits.

Conclusion

The way political communities construct rules matter. Limits codify judgments about ethically significant thresholds of action by clearly delineating the permissible from the impermissible. Rules may also reflect and reenforce the processes of deliberation, reasoning and judgement that gave rise to them, and the forms of deference, trust and solidarity that those processes promise or presume. In short, the stakes of the fourteen-day rule—and of the emerging efforts to unwind it—go beyond what experiments may take place to public trust in governance of science and technology more broadly (Hurlbut et al., 2020).

Thus, the fourteen-day rule raises broader questions about the role of limits in the governance of scientific research, particularly in research that touches upon fundamental dimensions of human integrity and dignity. The fourteen-day limit is more

than a mere rule insofar as it is also an expression of processes of judgments about the necessity of limits, about the how those limits engender accountability and trust between science and society, and about the processes through which limits should be set and bright lines should be drawn in public ethical decision-making and policymaking about science and technology—with what accountability to the public, grounded in what forms of deliberation and ethical discernment, and drawing on what forms of expertise, authority and reasoning.

In the UK, the rule grew out of a process of democratic deliberation and judgment. In the US, it was achieved more by asserting scientific jurisdiction the parameters of ethical uncertainty, thereby delimiting debate and grounding the rule in features of fixed biology that were presented as incontestable for purposes of public policy (if not for matters of private belief). These distinct genealogies offer insight into how the warrant for setting limits—and the power and authority invoked to do so—is fundamental to bioethical decision-making, even if such warrants and tacit forms of authorization may not themselves to be subjected to adequate critical scrutiny and ethical deliberation.

Regardless of these differences in formation, however, in both the US and the UK, limits have been essential to the sense that controversial scientific research would restrain itself in deference to public concerns and thus could be set free within the boundaries of those limits. Clear limits could help to quiet controversy even in the absence of consensus about the ethical (im)permissibility of research.

This is an important lesson of the fourteen-day rule. Yet it is a lesson that has apparently gone unlearned by the research community. The growing chorus of scientists and scientific organizations pushing to abandon the rule are likewise calling for abandoning limits and adopting processes of oversight that allow for incremental liberalization. This is not merely a revision in rule, but a shift in modes of bioethical decision-making that displace public participation in regimes of scientific accountability.

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Chapter 10
Human/Non-Human Chimeras

Iñigo de Miguel Beriain

Abstract The creation of human-animal chimeras involves complex ethical issues. First, they sometimes involve harming animals, which can only be justified under some special circumstances. Furthermore, the entities created might not be treated according to what their special statute demands. This would have a negative impact on their quality of life, depriving it of many of the factors that usually bring happiness to living beings. On the other hand, there are substantive concerns about the safety of the research or the allocation of resources to a practice that might not justify such expenditure. Above all, however, chimeras are extremely challenging creatures, since they defy the fundamentals of the anthropocentric ethics that still prevail in our culture. They blur the boundaries between species and introduce moral confusion due to their particular features. A superchimp able to show rational attitudes could create an impossible dilemma for an ethical paradigm based on the idea of human dignity. However, none of these reasons seems strong enough to ban all types of human-animal chimeras.

Keywords Human-animal chimeras · Non-Human chimeras · Anthropocentric ethics · Species integrity · Hybrids

Introduction

On April 15, 2021, the journal *Cell* published a novel paper (Tan et al., 2021) describing the production of chimeras that mix human and ape biological material. Specifically, the experiment involved injecting a particular type of human expanded pluripotent cells (hEPSCs), obtained by reprogramming from adult human cells into monkey (*Macaca fascicularis*) embryos. Since the experiment might introduce

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deep changes in the monkey's capacities, including mental capacities, it immediately triggered the debate about the ethical issues involved in mixing human and animal biological materials, that is, creating human-animal chimeras.

This, however, was not a new discussion at all. Indeed, concerns about the appearance of chimeras are very ancient. They were already present in Greek mythology, for instance. In fact, the name chimera derives from the mythological creature, daughter of Typhon and Echidna, which roamed the regions of Asia Minor terrorizing the populations, while gobbling up herds and animals, until it was finally defeated by Bellerophon with the help of Pegasus, the winged horse (also a chimera, by the way). Afterward, the concern about the emergence of such an entity was picked up by Roman law, in which the newborn was required to have a human form to be considered a person (see Code of Justinian, *Codex Justinianus*). Afterwards, the fear of chimeras fueled the discussions on the baptism of monsters in the Modern Age (Flores, 2014). More recently, stories such as The Island of Doctor Moreau, by H. G. Wells, or The Fly, by George Langelaan recovered the figure, always in the form of a creature capable of instilling terror in human beings. In the field of scientific research, highly controversial experiments have been carried out in the last century, such as those developed by the Soviet scientist Ilya Ivanov during the 1920s, with the aim to create an ape-human hybrid (De Miguel Beriain, 2011).

Do animal-human chimeras really involve such terrible ethical issues, as it seems at first sight? Academics have analyzed this question profusely over the past 60 years. A recent article devoted to conducting a systematic review of the literature found at least 88 articles devoted to this issue as of 2017 (Kwisda et al., 2020). Most of these publications do not focus on the reasons why this practice should be permitted or even supported. On the contrary, it is generally proposed that advances in basic and applied research are desirable. Indeed, "such research could be tremendously useful in understanding the etiology and progression of human disease and in testing new drugs, and will be necessary in preclinical testing of both adult and embryonic stem cells and their derivatives" (National Research Council, 2005, 30). Furthermore, the freedom of scientific research is a universal right and public good anchored in the UN International Covenant on Economic Social and Cultural Rights (Ministerial Conference on the European Research Area, 2020). Therefore, the burden of justifying any limit to the exercise of this right falls on the shoulders of those who seek to establish it. This is why most of the arguments developed by the literature are generally aimed at providing strong reasons that support a ban on the creation of human-animal chimeras.

Following this logic, this text will mainly analyze the arguments put forward by those who have effectively sought to limit the creation of these entities. The analysis of the academic literature shows that this could be a complex and extensive task, given that there are multiple variants of arguments. Nevertheless, in order to clarify the debate, the reasons have been grouped into four main types: reasons concerning the rights and interests of the entities involved in the research; reasons concerning the rights and interests of the resulting entities; reasons related to human dignity and the "species integrity" argument; and reasons concerning downstream effects. Finally, some conclusions have been added, mainly summarizing the key points in

the discussions. However, before entering into the discussion, it will be useful to begin by explaining why the analysis will focus primarily on chimeras, and not so much on hybrids, and why only on some types of chimeras.

Three Preliminary Debates: Chimeras Vs. Hybrids, Animal-Human Chimeras and Chimeras Non Affecting Particularly Relevant Features

The case of hybrids differs from chimeras in that hybrids are not entities that have been modified after existing as such, but creatures that arise as a product of the mixture of genetic material from two different species. A mule is not a horse to which genetic material from a donkey is introduced, but an animal that can only be created by mixing germ cells from both species while chimeras combine two lineages of cells, from two different species. This evidence has important connotations in the ethical debate. Unlike chimeras, hybrids cannot exist as beings possessing biologic material from only one species. Their existence depends, precisely, on the mixture of those materials. If this fusion of ova and spermatozoa belonging to different species does not occur, the hybrid does not exist. This means, in turn, that it is very difficult to use arguments such as the harm caused to the offspring in the case of hybrids. Unless we agree that the existence of the hybrid is going to be so terrible that it would have been better for it never to have existed, it is difficult to argue that "we should not create a hybrid because that would cause it harm".

As we show shortly, this does hold in the case of chimeras, because the alternative to their existence as chimeras is their existence as non-chimeras. In the case of hybrids, the only alternative to their existence as hybrids is their non-existence. Therefore, the non-identity problem and all the connotations it implies are perfectly applicable to hybrids. In conclusion, one has to keep in mind that, while it is true that all the problems that can affect chimeras also affect hybrids (e.g., the confusion of categorial barriers), the opposite is not so. Therefore, the analysis of the ethical, legal and social issues of human-animal chimeras also encompasses those specific to hybrids, so their study would be reiterative (note, by the way, that the opposite is not true: there are problems specific to chimeras, so we must choose chimeras as the benchmark).

Secondly, it should be emphasized that this piece will only analyze the problems generated by a certain type of chimera, those that mix human and animal materials. Those that do not involve a rupture of this barrier can be analyzed on the basis of many of the keys that are already present in the discussions on human-animal chimeras. Moreover, attention will be devoted exclusively to those cases in which this mixture may affect the capacities that we usually consider as specifically human (rationality, for example). This is because it is these and not the others that pose truly important challenges for the ethical discussion. Indeed, creating the so-called "Animals Containing Human Material" (ACHM) by mixing human and animal

genes or cells is already a standard practice in science (Haber, 2012). Some examples of such creatures are mice genetically modified to make them more susceptible to infection by human viruses, such as HIV (Berges and Rowan, 2011), or transgenic animals that can produce human proteins in their milk, such as human antithrombin in goat milk for the treatment of blood-clotting disorders (Edmunds et al., 1998). In general, the use of such modified animals does not raise any major ethical issues (beyond those related to issues such as biosafety, animal welfare, informed consent, etc.). Moreover, even if new advances in xenotrasplantation would allow animal to human organ transplantation in the future, this would not alter the ethical framework dramatically.

On the other hand, the alteration of the human or animal brain does seem to give rise to major disagreements. The rationale on this was perfectly exposed by the Pontificial Academy some years ago: "In light of a renewed appreciation of the body and of the symbolic understanding of it that much of contemporary anthropology offers, it should be observed that not all organs of the human body are in equal measure an expression of the unrepeatable identity of the person. There are some which exclusively perform their specific function; others, instead, add to their functionality a strong and personal symbolic element which inevitably depends on the subjectivity of the individual; and others still, such as the encephalon and the gonads, are indissolubly linked with the personal identity of the subject because of their specific function, independently of their symbolic implications. Therefore one must conclude that whereas the transplantation of these last can never be morally legitimate, because of the inevitable objective consequences that they would produce in the recipient or in his descendants,(61) those organs which are seen as being purely functional and those with greater personalized significance must be assessed, case by case, specifically in relation to the symbolic meaning which they take on for each individual person." (Pontificial Academy, 2001). These are the reasons why this piece focuses precisely on analyzing the ethical, metaethical and ontological implications of the creation of human-animal chimeras in which essential features of the human being, such as rationality, for example, are affected.

Reasons Concerning the Rights and Interests of the Entities Involved in the Research

A first argument against creating human-animal chimeras is that the animals participating in the experiments might be mistreated. This might happen in totally different ways. First, if we consider that adult animals might suffer the consequences of becoming the subject of an experimental practice, one must focus on general animal welfare concerns, since animals participating in the research might be harmed by the experiment itself. This would be particularly possible if we were considering existing great apes as being part of the research. In this context, de Grazia argued

that "Great Apes should not be used in research unless (1) their participation is realistically expected to pose no more than minimal risk to them or (2) greater risks are justified by the prospect of direct veterinary benefit to them and the absence of alternatives offering a better benefit/risk ratio" (de Grazia, 2007). At the EU level, the 3Rs research paradigm (replacement, reduction, refinement) are the normative benchmark for the use of animals in research. If the experiments in question do not meet these ethical standards, they should be prohibited.

Of course, this criticism is not shared by all those who consider that research with great apes, in the case of chimeras, meets the 3Rs criterion, and could be acceptable from a moral point of view (Shaw et al., 2014). Furthermore, this objection would not be as strong if only rodents were involved. Even de Grazia (2007) concedes that "rodent subjects may be used if there is no alternative that would avoid using rodents (or other animals with equal or higher moral status) and either (1) the Unequal Consideration Model is correct or (2) the Unequal Interests Model is correct and the experiments' promise is sufficient to pass consequentialist muster without violating any appropriate deontological constraints (the last qualification being relevant in a mixed consequentialist-deontological approach)". Thus, animal suffering might not be a definitive argument against human-animal chimera creation.

A very different argument points out that the creation of human-animal chimeras might involve the use of human materials obtained from human embryos (Mirkes, 2006). However, some other authors have highlighted that the creation and use of human-animal chimeras for research purposes is not regarded as presenting additional ethical concerns alongside those related to the destruction of human embryos (Palacios-González, 2015). Thus, it does not seem that this argument should be considered as a key piece in the discussion about the ethics of creating human-animal chimeras. However, some other authors have argued that, even though they were not embryos at all, human materials or, even worse, those who are providing them, could yet be treated in a disrespectful manner (Streiffer, 2010). This is particularly true if these materials include human ova, for instance (Baylis, 2008). Curiously, one cannot but highlight the paradox of this objection if we bear in mind that one of the possible uses provided by chimeras is, precisely, the creation of human eggs. Indeed, human-animal chimeras intended for human gamete production have been proposed as a possible avenue for solving the egg shortage problem (Palacios-González, 2017). If this were possible, the objection would probably become quite feeble.

Last, but not least, one would have to keep in mind that, when we are talking about basic science experiments performed on rodent or primate embryos that will never be introduced into the uterus of a female of their species to achieve the birth of a creature, the scenario changes considerably. Indeed, it is difficult to think that the mere creation of a chimeric embryo might be per se particularly problematic from an ethical point of view. This, however, may ostensibly change if we focus on other arguments that we will develop in the next sections, such as the crossing of species boundaries, for example.

Reasons Concerning the Rights and Interests of the Resulting Entities

A different argument from the one made in the previous section is the complex status or likely infringement of the rights or interests of the human-animal chimera that is created by mixing genetic material. This objection has, in fact, different modalities. First, it could be that chimeras are created exclusively for the purpose of providing humans with biological materials that could be useful to us for therapeutic purposes. This could be highly problematic from an ethical point of view, since those entities would be used merely as a source of biological material. However, some authors have pointed out that farming already involves breeding millions of animals to feed human beings. Thus, "the fact that chimeric animals are raised for the purpose of human organ culture should not face more ethical debates than raising them for consumption." (Bourret et al., 2016). Nevertheless, this response can hardly be shared by all those who are against animal consumption, of course. Furthermore, it would never apply to chimeras that might develop in some way a human key feature, such as rationality.

On the other hand, it has been argued that chimeras might be treated in an unfair way, almost as a kind of attraction, instead of being treated as a being with its own moral value. For instance, a deliberately created human-animal chimera "would surely become a monster in the original sense, an object of human fascination and pity. This seems a harm to the creature and something that it would be wrong deliberately to bring about" (Jones, 2010). It is out of discussion that the situation described by Jones would bring a kind of devaluation of the chimera's moral status. This would be particularly true, of course, if it exhibited certain traits that we usually associate with the human. Indeed, Streiffer exposed that "research might cause an animal, which would have had a comparatively low moral status, to instead have the moral status of a normal human adult, and yet the animal might continue to be treated in ways typical of animal research subjects and which would be profoundly unethical given its new moral status." (Streiffer, 2019). However, some authors have convincingly argued against this rationale by maintaining that "our job is to clear this up (as philosophers such as McMahan have tried to do), not to perpetuate it or allow it to persist or base social policy on it." (Savulescu, 2003). An alternative argument holds that one might think that the chimera's existence could be absolutely conditioned by its origin. The entities created in this way would certainly be the object of multiple studies and analyses from different scientific angles, perhaps lasting all their lives. This would probably result in a considerable decrease in the welfare of the chimera, which could suffer as a consequence of these practices.

Finally, it is far from clear that the mere fact that we elevate the moral status of a creature to a human equivalent is, by itself, in its own interests. In principle, it may seem that raising the ontological status of a being must be good for it. If this were true, the creation of chimeras through the development of human abilities in animals would be a good thing. However, the starting hypothesis has been questioned by some authors, who have emphasized that conferring an enhanced moral status on an

individual is always objectionable from the individual's perspective (this is the so-called No-Enhanced view) (Streiffer, 2019). More probably, the fairness of the intervention would depend on the quality of life of the offspring, leaving apart its human or non-human status (the Instrumentalist Views approach).

Reasons Related to Human Dignity and the "Species Integrity" Argument

One of the main – if not the main – reason for opposing the creation of human-animal chimeras is that their mere existence contravenes the main beliefs that support our ethical framework. The roots of this assumption, in turn, are somewhat variable. There are some authors who appeal to the idea that the chimeras' mere existence would violate our moral taboos, producing an instinctive repugnance, for example (Seyfer, 2006; Streiffer, 2019). However, these kinds of arguments do not seem to be much more solid than those that, in previous times, repudiated interracial marriages, for example (Kelly & Morar, 2014; Thompson, 2003). Not much more consistent is the variant of the argument that holds that the existence of chimeras amounts to playing God or might be unnatural. Both notions appeal to some kind of order prior (and superior) to the human being. Unfortunately, this type of belief presupposes the need to share a view that is based on a form of faith. Too much to ask, probably, for a bioethics that claims to be universal.

There is, however, a much more promising alternative: the appeal to human dignity, which would be violated by the creation of human-animal chimeras. This claim, which has been supported by several authors, is related, on the other hand, to the idea that the creation of chimeras may blur species identities, which is an essential basis of the so called "species integrity" argument. For instance, Jason Scott Robert and Françoise Baylis argued in a classical paper published in 2003 that even though one might accept that there are no objectively given species boundaries, this belief is essential to conventional moral thinking. Therefore, any attempt to cross such boundaries might introduce moral confusion in our moral paradigm and diminish the dignity that human beings are currently assigned. This possibility, they argued, is so threatening to our social fabric that we need to keep tightly guarded conventional species boundaries between humans and nonhumans (Baylis & Robert, 2007).

Thus, this reasoning is based on the idea that the nature of the issue raised by the creation of human animal chimeras is so offensive that we should ban such practices. However, understanding why requires a deep understanding of the species integrity argument. It works in a relatively simple, but very solid way. Its foundation lies in considering that the idea of the separation of living beings into different species has fundamental moral consequences, especially when one of those species is the human species. In fact, what is usually affirmed is that the human being possesses a dignity (read, intrinsic value, in the Kantian sense of the term), different and

infinitely superior to that of other beings. This belief has enjoyed substantial success in recent years. In fact, it is reflected, without going any further, in the Universal Declaration on the Human Genome and Human Rights. Its article 1 states that "the human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity." If we consider that the concept of species is built on the idea of a common genome (which is mainly accepted), it is quite easy to conclude that it is the possession of a concrete genome –the human genome- that provides a being with dignity. Once this axiom is accepted, the next step is to appeal to a shared rational human nature possessed by all beings endowed with a human genome (Noonan, 1970; Devine, 1978; Schwarz, 1990). It is this nature that endows them with that value we call dignity, which corresponds to every human being, regardless of the traits he or she displays individually. Indeed, under this perspective species have explanatory priority over concrete individuals in the sense that the resemblances between individuals in a species are explicable in terms of the underlying "natural state" of each individual (Karpowicz et al., 2005; Wilson, 1999; Hull, 1999). In this way, we can talk about a shared human rational nature that, as generally accepted, other beings do not possess.

Of course, this paradigm is full of weaknesses. The definition of the concept from which we start, the species, is so complex that many have considered it the fundamental problem of biology (Barberá, 1994). In practice, "biologists typically make do with a plurality of species concepts, invoking one or the other depending on the particular explanatory or investigative context" (Baylis & Robert, 2007). Furthermore, its way of understanding moral axiology, based on a radical moral value distinction between humans and other animals, has been questioned in recent years from multiple points of view. The most famous – though not the only one – is the antispecist paradigm originally promoted by Peter Singer (1975, 1980). From his perspective, what makes a being morally relevant or not is not species membership, but its capacity to have interests or preferences. Therefore, any appeal to the idea of human dignity to oppose the creation of animal-human chimeras must begin by recognizing that, in reality, the axiological framework on which it is based is not universally accepted. However, its main problem is that, even if we accept that the distinction between species is morally significant, it would still not be able to give a satisfactory answer to the question of human-animal chimeras.

Perhaps this will be better understood if we introduce an example into the discussion. Let us imagine that an experiment in chimerism gives rise to the superchimpanzee of which authors such as Rachels (1989) have already discussed. Such an animal (?) would be able to learn to read and somehow converse about science, literature, and morals. Under such circumstances, should this chimera be treated as an animal because of his non-human genome or as a kind of dignified being due to its particular attributes? Or should we consider that the mere fact that showing such characteristics would qualify it as a human being? The "species integrity" argument could hardly adhere to any of these alternatives. If it were to say that this being should be treated as if it were a human being because it possessed the characteristics of a rational nature, it would be inherently recognizing that it is the fact of possessing those characteristics – and not the fact of belonging to a particular species – that

would define the moral status of a being. Thus, it would be betraying one of its basic postulates. If, on the contrary, it were to say that the animal would have become human by virtue of possessing these characteristics, we would in fact be pointing out that belonging to a species would depend on the possession of certain characteristics, not on the genome shown by an individual. Finally, if the species integrity supporters were to affirm that the superchimpanzee should be treated as an animal because, despite the fact that his characteristics would endow it with rationality, they would be breaking the postulate that it is belonging to a species -the human species- and not any other factor that provides a being with a rational nature. To sum up, a superchimpanzee would render the species integrity argument and the human dignity concept totally unsustainable.

Should this conclusion bring together the need to ban any research producing human-animal chimeras? In my opinion, this would be like saying that Heliocentrism theories should be banned because they contradict the Bible and this could put in danger a moral paradigm based on the wisdom of the Sacred Book. If a scientific experiment endangers a moral paradigm because the latter is unable to deal effectively with the consequences of that experiment, what we should do is modify the paradigm, not veto the experiment. To do otherwise is tantamount to refusing to face the evidence, a manifest rejection of the way the sciences, including the social sciences, should act. As Ankeny wrote, "our moral unease about chimeras might well be related not only to the fragile (and many would argue indefensible) line that we often draw between human and nonhuman animals, but more generally to the growing recognition of the very fragility of scientific categories themselves, as they are affected by technological and theoretical developments, the changing goals and context of scientific research, and social negotiation within the scientific community. The conceptually deepest difficulties arise in trying to determine what weight should be given to empirical information and scientific expertise when making decisions about whether it is scientifically and morally appropriate to redefine fundamental categories" (Ankeny, 2003). In addition, we should never forget that "if the foundations of an ideological position are knocked out from under it, new foundations will be found, or else the ideological position will just hang there, defying the logical equivalent of the law of gravity." (Singer, 1975, 231).

Reasons Concerning Downstream Effects

Some authors oppose chimeras due to reasons concerning downstream effects. This is a quite blurry argument, that in general claims that individual medical safety might be compromised (Anton, 2016) or third party interest might be infringed, since findings might threaten biosafety (by spreading new diseases) (Streiffer, 2010). For instance, in the case of xenotrasplantation, the fear that human tissues produced in animals might be the source of new zoonoses was broadly shared (Boneva et al., 2001). Furthermore, the impossibility to anticipate the potential risks

associated with the transplantation of human organs grown in animals was often considered as a call for caution (Bourret et al., 2016).

However, these appeals to safety are in general common to experimental research and can be addressed through conventional mechanisms aimed at dealing with such circumstances.

An alternative argument opposes human-animal chimeras research because it might contradict distributive justice. Indeed, some authors claim that there are much more sensible experiments in this area of chimaeras as a source of organs and tissues, such as those performed with livestock animals, such as pigs and cows, which are more promising and do not risk challenging ethical boundaries. Furthermore, "there is a whole field of organoids, which can hopefully do away with animal research." (Subbaraman, 2021). Thus, promoting research with human-animal chimeras would be unethical since it would be granted resources that could be more useful if devoted to alternative uses. This may be a consistent argument, but it can hardly be endorsed if we talk about private funding, for instance.

A Last and Extremely Challenging Argument

Last, but not least, it should be noted that this piece has not yet analyzed the conflicts that may be caused by the introduction of animal biological material into a human brain, altering its functionalities. Indeed, references to such practices are not at all present in the academic literature, leaving apart some exceptions (Pontificial Academy, 2001). This is because it is still practically inconceivable that this alternative could become a reality in the near future. The deliberate deprivation of such capabilities would surely be seen as an aberration, even from the most liberal perspectives. Even those who defend the freedom of a human being to choose euthanasia and thus end his or her life would probably consider it unacceptable for anyone to undergo such an experiment, even if he or she voluntarily consented.

In my opinion, however, this is not as clear-cut as it seems. Apparently, if we accept that terminal sedation can be a correct solution for those cases in which a person experiences a medical problem that has no other solution, it is difficult to think that the deprivation of capacities through practices involving xenotrasplantation can be prohibited in any case. Obviously, this will depend to a large extent on one's ethical and legal conception. If one ascribes to the movement that considers that there is a right to self-determination over one's own life, it is not at all absurd to think that the free choice to become a pig must be respected.

However, this kind of decision cannot be viewed only from the perspective of the subject concerned, but also from the perspective of all other human beings. If someone decides to die, he/she does not become a non-being (like an animal), but simply a deceased being. This is very important, because it influences both the construction and defense of the concept of dignity, as well as the concrete obligations that should be owed (or not) to that being. And, once again, we would have to face the debate on the ontological status of this chimerical creature. Nevertheless, these arguments

do not seem in any case definitive if we think of experimental treatments focused on fighting pathologies that do not know any other possible approach, for example. What would certainly be inhumane would be to force someone to keep his biological material intact in order to preserve a collective interest, if this would mean depriving him of relief from great suffering. Further discussion on this concrete issue is probably needed.

Conclusion

The conclusion one has to come to when analyzing the debate on the constitution of human-animal chimeras is that it is definitely a complex issue. First, one must clearly distinguish the ethical argumentation that relates to the creation of a hybrid and a chimera. In the case of the hybrid, it is a being that does not yet exist, as such, before its creation. Therefore, it is easier to justify such an experiment, since the non-identity argument would work in favor of its generation, unless we could foresee that the mere fact of living would be against the interests of the hybrid. Secondly, it must be kept in mind that there are enormous differences between making a chimera from an animal to which biological material from a human is introduced and creating a chimera from a human to which biological material from an animal is inserted. While the former may be subject to ethical discussion, the latter is in principle inadmissible, for the reasons already mentioned (loss of capacities linked to rationality, probability of suffering, etc.), even though some interesting discussion about the prevalence of self-determination might prevail under some concrete circumstances.

With strict regard to the creation of chimeras from the modification of animals, either in their embryonic or later stages, it must be borne in mind that there are no definitive answers, nor can they be extrapolated to all cases. To begin with, using great apes is not the same as using rodents. The former possess qualities much closer to those of humans and must therefore be much more protected, so the principle of proportionality should force us to be very demanding in the experiments involving these beings. To this we must add that it is perfectly possible that a chimera could become a circus animal, or an object of observation and scientific experimentation throughout its life. This would have a negative impact on its quality of life, depriving it of many of the factors that usually bring happiness to living beings. These considerations should be carefully borne in mind before proceeding with these experiments.

The creation of chimeras is, in short, a certain challenge from the perspective of those who hold moral theories close to utilitarianism. In their opinion, the fact that the animals involved suffer due to their particular status should impel us to protect them. However, these theories have the enormous advantage of not being radically affected by the creation of chimeras: it is enough for us to know whether a being generated in this way suffers or has interests in order to recommend our courses of

action. A traditional moral paradigm, such as moral anthropocentrism, faces much greater difficulties when it confronts the question of chimeras.

Overall, one must consider that chimeras defy the fundamentals of the anthropocentric ethics that still prevail in our culture. Indeed, it is extremely complex to qualify the ethical appropriateness of the creation of these beings since their existence defies precisely the conceptual framework from which we start. How can we use anthropocentric ethics to determine the morality of the creation of chimeras, when their existence highlights precisely the inability of this model to respond to the challenge they pose? Probably the most honest position to adopt on the basis of this evidence should not be to put an end to this avenue of research at all cost. Simply preserving a paradigm that, like all paradigms, is not a burden for human beings does not justify it. On the contrary, awareness of its flaws should invite us to solve them or to replace anthropocentrism with another more solvent model. In this sense, let us remember that man was not made for the Sabbath, but the Sabbath for man.

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Chapter 11
Human Cloning: Recent Advances and Bioethical Issues

Sidra Shafique

Abstract Human cloning is an ethical and scientific dilemma. The present chapter is a snapshot of human cloning from the scientific and ethical perspectives. At first, this issue raises a lot of questions including when, why, how, where, and for whom? Furthermore, society, religion, law, and culture entangle this issue even more. Human cloning discussions broadly consider a mass production of human clones. The therapeutic and reproductive cloning precede the "human cloning". The aim of this chapter is to put forward a conceptual framework in order to formulate decisions related to the issue of human cloning. Here I have encompassed the subject of cloning as a scientific technique with a brief historical background and recent advances. The practical components of human cloning such as surrogacy and risk-benefit analysis have been discussed. I have explained the bioethics and the framework of healthcare principles to approach the exemplary scenarios. Finally, the global rules, regulations and legislations of different countries are mentioned to understand regional variation in the subject of human cloning.

Keywords Human cloning · Reproductive cloning · In vitro fertilization (IVF) · Ethics-based guidelines · Ethics

Cloning – Scientific Perspectives

Therapeutic and Reproductive Cloning

Briefly, somatic cell nuclear transfer (SCNT) is a laboratory technique where a donor nucleus from a somatic cell is transferred into an enucleated oocyte or egg cell. The resulting oocyte has the genetic material of the donor nucleus and that of

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its own mitochondria. Now this egg cell is allowed to divide and create a viable embryo. The use of thus created cloned embryo could be therapeutic or reproductive.

In therapeutic cloning the cloned embryo is never implanted into a uterus or allowed to grow further but is only used to extract stem cells. These stem cells are genetically identical to the cloned person and can be stimulated to differentiate into any of the cell types present in the human body including the gametes. The purpose of these differentiated cells is to treat the medical conditions such as degenerative diseases without any risk of rejection by the immune system of the cloned person. The examples of such diseases include Alzheimer disease, Parkinson disease, diabetes mellitus, stroke or spinal cord injury (Trounson & DeWitt, 2013). Reproductive cloning, on the other hand, involves the implantation of a cloned embryo into a real or an artificial uterus with intention to allow the development into a fetus carried to term (Gambini & Maserati, 2018). The intention to further use of cloned embryo in reproductive cloning could be for the study of early human embryo development or the generation of a cloned person.

Interestingly, there are different yardsticks to ethically justify these two types of human cloning although they have a common basis. In fact, the ethical concerns related to the generation of a human embryo in lab through the procedure of in vitro fertilization and allowing the blastocyst formation till fourteen days for research as well as the therapeutic purposes are the same as of reproductive cloning. However, still reproductive cloning is heavily opposed on ethical grounds while therapeutic cloning is widely accepted by all stakeholders.

Reproductive Cloning, Then and Now

In 1996, for the first time in history, SCNT to a mammalian egg cell was performed resulting in the birth of the first cloned mammal, Dolly, the sheep, in February 1997 (Wilmut et al., 1997). The step-by-step cloning procedure by which Dolly the sheep was produced included enucleation of a mature oocyte, placement of the donor cell in the perivitelline space, electrofusion of the two cells, activation of the fused cells and in vitro culture (Wilmut et al., 1997). The genome of the cloned embryo comes predominantly from the somatic donor cell, however, the entire genetic material within each embryonic cell is not identical to the donor cell genome due to the contribution from the mitochondrial DNA in the oocyte (Choi et al., 2014). The widely used donor cells for the cloning purposes are the subcutaneous connective-tissue derived fibroblasts of the person to be cloned. These cells are used due to the simple procedure of their recovery and relatively less complicated culture conditions (Gambini & Maserati, 2018). Since 1996 to date, the reproductive cloning technique has been far advanced and become safe to produce cloned animals.

Here are a few recent examples of successful primate cloning. Liu, 2018 have cloned cynomolgus monkeys (Macaca fascicularis) by somatic cell nuclear transfer (SCNT) using monkey fibroblasts and ovum. In this study, out of six confirmed pregnancies two healthy babies were born showing about thirty three percent

success rate (Liu et al., 2018). Researchers were able to distinctively identify the genetic material in cloned monkeys to be related to the donor nucleus and the mitochondrial DNA from the ovum indicative of the genetic variability (Liu et al., 2018). Similarly, in another study, a unique genetic identity of cloned foals with a signature mitochondrial DNA of ovum origin was evident of genetic variability (Choi et al., 2014). A recent research has reported a successful primate cloning combined with gene-editing to develop a genetically identical primate model to study a particular disease. (Liu et al., 2019). In this study, five cloned monkey babies were reached to term and delivered successfully out of sixteen pregnancies indicating a similar success rate as of previous study i.e. thirty two percent (Liu et al., 2019).

There are multiple other examples of progress towards safety and improved success rate of cloning specific laboratory techniques. For example, an improved Well-of-the-Well (WOW) system of microwells created on the bottom of a laboratory dish to culture the embryos is a recent advancement. The human embryos cultured in WOW system developed to the blastocyst stage in a significantly higher proportion than traditional method (55% in WOW and 37% in conventional culture) (Vajta et al., 2008). In essence, the techniques of human and primate cloning are consistently being reviewed and improved to get better outcomes.

Other reproductive techniques that are used to create a human embryo in a laboratory include *in vitro* fertilization (IVF) and induced pluripotent stem cells (iPSCs). The bioethical importance of these procedures lies in the fact that these were also opposed like cloning. However, with time and improved outcomes, both techniques are now widely accepted clinical procedures. Here IVF is discussed as an exemplary pioneer artificial reproductive technique (ART) to understand the evolution and acceptance of an ART by a society.

In Vitro Fertilization (IVF)

In IVF the wife's egg is fertilized in lab using husband's sperm. The resulting embryos are implanted in the uterus of the wife to term followed by a childbirth. This is a standard scenario for the procedure and the source of gametes. The deviations from this standard procedure might include obtaining the ovum from a surrogate, using the sperm from a donor or sperm bank and/or using a surrogate uterus to implant the embryo.

IVF was started in clinics back then with the aim of using it as a treatment for infertility and help an infertile couple to have a baby. Recently some advanced technical steps have been added in IVF including intracytoplasmic sperm injection (ICSI), intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) to improve outcome. The ICSI is used where sperms are less motile or immotile therefore an egg is pierced under microscope and a single sperm cell is injected into it. The GIFT is the procedure where egg is retrieved, as in IVF, followed by the transfer of eggs and sperms together into the Fallopian tube to fertilize. The eggs get fertilized within the Fallopian tube and proceed to produce an embryo as of a normal

pregnancy. On the other hand, in ZIFT, fertilization and creation of a zygote are done *in vitro* followed by the placement of the zygote into the Fallopian tube rather than uterine cavity.

Back then in 1978, when this technique was used to give birth to first "test tube baby", Louise Brown, many objections and/or ethical issues were raised concerning the use of IVF for the production of the children "in test tube". IVF was then deemed 'unnatural' and risky for the offspring. IVF was also labelled as illicit as it involves masturbation to obtain semen, thus damaging to marital relationship. In addition, IVF was rendered as an expensive 'luxury' for rich and powerful only. Today, we do readily understand that in spite of all these objections, IVF has been widely accepted as one of very successful treatments for infertility. Why? The simple answer lies in utilitarian approach; it is beneficial to humanity and serves the purpose genuinely with proper rules and regulations in place. In my opinion, human cloning is standing today where IVF was about forty years back. The use of human cloning is facing almost identical objections such as being unnatural, damaging relationships due to asexual reproduction, expensive, luxury and a tool for the powerful. We might expect that human cloning would be gradually accepted by scientific and ethical stakeholders in future through a similar process.

A brief outline is here about induced pluripotent stem cells (iPSCs) as cutting-edge technology. The iPSCs are the stem cells that are produced by reprograming the somatic cells through the use of specific genetic factors (Shinde et al., 2016). The reprogrammed iPSC cells resemble the totipotent embryonic cells (Shinde et al., 2016). In the next step, the iPSCs are differentiated into a specific cell line to be used for stem cell therapy. Today, iPSCs have proved to be good enough and a well-supported alternative method for the generation of stem cells. These stem cells can be further differentiated into gametes as well and used as a source of gametes for IVF purposes. In the cases of male sterility, the iPSCs programmed may be used to generate sperms. Thus, produced sperms are considered a promising alternative of human cloning because there is no use of SCNT, however the iPSCs generated sperms will make the person a biological father of the created embryo.

It can be inferred that the ethical, social, and legal challenges are only around reproductive cloning whereas the therapeutic cloning is widely accepted. These challenges begin where the cloned embryo, produced from an egg and SCNT, is implanted into a uterus to develop into a cloned person.

Human Embryo Cultivation Regulations

To understand the ethical issues around human cloning, it is important to know the scientific basis of when an embryo is considered as an individual being. The discussion around human embryo cultivation informs on two futuristic aspects: (a) The duration in days for the acceptability of in vitro human embryo cultivation to investigate the cut off duration of embryo's individuality and (b) Directing a pathway for the gradual approval of cloned human embryos.

Ethics-based guidelines for human embryo research allow the human blastocyst cultivation till fourteen days (Appleby & Bredenoord, 2018). The embryonic development starting from the fifteenth day involves the formation of primitive streak and beginning of gastrulation when three germ layers differentiate into specialized cells. The rule of fourteen days in vitro human embryonic growth after fertilization was approved by UK in 1990 following "Warnock Report" and became Human Fertilization and Embryology Act (HFEA). At that point, a period of fourteen days was considered more than sufficient because it was very hard to keep a human embryo alive in vitro even for fourteen days (Appleby & Bredenoord, 2018).

As of today, however, it is possible to keep embryo alive and growing past 14 days with advanced scientific techniques. For example, three-dimensional embryo culture systems are being developed to improve embryonic growth and survival (Zheng & Fu, 2021).Therefore, the current proposal by International Society for Stem Cell Research (ISSCR) is to extend the window period of in vitro human embryo research up to 28 days. The arguments in support are: (1) It would allow the scientists to study development during gastrulation, (2) It would improve the safety and success rate of IVF. (3) It would help investigating the embryo-related causes of early miscarriages. (4) The 14 days limit has now become "limiting" thus it is totally justified to have the discussions around extending this limit till 28 days (Appleby & Bredenoord, 2018).

The International Society for Stem Cell Research (ISSCR) issues the research guidelines in the discipline of embryonic and stem cell culture in lab. ISSCR is the largest professional organization of stem cell researchers around the world with around four thousand members from sixty countries. The future of the stem cell research and associated clinical translation is evident from ISSCR's recent initiative to update the guidelines in view of rapid advances in stem cell research, its applications and the associated ethical issues (The International Society for Stem Cell Research, 2021). It is noteworthy that the updated guidelines have been generated following the input from the experts on ethics, policy, regulatory issue, and stem cell biology. The guidelines have highlighted to address two main issues, 14-day rule for in vitro human embryo research and human stem cell-based models of early embryo development such as blastoids (The International Society for Stem Cell Research, 2021; Zheng & Fu, 2021).

Further raised sister issues could be the development of a human embryo in an artificial uterus, developing a full human fetus in laboratories in three-dimensional systems and/or genetically engineered human embryos for creating the blastoid like diseased models solely for the purposes of the study of genetic diseases. Developmental biologists have successfully grown mouse embryos in lab using artificial womb set up for as far as 11 to 12 days that is equivalent to half of the mouse's natural gestation (21 days) (Regalado, 2021). Research were successful at creating early embryos with beating heart, a head, limb buds and without the need to placenta (Regalado, 2021). The next objective of this genre of research is experimenting with other species and then human embryos. This is a glimpse of the future possibilities of reproductive cloning research. The cloned human embryos would be aimed to be grown in the same manner and to avoid the use of surrogate womb.

Once this milestone is achieved, it would be a huge leap towards a comprehensive response to the ethical issues related to relationship questions of the cloned baby.

Following the above discussion, I have the following points to elaborate: First, where does the ethics stand in here? Second, does the scenarios of reviewing and extending embryo cultivation duration indicate the possibility of modifying rules as research advances and the society keeps on accepting the updations? Third, if in vitro development of human embryo and IVF technology are generally approved by the society, then why the same arguments are not valid to allow human cloning?

For the first question of ethics and embryonic growth, it was considered back then that an embryo acquires moral standing only after the fourteen days and gastrulation signifies it as a distinctive individual (Hyun et al., 2016). Now the stance in favor of extending the rule says that there is no evidence of personhood past 14 days either and no functional sensory or neural connections exist in the embryo, therefore developing the human embryo till 28 days would not be ethically wrong. Therefore, ethical justifications, as of embryo cultivation scenario, can be expected to modify in favor of human cloning following scientific evidence as well. For the second question, it seems that there is a vicious cycle of ever extending amendments in rules and definitions. In my opinion, the first and second questions lead to the answer of the third one i.e., we should expect the human cloning to be embraced by the ethicists, our society and the policy makers.

Human Cloning and Ethics

The technique of cloning known as somatic cell nuclear transfer (SCNT) warrants ongoing review with rapidly advancing scientific research, improved laboratory techniques, better biotechnical equipment, and evolving mindset of diverse societies all over the globe. Researchers, bioethicists, and policy makers must have universal definitions with uniform understanding and approved standards all over the globe. An international platform is important to avoid the situations where a point is a "fact" and totally justified for one country or group of experts and the same point being "not a fact" and "unacceptable" for the other. To proceed in a responsible way, a problem-solving approach would be the best while considering the issue of human cloning as an open-ended subject. In fact, the ethical issues are not related to SCNT itself but to create a human embryo that is genetically identical to a person to be cloned, implanted within a woman's uterus, and brought to term.

This section describes the ethical issues exclusive to human cloning and society. These ethical fundamentals are the pre-requisite to address the applied clinical scenarios of human cloning. This discussion is followed by three exemplary clinical situations and the approaches to address them.

Stakeholders in Human Cloning Issue

The identified stakeholders in the issue of human cloning include ethicists, theologians, scientists, scientific societies, and physicians. The legislation, policy, law and regulation authorities from the concerned country or the state create the guidelines and review constitutional challenges to allow or prohibit the human cloning and associated research.

Ethical Issues

Technology has advanced far more rapidly than our ethical considerations resulting in a gap between science and ethics. The gap in reviewing ethical dilemmas has possibly led to the failed access of new technologies and their advantages to the patients in need. Therefore, medical ethics and bioethics need better in-depth reviews with a futuristic approach related to human cloning.

The sum of the ethical issues, projected by Leon R. Kass (2001), include: (1) Cloning is unethical human experimentation with a high risk of producing unhealthy, abnormal, and malformed children which would end up in what? Slaughter? (2) Human cloning is expected to create issues of identity, individuality, and confusing trans-generational relationships. (3) Children would be 'manufactured' designed and ordered as artifacts. (4) Human cloning is despotic powering cloners over the cloned thus distorting parent-child relationship (Kass, 2001).

A consistent ethical argument against producing children using the technique of cloning is the 'prospective' harm to the children which could be physical and/or psychological. The birth defects, long-term physical and mental health issues are very real to consider. However, the question is raised that how we can find a solution without knowing the problem. Human cloning and its complications must be further researched to understand the types of health issues and their solutions.

According to John Robertson (1994), it is better to be born and have a life than not at all. Therefore, for the successful future use of these procedures, it is justified to allow the use of these techniques rather than banning them. Moreover, the incidence of the birth defects cannot even be ruled out in otherwise naturally conceived pregnancies. For argumentative purposes, Robertson says, "higher incidence of birth defects in such offspring would not justify banning the technique to protect the offspring, because without these techniques these children would not have been born at all. Unless their lives are so full of suffering as to be worse than no life at all, a very unlikely supposition, the defective children of such a union have not been harmed if they would not have been born healthy." (Vaughn, 2019). In essence, 'harm to the offspring' can be rejected as an ethical argument against continued research in human cloning.

The ethical debate around human cloning has been conducted by bioethicists and theologists. Main ethical issues about human cloning are where human

reproduction is associated with novel ideas of designing the human babies, artificially enhancing individuals and power play in human race. As a general consensus among ethicists, human cloning threatens humanity and relationships, violates human dignity, takes away uniqueness and could lead to "mass production of superior humans" (Häyry, 2018). However, ethicists have widely varied opinions, one group is altogether against human cloning while the other group of relatively "progressive" ethicists from futuristic school of thought have strong rebuttal to disprove the first group.

The ethical arguments against cloning include that human cloning is playing God, loss of genetic uniqueness, sense of worthlessness of human lives, loss of basic structure of society, and manipulation of power. The ethicists such as Leon Kass is not in favor of human cloning because it "distorts family relationships and our sense of human being". Human cloning is perceived as an asexual method of human reproduction which would distort the concepts of family and relationships thus destroying the sense of humanity (Häyry, 2018).

On the other hand, Ruth Chadwick, a representative ethicist of the supportive group and a British philosopher has some valuable insights. As of Ruth, playing God can be replaced with a better risk assessment and human gene pool is expected to get better by selection of best traits. Ruth argues that if the uniqueness is not affected in naturally born twins and their lives are not worthless then clones would be unique too. Ruth also suggests that the concerns related to society's infrastructure could be well controlled by an effective law enforcement. In fact the utilitarian approach of Ruth Chadwick reflects the utilitarian confidence in technology and thorough risk assessment of cloning with genetic screening (Chadwick, 1982).

The utilitarian approach of using a technology assumes that the benefits of the technology in question outweighs its harms whether it is artificial reproductive technique (ART), surrogacy or cloning. As of IVF and surrogacy, cloning seems to be acceptable by utilitarians if its risks are mitigated enough as Chadwick has advocated (Vaughn, 2019). After all, technologies are meant to contribute towards the "net" happiness of societies with a beneficial product.

On the other hand, for a Kantian supporter, IVF, cloning and/or all reproductive technologies could be using children a means to an end depending on the intention of producing the child. Kantians consider that humans have autonomy which is violated by clone creator i.e. the person who is being cloned (Tannert, 2006). In other words, a clone of the donor is a shadow or the slave of the donor and may not be equivalent or better than of donor. Therefore, the life of a human clone is jeopardized psychologically and philosophically violating human existence ethical maxim (Holm, 1998). In bioethics, human existence is identified by self-determination and autonomy (Tannert, 2006). Kantians believe that this basic right would be taken away from a human clone (Holm, 1998). It makes human cloning as a means to satisfy the ego of parents who want a child or that of in power to satisfy their power hunger. Therefore, this whole scenario makes cloning unethical from Kantian perspective.

In my opinion, an infertile couple's intention to have their "own" biological offspring to love is ethical and justified. In fact, the cloned offspring who is

autonomous and raised with love in the best possible way, irrespective of the means of bringing the child into this world, is desired in this case. It can be fairly asked that why it is not justified to have a clone of a deceased child for a parent in grief over the accidental loss of a child? Why is the clone of the deceased child not considered a twin of lost one? Why having a cloned twin is not fine from an ethical perspective?

Steinbock argues as of Ruth Chadwick that none of the arguments against reproductive and human cloning are persuasive enough. The claim of 'playing God' can be applied to almost every technology that changes outcome such as any surgical procedure whatsoever. Moreover, we should not expect that society will be 'swamped' with cloned individuals as it would be a treatment for infertile couple who are looking for an offspring to love and raise. Human dignity is not expected to be jeopardized either as treating fellow human beings is a choice made by society. As a matter of principle this choice is not based on their nature of origin anyways but on the individuality and personality of cloned person. Nevertheless, it can be expected that human cloning gets approved as a treatment only following the assured safety of the procedure. (Steinbock, 2015).

John A. Robertson (1994) is a prominent bioethicist who has taken an initiative towards advocating the futuristic reproductive technologies and human cloning. Robertson supports the use of IVF ethically by proposing the concept of "procreative liberty" based on autonomy and/or on individual rights. Robertson's conclusion "There is no better alternative than leaving procreative decisions to the individuals whose procreative desires are most directly involved," advocates "procreative liberty" (Abrams, 1994). Robertson seems very clear to state that, "Although procreative rights are not absolute, those who would limit procreative choice should have the burden of establishing substantial harm." (Vaughn, 2019).

Is Genetic Variability Outdated as an Ethical Issue?

Genetic variability is the presence of genetic difference among the members of a population. The opponents of human cloning believe that the clones are the exact genetic copies of the person to be cloned. However, no one should expect that a clone of a person is exactly the same person There are lot of players to shape the final product (a cloned person) such as epigenetics, mitochondrial DNA of enucleated ovum and genetic variability induced by the microenvironment of dividing cells (Choi et al., 2014). The clone has only a similar physical body and a stack of memories to the donor. The difference in genetic material comes from the mitochondrial DNA. Mitochondrial DNA is present in the cytoplasm of the enucleated ovum. The mitochondrial makes the cloned cells so variable that if you clone one horse with multiple maternal lines, you will get the cloned horses that are individually identifiable with their distinctive maternal mitochondrial DNA as a unique signature (Choi et al., 2014). Moreover, the cloned animals are not phenotypically identical to the donor animal as well (Choi et al., 2014). Thus, in essence, as a

researcher, one is not looking forward to a physical and genetic photocopy of the person cloned. This inference is from the current scientific facts which are expected to be far more advanced when human cloning will be offered clinically. What could be an evil intention in context with the human cloning? Getting immortality? Immortality per se must be living forever of an individual human in complete originality. In my view, with the discovery of mitochondrial DNA, the argument of loss of genetic variability now seems invalid.

Religious Perspective

The cultural and religious norms advocate to avoid the destruction of post-implantation human embryos only (Sadeghi, 2007). Overall, it can be justified and ethically explained that none of the step from getting a somatic cell of donor, finding an egg cell, transferring the nucleus to enucleated ovum, stimulating cell division is against any ethical or religious principle.

From an Islamic perspective, human cloning cannot be considered equivalent to playing God because, "Cloning is a mere manifestation of cause and like other causes its results will not occur without the will and inclination of the Almighty. A person who sown the seeds in the field is not the creator of the products. Similarly, a person who is carrying out a cloning procedure is not the creator of the cloned animal. Thus, from a theological perspective, it is incorrect to say that cloning is playing the role of God." (Sadeghi, 2007).

It is important to understand that cloning related emotional, social, family, relationship and inheritance issues should not be evaluated from a religious or theological perspective. Legislation and judicial grounds must be developed to address these issues. For example, what could be the scenario if the cloned person is considered a "twin"? In this case, "twin" will have a different set of rules for inheritance than a father-son established cloned person. It would be much more logical to set a new set of laws and regulations than discouraging the scientific progress in the discipline of human cloning.

Case-Based Approach to Human Cloning

SCNT is a proposed treatment for male as well as female infertility. However, there are multiple ethical dilemmas related to infertility treatment itself. Here are some of the ethical issues: Does it matter how an embryo is produced? What is the status of a cryopreserved embryo? What should be the use of stored unused embryos? Is it ethical to use these embryos as an adoption? Should these embryos be used for reproductive cloning? and so on. All stakeholders must understand that fast-paced scientific advances in cloning are surpassing the ability of human species to accept and do the ethical debate to provide a comprehensive ground to move forward. In

fact, the lack of our responsiveness is detrimentally affecting the accessibility and availability of novel assisted reproductive techniques.

To create and evaluate a framework to be applied for decision making in present and future cloning scenarios, we need to focus on basic principles of bioethics, evidence-based practice, and patient-centered care.

Step 1: Understanding the patient's request especially what, why, where and how?
Step 2: Knowing the patient's own ethical values and set of beliefs.
Step 3: Doing a risk benefit analysis in terms of success and failures.
Step 4: An Effective communication with patient on realistic basis with summary of asked and offered treatment options.
Step 5: Informed consent with a futuristic approach and reaching an agreement between patient and healthcare providers.

The question arises that on what bioethical principles we should base these steps? Bioethics in such a context is based on some established facts such as:

(a) Humans are living and thinking beings with a definitive set of physical and mental needs
(b) Health Care system has a defined purpose in the human society
(c) Individual human beings have essential and ethical dignity of their own (Husted & Husted, 2008).

Case A

Medical ethics is always defensive on its very basic ethical principles of autonomy, justice, beneficence, and non-maleficence (Gillon, 1994). Whether it is therapeutic cloning or reproductive cloning, it is justifiable for a patient to avail these treatment options based on these four ethical principles. For example, considering a scenario of male infertility of a couple Anne and John. John is sterile and cannot produce sperms. Anne is a healthy female with fully functional ovaries. The couple visits an ART specialist and do not want to use the sperm of a donor. They want their own biological offspring. The couple has the autonomy of thought, intention, action and choice. What are their options other than SCNT using the nucleus from John's cell and transferring to the retrieved ovum of Anne? Here comes the next question: where to implant the embryo? Theoretically, the embryo is a genetic twin of John. So here now comes the informed consent, explaining risk – benefit analysis and ethical issues. Should they use Anne or a surrogate mother's uterus? What is their background understanding of a cloned baby? How do they see the family and relationships? What are their beliefs? What are their own ifs and buts? What are their priorities? How have they decided to face and integrate into the society?

There could be multiple scenarios for Anne and John to approach this: (1) They understand that Anne's ovum makes her mother of the baby. They are informed that their baby will have genetic variability due to mitochondrial DNA. As John is the

nucleus donor so he is considered the father, thus they simply decide Anne's womb. (2) In case they consider the cloned baby to be a twin of John then they could opt for the surrogate uterus. In either option, the couple ends up having their own biological offspring justifying all the medical ethical principles.

The research in therapeutic cloning, reproductive cloning and early human development are overlapping disciplines. Should the experiments in any of these fields be regulated with just one word "consent"? Could the consent of the patient open the door for customized cloning? Do the ethical principles justify the human right of choosing fate of a person's own cells? These approaches are the ways to motivate the key stakeholders i.e., scientific community, society, policy, and ethics to adapt to the inter-related human embryo research dilemmas.

Case B

Now we see another case of Mike and Judi who lost their six-month baby boy, Sam, due to pneumonia. Sam was conceived via IVF because Judi had ovarian cancer and her eggs were preserved before removing her ovaries and uterus. As Mike was healthy, so they chose the option of IVF using Mike's sperm, Judi's preserved ova and a surrogate uterus. For the couple, Sam was a very precious baby, and they want him back. Now, they request to clone Sam using donor egg and a surrogate uterus. In their case, outcome of a successful cloning procedure would be a healthy baby boy. In my opinion the law, policy, ethics and religion cannot stop this couple to use the option of human cloning to get their child back. There is no obvious moral ground except if cloning is against the regional law, they are not allowed access this treatment option. Unfortunately, on ethical and moral grounds we are closing doors for everybody and treating all the scenarios under one law – STOP – NO Reproductive cloning is allowed.

Here comes another question of whether the cloned embryo has to be implanted in the uterus of a biological mother or that of a surrogate woman? **Surrogacy** becomes a part of the problem when relationships are discussed by ethicists, theologists and clerics. By definition, a surrogate is a woman whose uterus is used to implant the embryo till birth. In 'traditional surrogacy' the surrogate woman is artificially inseminated using the couple's male partner or a sperm donor. On the other hand, in 'gestational surrogacy' the surrogate woman does not contribute her ovum. The gestational surrogate receives an embryo created through IVF. Therefore, the traditional surrogate is biological and gestational mother while the gestational surrogate has no biological relation with the offspring. Surrogate arrangements are typically done under surrogacy contracts where the intended parents plan to raise the child (Vaughn, 2019).

Case C

In another case of a Muslim couple, Noor and Razi, who are unable to procreate due to Razi's sterility. Noor and Razi desire to have their own biological offspring. As they are Muslim, they are aware that Islam allows therapeutic cloning (Sadeghi, 2007). However, Islam does not support the reproductive cloning because, in that case, the offspring will be a genetic twin of Razi. When they consult ART specialist, they are offered an option of using Razi's cells to produce iPSCs. iPSCs can be differentiated into sperms (Shinde et al., 2016). Thus, generated sperms can then be used to fertilize Noor's egg via IVF and create an embryo. In such a case, any couple can be helped just by understanding available options, proper counselling, and permissible law. In essence, the discussion, counselling, and informed consent are keys to effectively deal with all clinical scenarios.

Laws, Regulations, and Policies

One can ask if SCNT-based treatment becomes clinically successful first and then then needs a legislative debate or vice versa. Can we predict that after successful monkey cloning humans are next? Can we consider successful primate cloning as a proof of concept? In my view, primate cloning experiments provide enough scientific basis to start legislative discussions around human cloning. In fact, legislation is the key to know where human cloning will be in next decade, after five decades or in next century. The developed countries, in general, allow therapeutic cloning. In United States of America (U.S.A.) does not have any federal laws to completely ban the human cloning. In essence, fifteen USA states prohibit reproductive cloning, and three states refrain from the use of public funds for human cloning research. However, ten USA states allow reproductive cloning while preventing the cloned embryo to be implanted for childbirth purposes (National Conference of State Legislatures, 2016). On the other hand, in European countries, The Charter of Fundamental Rights of the European Union explicitly prohibits reproductive human cloning (*EU Charter of Fundamental Rights*, 2009). Canada bans cloning humans, cloning stem cells, growing human embryos for research purposes, and buying or selling of embryos, sperm, eggs or other human reproductive material (Philipkoski & Philipkoski, 2004).

The UN Declaration on Human Cloning says that human cloning is "incompatible with human dignity and the protection of human life." Therefore, all member states are called to adopt a ban on human cloning (*GENERAL ASSEMBLY ADOPTS UNITED NATIONS DECLARATION ON HUMAN CLONING BY VOTE OF 84–34-37 | Meetings Coverage and Press Releases*, 2005).

The key to move forward are measures to increase awareness through timely knowledge dissemination among health policy creators and open dialogue among the stakeholders – ethicists, consumers, researchers, healthcare providers and

legislation. The debate of human cloning should be continued by stable institutes, problem-solving approach, positive attitude, innovative disciplines, and enlightened members. As a general opinion, the use of stem cells from blastocyst stage cloned human embryos is acceptable for therapeutic purposes. However, it seems ethical to establish that "whenever a fetus reaches the stages of growth, taking organs from it and transplanting them into the body of patients is unlawful and a crime against the fetus" (Sadeghi, 2007).

Conclusion

In essence, there seems a gap between discussion and real-life application of human cloning technique. The debate of cloning practices must be supportive of curing suffering, helping infertile couples and constructive. Moreover, laws and regulations should be based on up-to-date scientific knowledge and real-life scenarios such as mentioned in this chapter. All stakeholders concerned with the discipline of human cloning must identify the future issues expected to be confronted by humanity. Invariably, identifying the problem is the first step to find a solution (Shafique, 2020).

I guess, in near future, better risk assessment, elaborated laws and updated regulations would be the savior for bioethicists and governments. We might need altered explanation of 'words' and 'definitions' such as those of human autonomy, dignity and relationships. The science is of the view that the way IVF, animal cloning, and the fourteen days blastocyst cultivation has been justified, the human cloning will get the approval of society and all the stakeholders. I guess, as science will advance, may be five decades from now, utilitarian approach would predominate shaping a favorable argument in support of human cloning.

As of today, the researchers are aware of the embryo generating lab techniques, future focus would be the issues related to the procedures and their outcomes of a cloned human being. It is important to understand the grey areas around ethical issues from all these technologies because one cause may lead to multiple effects, or one effect could be the outcome of many causes. A prospective human clone needs to be understood in the wide context of: Why created? Where raised? What was the place, environment, society and values around? One can clone biological aspect of a person, but cultural inheritance cannot be copied. In essence, the survival of human species depends on the policies developed by the stakeholders based on laws and regulations able to preserve human identity, self-esteem and individuality yet opening the doors of SCNT for patients in need.

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Part II
Biomedical Research: *Enhancement Research*

Chapter 12
The Evolutionary Optimality Challenge

Nick Bostrom, Anders Sandberg, and Matthew van der Merwe

Abstract Human beings are a marvel of evolved complexity. When we try to enhance poorly-understood complex evolved systems, our interventions often fail or backfire. It can appear as if there is a "wisdom of nature" which we ignore at our peril. A recognition of this reality can manifest as a vaguely normative intuition, to the effect that it is "hubristic" to try to improve on nature, or that biomedical therapy is ok while enhancement is morally suspect. We suggest that one root of these moral intuitions may be fundamentally prudential rather than ethical. More importantly, we develop a practical heuristic, the "evolutionary optimality challenge", for evaluating the plausibility that specific candidate biomedical interventions would be safe and effective. This heuristic recognizes the grain of truth contained in "nature knows best" attitudes while providing criteria for identifying the special cases where it may be feasible, with present or near-future technology, to enhance human nature.

Keywords Enhancements · Evolution heuristic · Evolutionary optimality challenge (EOC) · Cognitive enhancements · Evolutionary incapacity

Introduction

We marvel at the complexity of the human organism, how its various parts have evolved to solve intricate problems: the eye to collect and pre-process visual information, the immune system to fight infection and cancer, the lungs to oxygenate blood. The human brain is arguably the most complex thing in the known universe.

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Given how rudimentary our understanding of these highly complex systems, particularly the brain, how could we have any realistic hope of *enhancing* them?

To enhance even a system like a car or a motorcycle—whose complexity is trivial in comparison to that of the human body—requires a fair bit of understanding of how the thing works. Isn't the challenge we face in trying to enhance human beings so difficult as to be hopelessly beyond our reach, at least until the biological sciences and our overall capabilities have advanced vastly beyond their present state?

It is easier to see how *therapeutic* medicine should be feasible. Intuitively, the explanation would go as follows: Even an excellently designed system will occasionally break. We might then be able to figure out what has broken and how to fix it. This seems much less daunting than to take an excellently designed, unbroken system and enhance it beyond its normal functioning.

Yet we know that even therapeutic medicine is very difficult. It has been claimed that until circa 1900, medicine did more harm than good (McKeown & Lowe, 1974).

Various studies suggest that even much of contemporary medicine is ineffectual or outright harmful (Newhouse & Group, 1993; Frech & Miller, 1996; Kirsch et al., 2002; Bunker, 2001).

And, according to one estimate, iatrogenic deaths are the third leading cause of death in the US (Makary & Daniel, 2016). We are all familiar with drugs, therapies, and nutritional advice once promoted by health authorities yet later found to be damaging. In many cases, those initial recommendations were informed by large clinical trials.

When even therapeutic medicine, based on fairly good empirical data, is so hard to get right, it would seem prudent to be wary of purported *enhancements*, especially when supported by much weaker data. Evolution is a process powerful enough to have developed systems far more complex and capable than anything human scientists or engineers have managed to design. Surely it would be foolish, absent strong supporting evidence, to suppose that we are currently able to do *better* than evolution,[1] especially when we have not even managed to fully understand the systems evolution has "designed" and when our attempts just to repair them often misfire!

We believe that these informal considerations contain a grain of truth. Nonetheless, there are several particular classes of cases where we believe it is feasible to improve human nature. The evolution heuristic is our explanation of why this is so. If the evolution heuristic works as we suggest, it shows that there is *some* validity to the widespread intuition that nature knows best, especially in relation to proposals for human enhancement. But the heuristic also shows that this validity is limited, and it reveals important exceptional cases in which we *can* hope to improve on nature using even our present or near-future science and technology.

The evolution heuristic might be useful for scientists working to develop enhancement technologies. It might also be useful in evaluating beliefs and

[1] At more advanced stages of technological development, it will be more reasonable to assume we can beat evolution at its own game.

arguments about the ethics of human enhancement, because intuitions about the wisdom of nature appear to play an important role in the cognitive ecology of many anti-enhancement advocates.[2] While sophisticated bioconservatives (cognizant of the distinction between "is" and "ought") may not *explicitly* base their arguments on the alleged wisdom of nature, we suspect that such intuitions often influence their judgements about mid-level moral principles invoked in the bioethical literature on human enhancement. Thus, addressing such hidden empirical background assumptions may help illuminate important questions in applied ethics.[3]

The Evolutionary Optimality Challenge

The basic idea is simple. In order to decide whether we want to modify some feature of a system, it is helpful to consider why the system has that feature in the first place.[4] Similarly, if we propose to introduce some new trait, we might ask why the system does not already possess it. The system of concern here is the human organism. The question of why it has a certain feature can be answered on multiple levels of explanation. Here our focus is on its evolutionary history.

We define an enhancement as an intervention that either improves the functioning of some subsystem (e.g. long-term episodic memory) beyond its normal healthy range, or adds a new capacity (e.g. magnetoreception).

Note that on this definition, an enhancement is not necessarily desirable, either for the enhanced individual or for society. For instance, we might have no reason to value an enhancement of our sweat glands that increases their ability, beyond the normal range, to produce perspiration in response to heat stimuli. In other instances, we might benefit from increased functionality or a new capacity, and yet not benefit from the enhancement because it also causes unacceptable side-effects.[5] The evolution heuristic is a tool to help us think through whether some proposed enhancement is likely to yield a net benefit.

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[2] See, for example, Kass (2003).

[3] On the role of mid-level principles in one area of applied ethics, see Beauchamp and Childress (1979). Earlier work has explored the extent to which opposition to enhancements results from an (irrational) bias for the status quo (Bostrom & Ord, 2006).

[4] This is analogous to "Chesterton's Fence" — "*There exists in such a case a certain institution or law; let us say, for the sake of simplicity, a fence or gate erected across a road. The more modern type of reformer goes gaily up to it and says, 'I don't see the use of this; let us clear it away.' To which the more intelligent type of reformer will do well to answer: 'If you don't see the use of it, I certainly won't let you clear it away. Go away and think. Then, when you can come back and tell me that you do see the use of it, I may allow you to destroy it.*'" (Chesterton, 1929).

[5] Which side-effects are acceptable depends, of course, on the benefits resulting from the enhancement, and these may vary between subjects depending on their goals, life plans, and circumstances.

The Starting Point of Our Evolution Heuristic Is to Pose the Evolutionary Optimality Challenge

(EOC) If the proposed intervention would result in a beneficial enhancement, why have we not already evolved to be that way?

Suppose that we "steelman" evolution by likening it to a surpassingly great engineer (Messinger, 2012). We can then re-express the EOC as the question, "How could we realistically hope to improve on this great engineer Evolution's work?" Note that it is the *limitations of this metaphor* that make it useful for our purposes. One does not have to actually believe that evolution is a great and wise engineer; rather, it is a useful exercise to consider precisely the ways in which this is *not* so, because those are the ways in which we may hope to do better.

We Propose that There Are Three Main Categories of Possible Answers to the EOC: Altered Tradeoffs, Evolutionary Incapacity, and Value Discordance

Altered Tradeoffs

Evolution "designed" the system for operation in one type of environment, very different from the one we inhabit today. Modern conditions arose too recently for our species to have fully adapted to them, thus the tradeoffs struck by evolution may no longer be optimal today. It would not be surprising, then, if we were able to modify the system to better fit the novel requirements. It is much harder to design and build a car from scratch than it is to make some tweaks to improve function in a particular setting, for example, fitting it with a new set of tyres for icy roads. Similarly, the human organism, initially developed for operation as a hunter-gatherer on the African savannah, must now function in the modern world. We may well be capable of making some enhancing adjustments to fit the new environment even if our engineering talent does not remotely approach that of evolution.

Evolutionary Incapacity

Even if some trait would have been adaptive in our ancestral environment, there is no guarantee that evolution would have discovered it. We have access to various tools, materials, and techniques that were unavailable to evolution. We can work backwards, starting with a goal in mind and figuring out the steps necessary to attain some trait. Even if our engineering talent were far inferior to evolution's, we may nevertheless be able to achieve certain things that stumped evolution, thanks to

these novel aids. We should be cautious in invoking this explanation though; evolution often managed to achieve with primitive means what we are unable to do with state-of-the-art technology. But in some cases, we can show that it is practically infeasible to create a certain feature without some particular tool—no matter how ingenious the engineer—while the same feature can be achieved by any dimwit given access to the right tool. In these special cases, we might be able to overcome evolutionary restrictions without presupposing that our talent exceeds that of evolution.

Value Discordance

Even if evolution had managed to build the finest reproduction and survival machine imaginable, we may still benefit from changing it because what we value is not primarily to be maximally effective fitness optimizers. There is a discrepancy between the standards by which evolution measured the quality of its work and the standards we wish to apply. It is not surprising that we can modify a system to better meet our goals if they differ substantially from the ones that (metaphorically might be seen as having) guided evolution in designing the system the way it did. Again, this explanation does not presuppose that our engineering talent exceeds evolution's. Compare the case to that of a mediocre technician, who would never be able to design a car, let alone a good one, but who may well be capable of converting the latest BMW model into a crude rain-collecting device, thereby *enhancing* the system's functionality in this respect.

In the following sections, we explore each of these categories of possible answers to the EOC in more detail.

Altered Tradeoffs

Evolutionary adaptation requires striking tradeoffs between competing "design criteria". Evolution has fine-tuned us for life in the ancestral environment, which, for the most part, was life as a member of a hunter-gatherer tribe roaming the African savannah. Because modern societies differ in many ways from the environment of evolutionary adaptedness, the tradeoffs struck by evolution may no longer be biologically optimal.

In evolutionary biology, the "environment of evolutionary adaptedness" (EEA) refers not to a particular time or place, but to the environment in which a species evolved and to which it is adapted (Bennett, 2018). It includes both inanimate and animate aspects of the environment, such as climate, vegetation, prey, predators, pathogens, and the social environment of conspecifics. We can also think of the EEA as the set of all evolutionary pressures faced by the ancestors of the species over recent evolutionary time—in the case of humans, at least 200,000 years.

Hunting, gathering of fruits and nuts, courtship, parasites, and violent encounters with wild animals and enemy tribes were elements of the EEA; speeding cars, fast food, desk jobs, and tax returns were not.

If we can identify specific changes to our environment that have shifted the optimal tradeoff point between competing design desiderata in a determinable direction, then we may be able to find interventions that would "retune" the tradeoff to a point closer to the present optimum. Such retuning interventions might be among the low-hanging fruits on the enhancement tree—ones we could reach even without recourse to super-advanced biomedical technology.

Enhancements that aim to retune altered tradeoffs can often meet the EOC. A new trait might have been maladaptive in the EEA even though it would be adaptive now. Alternatively, the new trait might be intrinsically associated with another that was maladaptive in the EEA but has become less disadvantageous (or even beneficial) in the modern environment. In either case, the enhancement could be adaptive today without having been so in the EEA, providing an explanation of why we do not already have that trait, thus meeting the EOC.

We can roughly distinguish two ways in which tradeoffs can change. Firstly, new *resources* may have become available that were either absent or available only at great cost in the EEA. Secondly, the *demands* placed on one of the human organism's subsystems may have changed since we left the EEA. Let us consider these two possibilities in turn.

Changes in Resources

One of the main differences between human life today (for most people in developed countries) and life in the EEA is the abundant availability of food. In the state of nature, food is relatively scarce much of the time, making energy conservation important and implying tradeoffs between investments in metabolically costly tissues, processes, and behaviors. As we shall see, increased access to nutrients suggests several promising enhancement opportunities. We have also gained access to important new non-dietary resources, including improved protection against physical threats, obstetric assistance, better temperature control, and increased information availability.

We can illustrate these considerations by examining how they could apply to potential enhancements of the brain. (Throughout this chapter, the examples we give are designed mainly to be helpful in understanding how the heuristic works. They should not be read as a "favorite list" of the enhancements we think look most promising.)

Example: Size And Energy Consumption of the Brain

The human brain constitutes only 2% of body mass yet accounts for about 20% of total energy expenditure. Combined, the brain, heart, gastrointestinal tract, kidneys, and liver consume 70% of basal metabolism. This forces tradeoffs between the size

and capacity of these organs, and between allocation of time and energy to activities other than searching for food in greater quantity or quality (Aiello et al., 2001; Fish & Lockwood, 2003).

Unsurprisingly, we find that, in evolutionary lineages where nutritional demands are high and cognitive demands low (such as bats hunting in uncluttered environments), relative brain size is correspondingly smaller (Niven, 2005).

In humans, brain size correlates positively with cognitive capacity ($r \approx 0.4$) (McDaniel, 2005; Rushton & Ankney, 2009). Holding brain mass constant, a greater level of mental activity might also enable us to apply our brains more effectively to process information and solve problems. The brain, however, requires extra energy when we exert mental effort, reducing the normally tightly regulated blood glucose level by about 5% for short efforts and more for longer exertions (Fairclough & Houston, 2004; Scholey et al., 2001). Increasing blood glucose levels has been shown to improve cognitive performance in demanding tasks (Korol & Gold, 1998; Manning et al., 1998; Martin & Benton, 1999; Meikle et al., 2005; Smith et al., 2011).

The metabolic problem is exacerbated during prenatal and early childhood growth when brain development requires extra energy. Brain metabolism accounts for a staggering 60% of total metabolism in newborns (Holliday, 1986), intensifying the competition between mother and child for nutritional resources during gestation and infancy (Martin, 1996). Children with greater birth weight have a cognitive advantage (Matte, 2001).

Another constraint on prenatal cerebral development is the size of the human birth canal (itself constrained by bipedalism), which historically placed severe limits on the size of newborns' heads (Trevathan, 1987). These constraints are partly obviated by modern obstetrics (particularly the availability of cesarean section). One way of reducing head size at birth and perinatal energy demands would have been to extend the period of postnatal maturation; however, delayed maturation was vastly riskier in the EEA than it is now.

What all this suggests is that cognitive enhancements might be possible if we can find interventions that recalibrate these legacy tradeoffs in ways that are more optimal in the contemporary world. For example, suppose we could discover interventions that moderately increase brain growth during gestation, or slightly prolong the period of brain growth during infancy, or that trigger an increase in available mental energy. Applying the EOC to these hypothetical interventions, we get a green light. We can see why these enhancements would have been maladaptive in the EEA and why they may nevertheless have become beneficial now that the underlying tradeoffs have changed, thanks to the plentiful availability of food. If the "downside" of more mental energy is that one burns more calories, many of us would regard this as a pretty good deal.

Not *all* cognitive enhancements get an immediate green light from this line of reasoning. Consider, for example, stimulants like caffeine and modafinil, which enable increased wakefulness and control over sleep patterns (Caldwell, 2001). Sleep, however, serves important yet poorly understood functions besides energy conservation (Siegel, 2005). This should give us pause. Without a clear understanding of the terms of the tradeoff struck by evolution, we cannot be confident we have

met the EOC. In such cases, the heuristic counsels caution. If the reason we do not sleep less than we do has to do with these other functions, then reducing sleep might well turn out to have more problematic side-effects than increasing caloric expenditure.

Changes in Demands

Just as there have been changes in the available resources, as compared to our hunter-gatherer ancestors' world, so too have there been changes in the demands we face in the modern environment. These suggest another set of potential opportunities for enhancement.

Many "diseases of civilization" are thought to be caused, at least in part, by changed demands. For example, our ancestors needed to exert themselves physically to secure adequate nutrition, whereas easy and continuous access to abundant food can promote obesity. Comfortable modern indoor environments lead us to spend less time outside, leading to widespread vitamin D deficiency (Amrein et al., 2020; Thomas et al., 1998).

Below, we consider two examples of possible enhancement targets suggested by such changes in demand.

Example: Abstract Thinking and Mental Focus
A capacity for abstract reasoning seems to have become more rewarded in contemporary society than it was in the EEA. There is a positive correlation in Western society between IQ and income (Gottfredson, 1997; Neisser et al., 1996; Zagorsky, 2007). Higher levels of general cognitive ability are important not just for many well-paid high-status jobs, but also for success in everyday life, such as for being able to fill out forms, understand news, and maintain health. As society becomes more complex, people with low cognitive ability are placed at an increasing disadvantage (Gottfredson, 1997; Gottfredson, 2004).

And while above-average general cognitive ability may have been somewhat advantageous in the EEA, the degree of change in demand that has occured for some *particular* cognitive abilities (such aptitude for numeracy and literacy) is even more dramatic. It would not be surprising if there were relatively minor neurological changes—perhaps achievable via germline genetic interventions—that would greatly increase our faculties for formal mathematics and literacy, given that there has not been much specific selection for these traits (as opposed to selection for more general learning capabilities that can also be applied in these domains). Boosting our capacity for abstract symbol manipulation might be net beneficial in the modern environment even if it came at the expense of some other cognitive faculties—for example, if it left less cortical area for processing olfactory information, motor planning, landmark navigation, or visual motion detection.

The increased demand we now face for sustained attention on abstract cognitive tasks also suggests that we look for opportunities to adjust tradeoffs to favor such

focused mental activity at the expense of other forms of processing. For example, in the EEA, it may have been important to sustain a high level of peripheral awareness to scan for potential predators and enemies, and much less important to be able to focus on a piece of text or a spreadsheet for hours at a time. In a modern white-collar environment, the priorities are reversed. The result is that levels of distractibility and external stimulation-seeking that may have been adaptive in the EEA are now dysfunctional, and a significant fraction of the population is diagnosed as suffering from ADHD. The changed demand for different forms of mental activity suggests that we may hope to find cognitive enhancers that work by shifting the balance from one form to another in ways that improve the tradeoff. For example, drugs such as methylphenidate and amphetamine can enable sustained focused mental effort (at the expense of more relaxed, unfocused, meandering, environment-aware forms of cognition), and they are frequently used for enhancement purposes.

Example: Dietary Preferences and Fat Storage
In the EEA, we needed fat deposits, but now it's better to have bank deposits. When food is reliably available and we have better ways to store resources, we face reduced demand for consuming and accumulating calories, yet we still have our old evolved cravings for high-calorie foods. This suggests opportunities for enhancement by altering our taste preferences or recalibrating our bodies' set-points for appetite and fat storage.

In principle, there are many routes to effectuate such a recalibration—ranging from nutritional advice, diet pills, artificial sweeteners, indigestible substances that taste like fat, weight loss clubs and hypnotherapy, to genetic or pharmaceutical interventions that change our hormonal or neuroregulatory systems, or interfere with lower-level metabolic pathways. The EOC does not explain why success in this direction has so far been limited despite considerable investment, but it does hold out some hope that a solution to the obesity epidemic may be available (even with technology not much more advanced than the current state of art).

Evolutionary Incapacity

We have discussed opportunities for enhancement arising from altered tradeoffs. Even if we think of evolution as a surpassingly great engineer, whose skills we cannot hope to match, we can nevertheless hope to achieve some enhancements by fine-tuning evolution's work to better fit the modern environment. We now turn to another source of potential enhancement opportunities: ones that arise from the fact that there are certain fundamental limitations in what evolution is able to do. Couched in the 'great engineer' metaphor, we could express this by saying that we may, without hubris, hope to achieve certain things with our clumsy fiddling that stumped evolution, because we have access to certain tools, materials, and techniques that the great ingenious engineer lacked.

Metaphors aside, we can identify several restrictions of evolution's ability to achieve fitness-maximizing phenotypes even in the EEA. We can divide these into three classes:

- *Fundamental inability*: evolution is fundamentally unable to produce some trait (even though the trait would be boosted fitness).
- *Local optima*: perhaps for contingent historical reasons, evolution got stuck in a local optimum that excludes some trait that would have been fitness-increasing.
- *Lags*: the development of a fitness-increasing trait, while evolutionarily feasible, would require so many generations that there has not yet been enough time for it to arise.

These three classes are not sharply separable. For example, one reason a trait may take a vast number of generations to develop is that it requires escaping from one or more local optima. Conversely, given *very* long time scales, even some traits that we may regard as fundamentally beyond evolution's reach might conceivably have evolved. However, the partition into these three classes can serve as a useful rough guide.

Fundamental Inability

Biological evolution is limited in what it can achieve. For example, it seems unlikely that any biological organism could produce diamond. And while bacteria can produce microscopic metal crystals (Klaus et al., 1999), there is no way to unite them into contiguous metal. So it might not be surprising that evolution has not given us diamond tooth enamel or a titanium skeleton, even if these traits would have increased fitness in the EEA.

Examples are easy to multiply. Evolution could probably not have evolved high-performance silicon chips to augment neural computation, even though such chips might have been able to serve useful cognitive functions. A theoretical design of artificial red blood cells ("respirocytes") has been published, which would enable performance far outside the range of natural red blood cells, allowing us to hold our breath for 3.8 hours. But the design relies on materials and pressures that are unavailable to evolution (Freitas, 1998).

Engineered systems that radically depart from nature may create various complications with biocompatibility or functional integration with evolved systems. But at least there is no mystery as to why we have not already evolved these systems, even under the supposition that they would have been adaptive in the EEA. Enhancements that evolution is fundamentally unable to produce can therefore meet the EOC.

When invoking "fundamental inability", it is important to determine that the inability does not pertain merely to the specific means whereby one intends to achieve the enhanced trait. If evolution would have been able to employ some *other* means to the same effect, we would have to wonder why evolution had given us the trait via this alternative route, and the EOC would remain unanswered.

Local Optima

Evolution sometimes gets stuck on solutions that are locally but not globally optimal. A locally optimal solution is one where any small change would make the solution worse, even if some bigger set of changes might make it better.

Being trapped in a local optimum is especially likely to account for failure to evolve polygenic traits that are adaptive only once fully developed, but incur a fitness penalty in their intermediary stages of evolution. In some cases, the evolution of such traits may require an improbable coincidence of several simultaneous mutations that might simply not have occurred among our finite number of ancestors. In these cases, a crafty genetic engineer could have some hope of attaining a solution that surpasses the one found by natural evolution. A human engineer can *plan*—starting with a goal in mind, working backward to determine the genetic modifications necessary for its attainment, and then implementing the full set of needed modifications in one go. Goal-directed planning can often achieve outcomes that are infeasible to attain via myopic processes or random search.

Example: The Appendix
The human appendix is a vestigial remnant of the caecum in other mammals. While it has some limited immunological function (Fisher, 2000), it easily becomes infected. In a world without surgery and antibiotics, appendicitis is a life-threatening condition (and it often occurs at a relatively young age). There is also some evidence that surgical removal of the appendix might reduce the risk of ulcerative colitis (Andersson et al., 2001; Koutroubakis & Vlachonikolis, 2000). This would suggest that removal of the appendix might have increased fitness in the EEA.

A *smaller* appendix, however, *increases* the risk of appendicitis. Carriers of genes predisposing for small appendices have higher risks of appendicitis than non-carriers—and, presumably, lower fitness (Nesse & Williams, 1998). Therefore, unless evolution could find a way of completely doing away with the appendix entirely in one fell swoop, it might be unable to get rid of the thing, hence it remains, despite being a liability. If this story is correct, then an intervention that safely and conveniently removed the appendix might be a plausible enhancement capable of meeting the EOC.

Another source of evolutionary lock-in is *antagonistic pleiotropy*. This refers to a situation in which a gene affects multiple traits in both beneficial and harmful ways. If one trait is strongly fitness-increasing and the other mildly fitness-decreasing, the overall effect is positive selection for the gene (Leroi et al., 2005). The local optimum here is to retain the gene in question. But the global optimum would be to circumvent the antagonistic pleiotropy, by evolving new genes that specifically produce the beneficial traits without causing the detrimental effects on other traits.

Over longer timescales, evolution usually gets around antagonistic pleiotropy, for instance by evolving modifier genes that counteract the negative effects (Hammerstein, 1996). However, such developments can take a long time, and in the meanwhile a species remains trapped in a local optimum.

Example: The ε4 Allele

One well-known example of antagonistic pleiotropy is the ε4 allele of apolipoprotein E. Having one or two copies of this allele increases the risk of Alzheimer's disease in middle age but lowers the incidence of childhood diarrhea and may also have some protective effects during neurological development (Oria et al., 2005). One potential enhancement that might therefore pass the EOC could be to add these alleles for their benefit in early life but then remove them or silence them in later life, to avoid paying the cost of increased Alzheimer's risk.

Yet another way in which evolution can get trapped into a suboptimal state is exemplified by the phenomenon of *heterozygote advantage*. This refers to the not uncommon situation where individuals who are heterozygous for a particular gene (i.e. possess two different alleles of that gene) have an advantage over homozygous individuals (who have two identical copies). Heterozygote advantage is responsible for many cases where potentially harmful genes are being maintained at a finite frequency in the population.

Example: The Sickle-Cell Allele

The classic example of heterozygote advantage is the sickle-cell gene, where homozygous individuals suffer anemia while heterozygous individuals benefit from improved malaria resistance (Allison, 1954; Cavalli-Sforza & Bodmer, 1999). Heterozygotes have greater fitness than both types of homozygotes (those lacking the sickle-cell allele and those having two copies of it). Balancing selection preserves the sickle-cell gene in populations (at a frequency that varies geographically with the prevalence of malaria). The local optimum selected by evolution is one in which, by chance, some individuals will be born homozygous for the gene, resulting in sickle-cell anemia, a potentially fatal blood disease. The more global or ideal optimum—everybody being heterozygous for the gene—is unattainable by natural selection because of Mendelian inheritance, which gives each child born to heterozygous parents a 25% risk of being homozygous for the sickle-cell allele.

Heterozygote advantage suggests obvious opportunities for enhancement. Prenatal genetic screening could be used to guarantee that a child is born with exactly one copy of the allele, thereby securing the universal benefit of heterozygosity while avoiding the cost of some fraction of the population ending up homozygous. Other interventions could also be possible, such as somatic gene therapy or pharmaceuticals that reproduce the beneficial effects of heterozygosity in individuals lacking any sickle-cell allele.[6]

Another kind of evolutionary lock-in is that of an evolutionarily stable strategy: "a strategy such that, if all the members of a population adopt it, no mutant strategy can invade" (Smith, 1982). One way species can become trapped in such an

[6] Some individuals possess a variant allele (HbC) that provides malaria resistance without sickle-cell anemia in its homozygotic state. However, the HbC allele incurs a fitness penalty when heterozygous with either of the more prevalent alleles; and so exists only at low frequency in human populations (Wilkins & Godfrey-Smith, 2009). This suggests another enhancement option: to use genetic engineering to ensure homozygosity for the HbC allele.

equilibrium is via sexual selection. In order to be successful at wooing peahens, peacocks must produce extravagant tails which serve to advertise their genetic quality. Since only healthy peacocks can afford to grow and carry top-notch tails, it is adaptive for peahens to prefer to mate with peacocks that sport such impressive tails; and given this fact, it is also adaptive for peacocks to invest heavily in their rear plumage. However, it is likely that the *species* would have been better off (in the sense of becoming more abundant and more competitive relative to other species occupying the same niche) if it had evolved some less costly way for males to signal their fitness. Yet no individual peacock or peahen is able to defect from the evolutionarily stable strategy without thereby removing themselves from the gene pool. If there had been a United Nations of the peafowl, through which the birds could adopt a coordinated Millennium Plan to overcome their species' vanity, the peacocks might well have voted for a sumptuary law that required them all to trim their tail feathers and adopt more modest attire.

The concept of an evolutionarily stable strategy can be generalized to that of an evolutionarily stable state. A population is said to be in an evolutionarily stable state if its genetic composition is restored by selection after a disturbance, provided the disturbance is not too large (Smith, 1982). Such a population can be genetically monomorphic or polymorphic. Thus, while an evolutionarily stable strategy is one that is stable if *everybody* adopts it, an evolutionary stable state can encompass a set of different strategies whose distribution is stable under small perturbations. It has been suggested, for example, that the human population has been in a stable state in the EEA with regard to sociopathy, which can be seen as a defector strategy which can prosper when it is rare but becomes maladaptive when it is more common (Mealey, 1995).

Lags

Evolution takes time—often, a *long* time. If conditions change rapidly, the genome will lag. Given that conditions for our hominid ancestors were quite variable—due to migration into new regions, climate change, social dynamics, advances in tool use, and adaptation in pathogens, parasites, predators, and prey—our species has never been perfectly adapted to its environment. Evolution is running up fitness slopes, but when the fitness landscape keeps changing under its feet, it may never reach a peak. Even when beneficial alleles or allele combinations exist, they may not have had time to diffuse across human populations. For some proposed enhancements, evolutionary lag can therefore provide an answer to the EOC.

This manner of meeting the EOC is related to the "altered tradeoffs" category, but with the difference that it focuses on ways in which *even in the EEA* we were not perfectly adapted to our environment. So there is the potential for an additional set of mismatches—and consequently for low-hanging enhancement opportunities—beyond those that have arisen with the dramatic changes in resource and demand that have followed the introduction of agriculture.

The speed of evolution is limited by many factors (Barton & Partridge, 2000). Some are inherent in the process itself, such as the mutation rate, the need for sufficient genetic diversity, and the constraint that selection can only encode a few bits into the genome per generation (Worden, 1995). A recessive beneficial mutation will spread to an appreciable fraction of a fixed well-mixed population in time inversely proportional to its selective advantage. For example, if the mutation gives a 0.1% increase in fitness, it will take 9200 generations to reach 50% of the population from a starting prevalence of 0.01% (Cavalli-Sforza & Bodmer, 1999).[7] Reviews of published studies have found that for most traits in most species, directional selection is fairly weak, suggesting that beneficial new traits are likely to spread slowly (Hoekstra et al., 2001; Kingsolver & Pfennig, 2007).

There is evidence for recent positive selection in humans (Voight et al., 2006). Some of it may be in response to climate variations, producing a wide range of variation in salt-regulating genes and skin pigmentation in populations far from the equator (Ju & Mathieson, 2021; Thompson et al., 2004). Significantly, genes involved in brain development have also been shown to have been under strong positive selection, with new variants emerging over the last 37,000 years and 5800 years (Evans et al., 2005; Mekel-Bobrov et al., 2005).[8]

If we find a gene that has a desirable effect, and that evolved recently and has not yet spread far despite showing evidence of positive selection, interventions that insert it into the genome or mimic its effects would likely meet the EOC.

Example: Lactase Persistence

Humans typically lose the ability to digest lactose after infancy, due to decreased production of the lactase enzyme. While this may have been adaptive in the past, since it makes weaning easier, increased consumption of dairy products beyond childhood have stimulated selection for lactase persistence in humans over the last 5000–10,000 years (Bersaglieri et al., 2004). This is so recent that there has not been time for the trait to diffuse to all human populations—globally, 35% of adults are estimated to exhibit lactase persistence (Gerbault et al., 2011). Taking lactase pills enables lactose intolerant people to digest lactose, widening the range of food they can enjoy. This enhancement clearly passes the EOC.

[7] Population structure (especially low-population bottlenecks) can significantly shorten the time it takes for a new allele to reach fixation.

[8] The rapid growth of the brain in the human lineage also suggests that its size must be controlled by relatively simple genetic mechanisms (Roth & Dicke, 2005). It is noteworthy that, despite this, the selection differential for human brain weight during the Pleistocene was only 0.0004 per generation (Cavalli-Sforza & Bodmer, 1999).

Value Discordance

Our final top-level category of answers to the EOC focuses on the discordance between evolutionary fitness and human values. Even if human beings were optimal with respect to fitness in our current environment (and we have just seen that this is not always the case), this would provide no guarantee that we were optimal with respect to what matters to us. A great engineer may have built a system that efficiently serves one purpose; and it could still be unsurprising if a lesser engineer were able to tinker with it to make it better serve a different purpose.

Although our goals are not identical to those (metaphorically) pursued by evolution, there is considerable overlap. We value health; and health increases fitness. We value good eyesight; and good eyesight is useful for survival. We value musicality and artistic creativity; and these talents probably helped to attract mates in the EEA. If we are hoping to enhance some trait that is equally sought by evolution as it is by us, then we will not find an answer to the EOC in the discordance category, and we must either seek for an answer in one of the other categories or else suspect that what may *appear* to be an easy and unambiguous enhancement will in fact turn out to come at some large hidden cost. However, there are also many traits that we would value that would either have provided no evolutionary benefit in our ancestral environment, or else would not have done so to a sufficient degree to result in the extent of trait development that would be optimal from the perspective of our own values. These cases offer potential opportunities for feasible enhancement.

Example: Contraceptives
Contraceptive technologies can be viewed as a form of enhancement, since they increase our control over our reproductive systems. We may value this because it makes family planning easier and increases choice. But evolution frowns on these practices. There is no mystery why we haven't evolved an easy reproductive off-switch under volitional control—evolution (no matter how skillful as an engineer) didn't *try* to do that. Contraceptives thus easily pass the EOC.[9]

It is useful to distinguish two very different sources of value discordance. One is that the characteristics that would maximize an individual's fitness are not always identical to the characteristics that would be best *for her*. The other is that the characteristics that would maximize an individual's fitness are not always identical to those that would be *best for society*, or *impersonally best*. If our goal is to identify potential interventions that individuals would have prudential reasons for wanting, then we may perhaps set aside the second source of value discordance. If, however, we are interested in addressing broader ethical or public policy questions, then it is relevant to consider value discordance arising from either of these two sources. Let us review each of them in turn.

[9] Evolution might still have the last laugh if in the long run she redesigns our species to directly desire to have as many children as possible, or to have an aversion against contraceptives. Cultural evolution might beat biological evolution to the punch.

Good for the Individual

There is a vast philosophical and empirical literature on the question of which traits promote individual well-being, which we shall not review here. For our purposes, it will suffice to list some candidates which might, with some plausibility, be claimed to contribute to individual well-being in a wide range of circumstances.[10] (This list is for illustration only—lists could be substituted without affecting the argument.)

Some traits that may promote individual well-being:

- Subjective well-being
- Freedom from severe or chronic pain
- Friendship and love
- Long-term memory
- Mathematical ability
- Beauty
- Awareness and consciousness
- Musicality
- Artistic appreciation and creativity
- Literary aptitude
- Confidence and self-esteem
- Athletic skill
- Healthy proclivities
- Mental energy
- Ability to concentrate
- Intelligence
- Longevity
- Social skills

To illustrate the idea, take long-term memory. Suppose that we believe that having better memory would tend to make our lives go better—perhaps because it would give us competitive advantages in the job market, or perhaps because we believe that memory is linked to other abilities or outcomes that would increase our well-being. We are considering some intervention, perhaps a pill, that appears to improve memory. We then pose the EOC: Why has evolution not already endowed us with better long-term memory than we have?

Perhaps we find an answer in one of the categories covered above (altered trade-offs and evolutionary incapacity). Yet suppose that we don't. We may then seek an answer in value discordance. Even if the intervention would have been maladaptive

[10] The items in the list need not be restricted to final goods; it can include characteristics that are mere means to more fundamental goods. For example, even if one holds that musicality or musical appreciation is not intrinsically good, one can still include them in the list if one believes that they tend—as a matter of empirical fact—to promote well-being, e.g. by multiplying opportunities for enjoyment.

in the EEA, and even if it would still be maladaptive today, it may nevertheless be good for us, since what is good for us is not the same as what maximizes our fitness.

But we are not yet done. In cases like this, the evolution heuristic tells us that we should expect that the intervention will have some effect that reduces fitness. If we cannot form any plausible idea of what sort of effect this might be, then we should be wary. A fitness-reducing effect that we have not anticipated might be something very bad, such as a serious medical side-effect (which might manifest after a long delay) or some subtle functional deterioration that we cannot easily detect or attribute.[11] The EOC raises a warning flag.

If, however, we can give a plausible account of why the proposed intervention to improve long-term memory would reduce fitness, *and yet we judge this fitness-reducing effect as desirable or at least worth enduring for the sake of the benefit*, then we have met the EOC. This does not *guarantee* that the enhancement will succeed. It is still possible that the intervention will fail to produce the desired result or that it will have some unforeseen negative side-effect. There might be more than one sufficient reason why evolution did not already make this intervention to enhance our long-term memory. But once we have identified at least one sufficient reason, the warning flag raised by the EOC comes down.

Example: Happiness

Evolution is not really concerned with our happiness and has instead produced many adaptations that cause psychological distress and frustration (Buss, 2000). The "hedonic-treadmill" causes us to quickly habituate to positive changes; gains that thrilled us at first soon get taken for granted and become a new baseline that we experience as barely adequate—presumably this was adaptive in the EEA as a way to prevent complacency (Diener et al., 1999). Similarly, sexual jealousy, romantic heartaches, status envy, competitiveness, anxiety, boredom, sadness and despair may all have been conducive to survival and reproductive success in the Pleistocene and subsequently, yet they exert a heavy toll in human suffering.

An intervention that caused an upward shift in our hedonic set-point, or that down-regulated some of these negative emotions, would therefore meet the EOC. We can see why the intervention would have been maladaptive in the EEA, and yet believe that we would benefit from it because of a discordance between fitness and individual well-being: we value happiness more highly than evolution did.

Good for Society

Many characteristics that promote individual well-being also promote the wider good, but the two lists are unlikely to be identical.

[11] A relevant example here is the 'Doogie' lab mice, genetically engineered to have enhanced memory, but which also exhibited increased sensitivity to pain—something that would likely have been a fitness disadvantage in the EEA (Lehrer, 2009).

Some traits that may promote the social good:

- Extended altruism
- Conscientiousness
- Honesty and integrity
- Modesty and self-deprecation
- Originality, inventiveness, and independent thinking
- Civil courage
- Knowledge and good judgment about public affairs
- Empathy and compassion
- Nurturing emotions and caring behavior
- Just admiration and appreciation
- Sense of fairness
- Lack of racial prejudice
- Lack of tendency to abuse drugs
- Taking joy in others' successes and flourishing
- Useful forms of economic productivity
- Health

As with the list for individual well-being, this one is for illustration only. One could create alternative lists for various related questions, such as traits that are good for humanity as a whole, or for sentient life, or for a particular community, or traits that specifically help us become better moral agents. Such lists may overlap, but they will likely disagree about some traits or their relative importance. The evolution heuristic can be applied using any such list as input, and the procedure is similar to that for the "good for the individual" type of value discordance.

Example: Compassion

Suppose we have a drug that appears to make those who take it more compassionate. This might seem like a good thing, but why hasn't evolution already made us more compassionate? Presumably, we could easily have evolved to produce some endogenous substance with similar effects to the drug; so the likely explanation is that a higher level of compassionateness would not have increased fitness in the EEA.

We then press on and ask *why* it is that greater compassionateness would not have been adaptive. And we can plausibly surmise that the reason is that such a trait would have been associated with evolutionary downsides—such as reduced ability to credibly threaten savage retaliation, or a tendency to spare the lives of enemies allowing them to come back another day and reverse their defeat, or an increased propensity to offer help to those in need beyond what is useful for reciprocity and social acceptance, and so forth. But these very effects, which would have made heightened compassion maladaptive for an individual in the EEA, are precisely the kinds of effects which we might believe would make it beneficial for the common good today. Note that we don't have to assume that the relevant tradeoffs have changed since the EEA. Even in the EEA, it might have had net good effects for a local population of hunter-gatherers if one of their members were born with a mutation that caused an unusually high level of compassion; we just need to assume that the individual

herself would have incurred a fitness penalty. If we accept these premises, then the hypothetical drug that increases compassionateness would pass the EOC.

The Heuristic

The evolutionary optimality challenge asks, of an apparently attractive enhancement, why we have not already evolved the intended trait if it really is such a rad innovation. When trying to answer this question, we might find ourselves in one of several possible epistemic positions:

Current ignorance prevents us from forming any plausible idea about the evolutionary factors at play

This should give us pause. If we do not understand why a very complex evolved system has a certain property, there is a considerable risk that something will go wrong if we try to modify it. The case might be one where nature does indeed know best.

We are not claiming that it is *always* inadvisable to proceed with an intervention in a case like this. We might have other sources of evidence that reassure us that it will produce the intended result without causing unacceptable side-effects. For example, we might have used the intervention many times before, always to great success; or we might have experimental evidence from a closely analogous system, such as an animal model, suggesting that it should work in humans too. The evolution heuristic here delivers only a weak recommendation: that absent a good answer to the EOC, we should proceed with great caution, and we should be on the alert for the possibility that the intervention will turn out to have significant (though perhaps subtle) side-effects.

We come up with a plausible idea about the relevant evolutionary factors, and they suggest that the intervention would be harmful.

In this case, our initial hopes of having identified a useful enhancement are undermined when we apply the evolution heuristic. None of the three categories we have described yields a satisfactory answer to the EOC: relevant tradeoffs have not changed since the EEA; evolution would have been capable of producing the intended modification by now; and there is no significant value discordance in relation to the targeted trait. Here, the heuristic gives us a strong reason for thinking that the enhancement intervention will fail or backfire. This is a case where we should respect the wisdom of nature.

We come up with several different plausible ideas about the relevant evolutionary factors.

A third possibility is that we come up with two or more plausible but incompatible accounts of the evolutionary factors at play. We must then consider the implications of each of the different evolutionary accounts separately with respect to the EOC. If all of them show green lights, we are encouraged to proceed. If some of the evolutionary accounts show green lights but others show red lights, then we face a

situation of familiar scientific uncertainty, and we can use decision theory to determine how to proceed. We might take the gamble if we feel that the balance of probabilities sufficiently favors the green lights; otherwise, we can attempt to acquire more information in order to reduce the uncertainty, or forgo the potential enhancement and try something else.

We develop a plausible idea about the relevant evolutionary factors, and they imply we wouldn't have evolved the enhanced capacity even if it were beneficial.

The final possibility is that we find a convincing account of the pertinent evolutionary factors which provides a satisfactory explanation of why we would not have evolved some trait even if it were overall beneficial. Then the heuristic gives us a green light to proceed. We have found grounds for a justified belief that, in the case before us, it would not be hubristic to suppose that we may be able to improve upon nature's work. Of course, it is still perfectly possible for us to fail—any specific intervention could have any number of *incidental* side-effects—and all the ordinary reasons for care and caution still apply; but there is no special "wisdom of nature" reason for pessimism in this case.

Discussion

There is a widespread belief in some kind of "wisdom of nature". Many people prefer "natural" remedies, "natural" food supplements, and "natural" ways of improving ourselves (such as training, diet, education, and grooming). Offerings that are construed as "unnatural" are often viewed with suspicion. This negative attitude is especially strong in relation to biomedical means of enhancing human capacities, which are often viewed as unwise, short-sighted, or hubristic. We believe that such attitudes also influence normative intuitions in debates about human enhancement ethics.

While it is tempting to dismiss intuitions about the wisdom of nature as vulgar prejudice, we have argued that they contain an important grain of truth. We have attempted to extract this truth in the form of the evolutionary optimality challenge, which asks for any proposed enhancement: if it would indeed be so beneficial, why haven't we already evolved to be that way?

After posing this challenge, our heuristic instructs one to examine three broad categories of answers: altered tradeoffs, evolutionary incapacity, and value discordance. These categories correspond to systematic limitations of the wisdom of nature idea. For some potential enhancement interventions, the challenge can be met with an answer from one of these categories; for others, it cannot. The latter interventions do warrant extra suspicion, and attempting them may indeed be unwise and hubristic. In contrast, interventions for which we can meet the EOC do not defy the wisdom of nature, and have a better chance of turning out well.

Pace Powell and Buchanan (2011), our argument does not rely on a (false) "strong adaptationist" assumption of evolutionary optimality. On the contrary, the heuristic we have presented seeks to zoom in on the ways in which evolution is *not*

optimal, although it does simultaneously emphasize that evolution can—in a certain circumscribed sense and within certain limits—usefully be characterized as a biological optimization process. If one overestimates the degree of evolutionary optimality that is typically found in nature, and one then applies the EOC and finds that it gives a green light to a particular proposed enhancement, this should *increase* one's confidence that it would in fact be safe and beneficial. (The cost of overestimating evolution's optimality, in the present context, is that it would increase our heuristic's false-alarm rate—giving wisdom of nature arguments more credit than they are due.)

It should go without saying that we do not think that our heuristic should *replace* other more familiar ways of evaluating candidate enhancement interventions, such as via a detailed mechanistic level understanding of relevant biological systems or via well-designed clinical trials. Our claim is far more modest; that the heuristic can serve as a sometimes useful complement—an additional lense through which the (typically very messy) empirical situation can be viewed. It may be helpful in nominating promising candidate enhancement interventions and in setting reasonable prior expectations for the likelihood of success. The need for the heuristic would disappear if one had a complete and fully accurate understanding, at the mechanistic level, of all the relevant genetic and biochemical pathways involved. However, at present and for the foreseeable future, such a full understanding will often be unavailable, owing to the immense complexity of many biological systems—and the consequent possibility of subtle or delayed side-effects and unwanted interactions.

Conclusion

By understanding both the sense in which there is validity in the idea that nature is wise, and the limits beyond which the idea ceases to be valid, we are in a better position to identify promising interventions and to evaluate the risk-benefit ratio of existing enhancements. Furthermore, if we are right in surmising that intuitions about the wisdom of nature can exert an inarticulate influence on moral intuitions about biomedical enhancements, then our heuristic—while primarily a method for addressing empirical questions—may also contribute to normative debates surrounding (real or hypothetical) human performance enhancing technologies.

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Chapter 13
Mood Enhancement

Daniel Loewe

Abstract The chapter addresses mood enhancement from an ethical perspective. First it examines five versions of the side-effects critique. By focusing on individual autonomy and on medical supervision most of these criticisms are avoidable. Secondly, the paper focuses on some social problems that follow on from access to mood enhancement, arguing that while there are ways to overcome them, they raise other problems. Thirdly, it examines issues of normalization, coercion and paternalism, and fourthly, some criticisms on the grounds of loss of authenticity.

Keywords Mood enhancement · Enhancement ethics · Medicalization · Selective Serotonin Reuptake Inhibitors (SSRIs) · Cosmetic pharmacology

Introduction

Mood enhancers are often prescribed for people suffering from mental or rheumatological illnesses or conditions (like some antidepressants that help with pain in fibromyalgia or some anxiolytics that have an effect on rheumatological diseases such as arthritis, for example).[1] In this article, however, I will examine their non-prescribed use, namely their use in people *without underlying medical conditions* to improve some aspect of their personality. The analysis to be carried out will be of an ethical nature.[2]

What precisely can we consider to be a mood enhancer used for non-medical purposes? A classical definition may be the following: "interventions designed to

[1] Some studies can be found at www.ncbi.nlm.nih.gov.

[2] A Kantian-type ethical analysis can be seen in Clewis, R. R. (2017).

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improve human form or functioning beyond what is necessary to sustain or restore good health" (Juengst, 2000, p. 29). In some cases, such as in rheumatology, an improvement factor can be seen on the basis of better functioning of certain joints or a considerable improvement in the patients' affliction, especially in terms of being able to lead a life with less restrictions caused by high levels of pain. In the case of some mental illnesses, there may be an improvement in the person's mood and a decrease in intrusive thoughts or risky behaviors. In the case of healthy people who consume it on a non therapeutic basis, the improvement is not marked by any previous physiological parameters: they were doing well, and now they are doing well too.[3]

Note that while there are objective elements for the diagnosis of diseases, the boundary between health and illness is less clear in cases where social elements are taken into consideration. An example of this is *medicalization*. Medicalization focuses on how medical categories are applied to the spheres of life not previously medicalized, and "on how the populace has internalized medical and therapeutic perspectives as a taken-for-granted subjectivity" (Conrad, 2007, p. 14).

Although subjectivity as such is not a bad thing (for example, when evaluating pain), Davis (2006: 51–56) criticizes that, since there is not an universal and legitimate notion, the use of medicalization has been extended to every problem that can be explained in medical terms. An example of this is the over-use of medicines for issues that do not require prescriptions.

Despite the presented difficulties I will assume that some line can be drawn about this issue. I will sustain that a threshold can be stipulated -obviously, social considerations enter into this stipulation. Below this threshold the use of mood enhancers will be considered therapeutic. Above the threshold, they will be considered as enhancement. Thus understood, then, enhancement is -in the words of Peter Kramer (1993)- about becoming "better than well".

In the present paper I will examine mood enhancement thus understood, but from an ethical perspective. I will first examine five versions of the side-effects critique. While these critiques have a point, I will argue that the *autonomy* of individuals must also be considered, and that many of these side-effects are avoidable through medical supervision. Secondly, I will examine some social problems that follow on from access to mood enhancement. While there are ways to overcome them, they raise other problems. Thirdly, I will examine issues of normalization, coercion and paternalism related to mood enhancement. Fourthly, I will examine some criticisms of mood enhancement on the grounds of loss of authenticity. Finally, I will draw some considerations.

[3] See, for example, Pérez Triviño, J.L. (2014).

The First Issue: Side-Effects for the Agent

Choosing the right medication for a patient is often a challenge: the remedy may not work, may work only slightly, or may cause adverse effects that worsen the patient's situation. Although medications are approved by higher agencies, every patient reacts differently. This is why, to some extent, it is trial and error when prescribing medications such as anxiolytics and antidepressants (even though there are some which, supported by studies, seem to be better tolerated by the body than others).[4] In addition, in *some* cases, laboratory studies can be done to discern which one might be more suitable for the patient.

However, what happens when these mood enhancers are used by people without underlying medical conditions? At this point it is worth considering how anxiolytics and antidepressants work. Selective Serotonin Reuptake Inhibitors (SSRIs) are the antidepressants that can be considered to have the least adverse effects compared to other kinds of antidepressant-type medication.[5] They are also used for some anxiety disorders. What they do, in other words, is increase serotonin in the brain while blocking its absorption, thus making it available for better transmission. Furthermore, they affect the norepinephrine and dopamine neurotransmitter systems. Thus, it is worth mentioning that mood enhancers *are not innocuous medications*, as they produce changes at the brain level.

Among the most typical SSRIs we can find the following adverse effects: insomnia, nervousness, dizziness, impact on appetite, nausea, drowsiness, and so forth. As required by the FDA (Food and Drug Administration),[6] it should be made explicit in the medicines that the first few weeks with these types of medication may induce an increase in suicidal thoughts and attitudes when treatment is started or the dose is elevated.

In the case of medical use these side-effects are tolerated since, in the long term, they would imply an improvement in the patient's quality of life or, in my terms, will make it possible to reach the threshold of capabilities. In the case of healthy people seeking to be "better than well" some ethical issues arise.

Firstly: even if the person is given an "adequate" mood-enhancer they are likely to spend weeks with these symptoms. However, if we give any weight to people's autonomy, this would not be a reason against mood enhancement - after all, everyone can estimate how much discomfort they are willing to suffer in order to use mood enhancements and feel "better than well".

Secondly: the adverse effects mentioned above may restrict the autonomy and free agency of the patient, as they are now in a condition that they were not before. This is worrying when this kind of medication may even increase suicidal ideation. This is a serious argument. If indeed chemical changes substantially affect people's

[4] See "Selective serotonin reuptake inhibitors (SSRIs)" at Mayo Clinic (www.mayoclinic.org).

[5] See, for example, www.mayoclinic.org/diseases-conditions/depression/in-depth/ssris/art-20044825 for more information.

[6] See "Selective Serotonin Reuptake Inhibitors (SSRIs) – Information" at www.fda.gov.

agency, we might think that it is inappropriate for people to assess whether they should bear the risk because their agency is compromised. But while this reason seems to speak against mood enhancement, if we examine it carefully, we notice that it is only necessary true for mood enhancement without medical supervision. Mood enhancement under supervision may avoid the worst outcomes without necessarily implying paternalism - given that agency is (it is hypothesized) compromised. But this will obviously depend on the willingness, quality and extent of supervision, which, it must be said, does not currently meet the required standards. In any case, the question that would arise is to what extent people can be held responsible for possible suicidal tendencies and thus for the increased likelihood of suicide generated by (non-medically required) medication if they have knowingly chosen to make use of it. The more value we place on autonomy, the more responsible we can make people, and *vice versa*.

Thirdly: as Berghmans et al. (2011) point out, we know that certain mood enhancement medications have risks of addiction. Evans and Sullivan (2014) stated that prescription medication abuse has become a pandemic in some countries, coming second and third after opioid medication abuse. This also impacts the now oversaturated health system as a whole, as the treatment for addiction is interdisciplinary in nature. Their study demonstrates the following:

While the majority of those using prescription medications non-medically do not meet criteria for DSM-V substance use disorder, some individuals will develop such a disorder, and early nonmedical prescription drug use may be a predictor of lifetime development of prescription drug abuse or dependence (Evans & Sullivan, 2014, p. 120).

It is even claimed that some patients reach a state of psychotic-like symptoms in combination with such addiction (*ibid*). But this only reinforces the previous point that there are reasons for mood enhancement to be performed under medical supervision. It is worth mentioning that the above study also demonstrates that when medication is used in controlled medical situations, and by people who need it, it is not usually abused.

Fourth, there are multiple concerns about the well-being or happiness associated with mood enhancement. Brülde (2007) presents his concern that the wellbeing or happiness achieved by these medicines is short term.[7] As the underlying issues - meaning, why the person decides to take this medication when they are not ill- are not being addressed, they will not achieve a stable level of satisfaction. That said, if higher and higher doses are required, the side effects may increase: If the brain's serotonin levels are already high in the absence of an underlying medical condition, abuse of SSRI-type medication or mood enhancers can cause *serotonin syndrome.* According to the Mayo Clinic,[8] its consequences are loss of muscle coordination, shivering, high blood pressure, heavy sweating, muscle rigidity, among others, and

[7] On how the acquisition of this happiness can be seen as an effortless shortcut, see Schermer, M. (2008).

[8] For more information, www.mayoclinic.org/diseases-conditions/serotonin-syndrome/symptoms-causes/syc-20354758.

in severe cases, loss of consciousness, seizures, arrhythmia, etc. In other words, it can be lethal.

I cannot say, as in response to the first criticism, that everyone can estimate how much discomfort they are willing to endure in order to achieve the desired happiness, because - this is the argument - the impossibility of obtaining happiness leads to increasing doses and thus side effects up to serotonin syndrome. In any case, the argument that doses will be increased is based on the assumption that since "*the underlying issue has not been addressed, they will not achieve a stable level of satisfaction*", which assumes that there is an underlying issue to the desire to be "better than well". Clearly there is an underlying issue, *but it should not be negatively connoted*. The point of reference for these arguments seems to be the phenomenon of aesthetic enhancement in which, due to "underlying issues", interventions are compulsively multiplied in order to reach an ever more distant ideal. Without being conclusive, I believe that arguments of this type medicalize the world of life in an inappropriate way. The phenomenon of aesthetic enhancement described above is not generalized, and does not seem to be so in mood enhancement either.

Fifth: Horowitz and Wilcock (2021) have also reported that taking antidepressants for long periods of time has an impact on people's well-being. These effects may even be long-lasting, *i.e.* they do not cease with the withdrawal of the medication. Such effects, according to the authors of the study, are as follows: "In a survey of a self-selected population on long-term antidepressant use (62.5% for >3 years) adverse effect rates were even higher, with 71% reporting emotional numbness, 70% reporting feeling 'foggy or detached', (...) 66% reporting sexual difficulties, and 63% reporting drowsiness" (Williams, 2018 in Horowitz & Wilcock, 2021).

Pérez Triviño (2014) analyses the fact of living an existence without contrasting emotions. When these mood enhancers are abused, certain emotions and sensations are eliminated or narrowed, so that the spectrum of human life is reduced in terms of feelings. Chatterjee (2004) in a similar line of study, asserts that the recall of events is also affected: as there are no concordant strong emotions (be they happiness, sadness or others) the events recalled by the agent become neutral in character, which affects the perception of the life they have lived and its unfolding events. In other words, the subject's life would come to feel numb or anaesthetized to themselves.

Given all of the above, the use of medication to be "better than well" has multiple potential risks for the agent. Furthermore, it should be noted that -as mentioned-, the worsening of the agent's health and its bad consequences (such as addiction) must be treated by the health care system, thus implying an additional expenditure of resources and medical space that could have been avoided. This could result in people who should be treated having to wait even longer for medical treatment that turns out to be necessary and not "cosmetic". But I also consider that a mood enhancement under medical supervision may be able to avoid many of the side effects on the agent and thus on the health system - although the evidence has yet to be presented. The argument concerning the quality of happiness achieved, characterized by a feeling of numbness and lack of emotional contrasts, is important. But again, a medically supervised mood enhancement can make it clear to those who

want to access it that the state of happiness achieved is perhaps different from what they imagine. If one balances these risks in terms of gains and losses, my opinion is that the answer is that, under the condition that it is done under medical supervision, individuals must assess the risks. All this depends, in any case, on the quality of the drugs. The fewer the side effects, the less reason to restrict their use in the case of mood enhancement. Also, note a general issue: discounting suicidal tendencies, and focusing on consequences such as feeling of numbness and lack of emotional contrasts, it is clear that if these possible consequences do not appeal to people, it is always possible to suspend (again: under supervision) their use, and return to the situation before the unsuccessful "better than well" level, when one was only well.

Second Issue: Access to Medication

While universal access to medicine is a goal, is not yet a reality (World Health Organization, 2019).[9] Medicines account for up to 60% of household expenditure in low- and middle-income countries (WorldBank, 2017). That said, the social use of enhancers to improve productivity or certain key traits will be a benefit for only a few (see, for example, DeGrazia, 2000).

Specifying further, globally one third of the population has no access to *needed* medicines and it is estimated that "15% of the world's population consumes over 90% of the global production of pharmaceuticals (by value)" (World Health Organization, 2008).[10]

As a result, "cosmetic pharmacology" -i.e. the use of medication in healthy people- appears to be unsustainable in that it would create major social disadvantages (DeGrazia, 2000).[11] Only a minority would be able to access these medicines, while at the same time causing their stock to fall in countries where their access and availability is already low. It might be thought that a system could cover those costs, but the current health systems and respective insurances do not fully cover medical expenses, as shown in the previous paragraphs. That said, the issue of access is further complicated by the fact that these are not necessary remedies for health, but something that the agent wishes to take to be "better than well".[12]

Note that none of these arguments is conclusive. It is not, however, that the use of cosmetic pharmacology will diminish the stock of medicines by preventing them from being available to those who require them for medical reasons: markets are information systems and an increase in the number of medicines available to those who require them for medical reasons, under competitive conditions, should lead to

[9] See "Universal Health Coverage" at www.who.int.

[10] See www.who.int/medicines/areas/access/OMS_Medicine_prices.pdf.

[11] See the case study on Marina in DeGrazia, D. (2000).

[12] Forlini et al. (2013) even go to the extent of arguing that drugs used primarily recreationally or as "lifestyle drugs" -since people do not have a medical diagnosis- may not be covered by health insurance or third-parties at all.

increased production. It is even arguable that the prices of the products would decrease, thus increasing the accessibility of the products for those with fewer resources. Moreover, consider that the counterfactual is not self-evident: no pharmacological cosmetic use does not mean more availability for those who require it for medical reasons, as production may simply be reduced to match demand. Given that in this article I assume an order of importance according to which the treatment of diseases is more relevant than cosmetic pharmacology, and argue for the use of mood enhancement to be under medical supervision, if we now add that access should be mediated by medical prescription, we can organize the system in a way that avoids what DeGrazia fears: that "it would create major social disadvantages". One option is for everyone to access these products through the health system's coverage. Given that this is probably not possible in a world of limited resources, the second best option is that access to these products is not covered by public insurance for those seeking mood enhancement but for those who require them for health reasons. If this is also not possible, then we have a third best option to avoid social disadvantage: those who access these products for mood enhancement purposes could pay an extra tax which, in turn, helps to fund access for those who require them for medical reasons.

But what about the disadvantages that occur between those who want access to these drugs for mood enhancement and have the resources and those who do not?

There is indeed a disadvantage here. If it cannot be reversed by subsidizing the worse-off access,[13] the following consideration may be worthwhile: since it is not about treatment to reach a certain threshold defining health but to be above it, it should be considered a luxury, so that everyone bears the costs of their own preferences. While being better than well surely corresponds to the interests of many people, it is not as important as being well enough, and therefore to be protected by a positive right of access. In this sense, the advantage and the correlative disadvantage would be no different from other advantages and disadvantages that occur in society through access to luxury goods.

I am assuming, as I argued in the first section, that through medical accompaniment, side-effects would be kept low, so that those seeking mood enhancement would not pass on the cost of their preference to third parties who would thus lose health care options. But it is reasonable to assume that some costs would be passed on. Would this be an argument for denying them access? I do not think so. All ways of life produce costs on third parties and it cannot be the aspiration in a liberal democracy to eliminate all such costs through coercive policies. Obese people also burden the health care system as do those who drink alcohol and those who engage in unsafe sex, and while we can implement public policy programmes against obesity, we can raise taxes on alcohol and we can organise educational policies, we cannot coercively prevent people from engaging in these practices. Not as long as we respect people's rights and freedom. In a different context, G.A. Cohen (1989)

[13] I have argued -following a Rawlsian egalitarian liberal framework- in favor of these subsidies in the case of cognitive enhancement. See Loewe, D. (2016).

has argued that, instead of each member of a sports club paying according to the activity they do, so that chess players pay less than swimmers (because the infrastructure required is different), everyone should pay the same to ensure that each member can choose the activity that suits them best. It is about equal opportunities in access to welfare.[14] In a certain sense, a society that gives its members the possibility to try out and follow different lifestyles and life plans by cross-subsidising them increases their freedom. In the case of mood enhancement the same may be true: its possible consequences on third parties must be accepted in the name of the freedom of all, just as the obese are accepted - and if they are not (*e.g.* when taxes are proposed or social benefits are made conditional on weight), they should be.[15]

It can obviously be better that if a person would like to improve their mood and some aspect of their personality, to go to psychological therapies or psychotherapies. These are meant to work on the individual themself, whether the person is healthy or not. In other words, it is a general service for well-being where the person could work in a space to feel -even- better. Moreover, it has no side effects. But therapies are long and expensive processes, requiring huge amounts of energy and time that not everyone (in fact very few) can or are willing to afford. As a matter of advice, I would recommend anyone who wants to be better than well to do so, as I would also recommend meditation techniques, but I would not thereby prevent people from having a chance to be better than well through pharmacology. Otherwise, preventing it would cause the disadvantages that DeGrazia fears: few people in our world can afford the "luxury" of psychological therapy - especially those of a psychoanalytical bent, who are perhaps the most productive in this respect.[16]

Normalization, Coercion and Paternalism

Along the same lines, one problem with standardizing non-medical treatments and making them open to the public is that, as mentioned above, they will only be available to a restricted few. However, this could lead to unfair competition if some industries or jobs could require them on the assumption that they would lead to improved efficiency on the part of the employee. That could also lead to social pressure for people to improve their mood through pharmacological substances -on penalties of "social sanction": some individuals will be pressured to accede as well unless they are willing to bear the costs of the corresponding disadvantage.[17] The

[14] See, for example, Cohen, G.A. (1989).

[15] See, among others, Loewe, D. (2020).

[16] Evidently behavioral therapy is a very popular option; thus in the UK such therapies seem to be the preferred way to achieve increases in happiness as desired by the now very fashionable policies based on empirical studies of happiness.

[17] For example, see a parallel with Farah (2002) on the excessive use of Ritalin in competitive schools.

pressure may reach the level that even if they don't want to do it, they have to do it to avoid higher costs.

On the other hand, normalizing their use could cause hedonism in citizens, thus making them even less active in terms of social life and in their own life goals (see, for example, Pérez Triviño, 2014). Perhaps the drug that best expresses this lack of initiatives for life and hopelessness is *soma*, from Aldous Huxley's (1932) dystopian novel *Brave New World*. Esposito (2005) further argues that normalizing the use of mood enhancers in healthy people would change the standard of happiness and, with it, its normality. Arguably, those who are "less happy" because they do not use certain mood enhancers could be considered as "sick" people. Along the same lines, Reinoud de Jongh et al. (2008) make explicit that there are even groups interested in rendering certain conditions as illnesses, *i.e*. we are once again facing the over-medicalisation of the spheres of life.

These are serious problems. If the social normalization of the use of drugs to be "better than well" implies significant penalties for people who do not want to use them, it may imply indirect forms of coercion, *i.e.* be an illegitimate way of limiting individual freedoms. Note, however, that two scenarios[18] must be distinguished. In the first, employers or social providers may condition access to employment and promotions, or to certain benefits, on the use of these mood enhancers. In the second, it is social pressure. While the two cases are related, they need to be distinguished. The first should be dealt with in accordance with anti-discrimination policies. There seems to be no reason to consider that an employer or provider can legitimately exclude certain individuals on the basis of their use of mood enhancers. Being "better than well" does not seem to be a condition for fulfilling the conditions of an employment activity (being "worse than well", *i.e.* states of anxiety, depression and so on, should also not be considered as a condition for legitimate discrimination, but are pathological modes to be dealt with as they require), and therefore discriminating on the basis of such criteria cannot be acceptable and certainly would not withstand any judicial review.

The second case is more interesting: the actions of others always have consequences for our relative social position. If others are faster, then we are slower; if others are smarter, then we are less so. And in a context of competitive interaction for desired and scarce goods, relative position is crucial. A well-known joke can serve as an illustration: two people walking through the jungle come across a hungry lion. While the first person phlegmatically exchanges his shoes for trainers, the other, desperate for the fate he foresees, shouts at the first: "You' re crazy, do you think that you can run faster than the lion?". But the first person responds with parsimony: "I don't need to run faster than the lion, I just need to run faster than you".

This is precisely the situation in which we find ourselves in competitive contexts, which leads to escalation of titles and training processes in work contexts. And it is precisely the situation in which all those who "compete" with third parties who can

[18] While the role of the Big Pharma in over-medicalization will not be the subject of this paper, it is necessary to evidence it and show that it is a fact that is occurring when definitions of what medicine is about are unclear or diffuse. See, for example, Schermer, M. (2015) and Healy, D. (2004).

be positively perceived on the basis of their improved morale can find themselves. Note that if it is a situation in which one is "better than well", it is implausible to consider it as one in which one is more productive because of enhanced physical or mental capacities, such as strength or intelligence. The mood of those who are well and better than well can be expressed in different ways in competitive contexts, as how it is expressed depends on how it is decoded by others, since it is not purely a matter of performance. So there is no reason to think that those who are "happier" will be more successful. In other words: the conversion rate of mood, at least above the threshold of "good enough", depends on exceedingly complex variables (and depends on many eminently contingent things: such as the context of interaction, culture and so on). I would even speculate that, in a context where the vast majority are "better than well", being well enough may even be an advantage.

Moreover, prohibiting access to pharmacology to be "better than well" to informed people who wish to use them autonomously, to protect themselves from becoming overly "hedonistic", or to protect third parties - because of the outcomes of social interactions - from possible pressure to use them, can hardly be considered as non-paternalistic. Certainly, though less and less, the context of medicine assumes a certain condition of paternalism in that a practitioner knows what is "best" for a user, understanding "best" not only as a relation between ends pursued by the user and the means to achieve them, but understanding "best" in a sometimes quasi-absolute sense, as what is best for the person. Although I will not discuss it now, I have no doubt that this is questionable. Note, however, that pharmacological use to be "better than well" is not medical, and this – wrong, in my opinion - way of understanding the doctor-patient relationship as one governed by paternalistic assumptions has no place here. Can the State arrogate to itself the right to prevent people from autonomously agreeing to use drugs to be "better than well" on the assumption that they are not excessively harmful? –What is "excessively harmful" is, of course, a debatable issue. I don't see how it could be justified without assuming paternalistic premises that are hardly compatible with considering people as free and equal and as agents accountable for their ends.[19]

Naturality and Authenticity

It is common to criticize enhancement in general -and mood enhancement in particular- by appealing to its unnaturalness. Criticism can be articulated with regard to the means and with regard to the ends. With regard to the means is the most common. The idea is that by means of direct pharmacological action to produce an effect, the natural ways of producing it are interrupted. For example, achieving a state of relaxation and stillness through meditation techniques or the use of opiates

[19] Discussions about paternalism are complicated. In a general overview, consider the various ways of understanding paternalism as presented by Dworkin, G. (1988). See also "Paternalism", *Stanford Encyclopedia of Philosophy* (www.plato.stanford.edu/entries/paternalism/) and Loewe, D. (2022).

is not the same thing. And this would imply that the value of the effect would be compromised in some way. Some interpretations even argue that through this shortcut, beneficial evolutionary processes are interrupted, which may have unforeseen results.[20] With respect to the first criticism it is not obvious why the origin (natural vs. artificial) would be relevant for assessing the value of the state thus obtained. In the first place, it is not obvious what it means that the origin is natural - at what point do external *stimuli* cease to give rise to a natural origin and become artificial? Secondly, if we take it seriously, this would mean that states of mind that arise from artificial stimuli such as, for example, watching a film, are of lesser value. This is absurd. For the second interpretation (that the shortcut interrupts an evolutionarily established process) the criticism is even weaker. Firstly, evolution does not care about your well-being. All that matters is that the genes are maintained in the future. Secondly, if evolutionary processes are indeed not to be interrupted by artificial mechanisms, then we would have to ban not only most medical treatments, but also contraceptives.[21]

As I announced, the critique of naturalness can also arise with respect to ends. This would be the case if by some kind of enhancement, a state is generated that is not "natural" in the sense that it does not belong to the species. Having the ability to fly, or a built-in radar, would be examples. In these cases, what you get would be unnatural, in the sense that it would not be human, and would therefore be improper or of diminished value. In the case of mood enhancement, it is difficult to imagine how non-human states can be obtained. Therefore, although this point raises important issues, I will not consider it.

Note that if you argue that medical paternalism is appropriate for any of the reasons presented, it is not welfare paternalism as in the previous section, but rather a moral paternalism, *i.e.* one that argues that there are better ways of being human: in this case those that follow from naturally occurring stimuli. But as we have seen, this view is hardly sustainable. Resorting to the natural as a measure of what is valuable or right is inadequate.

Linked to the above-mentioned problem, but in a different way, the problems most commonly associated with mood enhancement concern authenticity. The idea is that authenticity is a central part of our understanding of ourselves as modern beings.[22] We are unique beings, and in our process of defining ourselves as the unique being that we are, we have to discover our identity. In an extreme reading, identity is given (for example, through social factors) and our role is to discover it.

From this perspective, the critique of mood enhancement points to the fact that the way we are in the world, the identity we express and our personality, which are thus obtained, are not authentic. That is, they are not an expression of who we really are. They would be the product of pharmacology, and do not respond to a process of

[20] See Wall, H. (1999).

[21] See Wolff, J. (2011).

[22] See Taylor, C. (1991).

discovery of our identity. So they would have a lesser value, if any.[23] We would simply be impostors (even if we believe our imposture). In this line of argument, Carl Elliott argues that deliberately changing our personality by means of Prozac is inauthentic, because the result is a personality that is not ours: "I would be worrying if Prozac altered my personality, even if it gave me a better personality, simply because it isn't my personality" (Elliott, 1998, 2003) "What could seem less authentic, at least on the surface, than changing your personality with an antidepressant?" (*ibid*).

DeGrazia has plausibly argued against this position. In his view, what he would express would be a static understanding of the self (or of identity, or of personality, DeGrazia moves from one concept to the other as if they were synonyms).[24] That is to say, the self that is obtained through mood enhancement would be inauthentic because it would not be our own, which is already given and probably cannot be modified. Evidently, if this is what the argument of inauthenticity holds, then it is implausible. The process of constructing the self involves activity. Even the process of discovering what makes us unique involves a creative process of introspection. The idea of one's identity as given is extreme. It is at the limits of essentialization, if not essentialization. But DeGrazia has plausibly argued that the other extreme is not plausible either: the existentialist idea of self-creation in radical freedom would not hold because there are limits to what we can do. This is obviously an incorrect understanding of the existentialist thesis of radical freedom. The thesis is not that there are no limits, but that we are always radically free, even if our possibilities of action are limited. But the idea is understandable (although it is not a critique of the existentialist conception of the self): we can modify aspects of our identity, as we usually do, but we cannot modify everything (there are, for example, genetic determinants relating to the life cycle).

DeGrazia holds the idea of identity as a creative process, a process in which what matters is the narrative self, *i.e.* the story we tell ourselves about ourselves and which forms the basis of our identity, understood as identification. From this perspective, what is important for authenticity is one's conception of oneself. That is, whether one identifies with the characteristics of one's personality. And if this is so, then how this is achieved is irrelevant: if we identify with the self that we obtain through pharmacology, then it is an authentic self.

If authenticity has to do with the narrative identity we have about ourselves, then it does not depend on how it is obtained. Strictly speaking, we can feel inauthentic or authentic in the explicit sense, *i.e.* we do not identify or identify with who we are in the world, even if no psychopharmacology is involved, and we can feel inauthentic or authentic with pharmacology.

Let's consider the critique in more detail.[25] Inauthenticity can occur in the relationship of ourselves to the way we are in the world. Here we might detect

[23] Compare the conservative position of Pugmire, D. (2005).

[24] See DeGrazia, D. (2000).

[25] See Kraemer, F. (2011).

irrationality or lack of coherence, thus losing identification with our expression in the world, which can lead to alienation. This can happen in the case of mood enhancement, when someone does not identify with the way they are in the world. But of course, in the case of reversible treatments, this possibility does not necessarily imply a criticism: those who feel that there is no coherence between who they are and how they express themselves in the world, can give up taking the drugs. Note that again, seeking to coerce or prevent actions by individuals in pursuit of authenticity is a kind of moral paternalism.

Conclusions

So what is the problem with mood enhancement? In this article I have examined four types of common criticisms. The first is constructed on the grounds of side effects. I have argued that, under certain assumptions, they can be at least partially weakened. The second is built on some likely social consequences (there may be others than the ones I discussed). I have argued that this type of criticism is less far-reaching in the case of mood enhancement than in the case of other kinds of enhancement directly related to performance. I have also dismissed the third type of criticism that appeals to paternalistic considerations. Finally, I considered criticisms based on naturalness and authenticity, and argued that the former are not based on serious normative arguments, and the latter are built on implausible assumptions. So considered, and if the articulated arguments are correct, there are fewer reasons against mood enhancement than those usually articulated in the debates.

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Chapter 14
Superior Sport Performance: Ethical and Legal Issues

Elena Atienza Macías

Abstract In recent years, new ways of understanding and treating mental and emotional capacities have undergone an unparalleled development. We are referring to neuroscience and pharmacology, both of which have the human brain as their grounds of study. One of their aims is to alter emotional states in order to help individuals to overcome stages of depression and personality limitations, such as shyness, fear or anxiety. A parallelism can be made here with the sports sector, as these emotional *enhancements* can have a direct impact on the athletes' performance. This raises numerous questions: what can be said about doping and cognitive or mood enhancement? what does it mean and imply to increase the emotional capacities of athletes? are enhancement treatments in humans ethically acceptable and legally viable in the sporting context? and if so, where should we draw the line between what is legal and what is not? and if so, where should we draw the line between what is legal and what is not, in other words, what should be the criteria for the ethical and legal evaluation of these treatments? In simple terms, what should be the criteria for the ethical and legal evaluation of these treatments?

Keywords Emotional enhancements · Enhancement in sports · Cognitive enhancement · Doping · Gene Doping · Sports Law

Cognitive and Emotional Enhancement in Sport

Unfortunately, it comes as no surprise to see the cases of athletes who display an aggressive behaviour in the field of play. These are provocative attitudes, full of aggressiveness and, therefore, far removed from sportsmanship. Such is the case of some tennis players —who break their racquets— when they feel their defeat

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approaching, or the shameful image of violence in football, which is undoubtedly a damaging spectacle for sport and its essence. In the end, that kind of attitudes has nothing to do with fair play.

In the light of these cases, one should reflect: couldn't these athletes be given a "miracle" pill that would change their character and improve their behaviour to one more in line with what is expected from elite athletes? This simple approach is known, in more technical terms, as "mood enhancement" or "cognitive enhancement" and, from a pejorative or negative perspective, as "emotional doping" or "mental doping". On the one hand, the term "doping" is used because it is associated with the world of sport, although this is highly controversial, as we will explain in this chapter. On the other hand, the term "mood" refers, in some cases to moods, in others to emotions, and even to illnesses such as depression and other affective and anxiety disorders. (De Miguel-Beriain & Morla-González, 2020).

Thus, while doping in the physical (*versus* psychological) sphere has been the subject of heated debates from a variety of perspectives, less attention has been paid to other factors that are relevant to improving sporting performance, such as cognitive and emotional enhancement.

Since the origin of sports, psychological strength has been considered to have a decisive impact on sporting performance. It is not surprising, therefore, that what is known as "sport psychology" has been definitively established. It is often said in the world of sport that the difference between winning and losing is 99% psychological (Williams, 1986) or that 90% of sport is mental (Garland & Barry, 1990). Not surprisingly, every major sports clubs or federation should have a psychologist within its support team (coaches, doctors, physiotherapists, among others). Therefore, it is not unusual that every large sports club or federation should have a psychologist among its support team (that is to say trainers, doctors, physiotherapists among others).

Over the last few years, new ways of understanding and treating mental and emotional capacities have undergone an unparalleled development. We are referring to neuroscience and pharmacology, whose grounds are in the brain (Pérez-Triviño, 2014). One of their goals is to alter emotional states in order to help individuals to overcome stages of depression and personality limitations such as shyness, fear or anxiety.

In a parallel effort, these emotional enhancements can have a direct impact on the athletes' performance. This raises several questions: what can be said about doping and cognitive enhancement?, what does it mean and imply to increase the emotional capacities of athletes?, are enhancement treatments in humans ethically acceptable and legally viable in the sporting context?, and if so, where should we draw the line between what is legal and what is not?, and if so, where should we draw the line between what is legal and what is not, in other words, what should be the criteria for the ethical and legal evaluation of these treatments? In other words, what should be the criteria for the ethical and legal evaluation of these treatments?

There are many questions and a polyhedral approach to this issue, which brings us into the everlasting debate on doping in sport.

Some Preliminary Concepts: "Doping" *Versus* the So-Called "Doping in Everyday Life"

Although doping is not of a recent origin, it is only in the past few years that it has become known and recognised as a sport-specific practice directly linked to competition. Thus, it is inappropriate to adopt the term "doping" for a segment other than sport.

Nevertheless, if we review the history of doping and its origins, we can see that in other physical activities, even if they are not strictly sporting activities, similar means to doping have been used (Rodríguez-Bueno, 2008), are still being used and are likely to be used in the future, to a greater or lesser degree and to a greater or lesser extent, in order to achieve similar objectives to those sought by their practice.

In this sense, the use of a type of extra-sporting doping, i.e., developed in society in general, dates back to immemorial times. In fact, human beings have always been tempted to resort to all kinds of means to increase their qualities. We can speak of "doping" used as a military weapon -to prove the supremacy of an individual, a tribe, a regime or a race- up to the so-called socio-economic doping, as it is currently configured, to which human beings resort in order to fulfil their work commitments in short periods of time, for purely monetary purposes or to improve their position in society.

Thus, attempts to enhance certain bodily characteristics or faculties of human beings are not new.

The Case of Cosmetic Interventions

In this regard, it is pertinent to quote cosmetic interventions as an example, which leads us to the inevitable comparison between sports competitions and beauty competitions. This raises a two very important questions: if beauty competitions admit participants (whether male or female) who have been subjected to cosmetic surgery, i.e., who have undergone artificial procedures or enhancement interventions to increase their natural attributes and be closer to the canons of beauty, why is doping not allowed in sport as a method or "enhancement" intervention, and why is it allowed in the contexts we have described?

The Case for Increasing Sexual Capabilities

Another significant example of its projection in today's society can be found in the use of drugs to stimulate sexual capacities. For example, the famous "blue pill", technically Sildenafil Citrate, sold under the better-known brand name of *Viagra*, which is fully established and marketed in its male version, and the so-called

"pink pill" or, strictly speaking, Flibanserin, which has been approved as the new female Viagra, already on the market.

The curious thing is that Viagra also seems to help to improve athletic performance (or so the experts think). In this regard, a paper from Stanford University published in 2006 in an issue of the Journal of Applied Physiology (Hsu et al., 2006) noted that it was possible to use sildenafil citrate to increase the physical performance of cyclists at high altitude by approximately 45% (American Physiological Society or APhS, 2006), suggesting the existence of a new class of performance-enhancing substances that could be used in any sport (Baron et al., 2007).

The Case of Students and the Improvement of Intellectual Capacity

Other examples relate to the use of substances and products to stay young or for transient memory enhancement with drugs among students (Romeo-Casabona, 2004). Thus, university students have often consumed a lot of stimulants -amphetamines and others- in order to perform better and achieve higher marks.

In light of the above, we should start by asking if it is not cheating to use "smart drugs" to pass competitive examinations and it is indeed cheating (Mayor et al., 2019) for athletes to use steroids (Rose, 2006; Harris, 2010).

Doping in Everyday Life Contexts

The use of psychotropic drugs —mainly anxiolytics and antidepressants— is increasingly common among patients with disorders caused, not infrequently, by the stress of modern life, such as anxiety or depression. Professionals with higher mental strain, for example researchers, computer scientists, high-level executives (for instance stockbrokers or workaholics) have for years resorted to certain substances such as Ritalin or Modafinil (Cakic, 2009) —one of the most widespread "smart drugs" (even astronauts on the International Space Station)— to get that extra boost. It is worth noting that such use is highly controversial in "risky" professions such as firemen, policemen, soldiers, drivers, medical personnel (for instance surgeons, anaesthetists) or commercial airline pilots. In the field of commercial pilots, an unprecedented "surprise medical check" —which bears some resemblance to anti-doping tests in sports— has been proposed to detect whether pilots are taking antidepressants, following the controversial case of the co-pilot who crashed the Germanwings Flight 9525, an Airbus A320, in the Alps on 24 March 2015, and who was reportedly regularly taking antidepressants to alleviate symptoms linked with his mental health. The company Lufthansa announced in May 2015 that pilots would be subject to surprise medical checks to detect medication

and drugs. The Bundestag (the lower house of the German Parliament) is considering similar fitness-for-duty measures that would apply to all pilots within the German airlines. Officials in other countries have also proposed periodic psychometric testing of air carrier pilots.

All of this brings to mind the book *The dark fields*, by Alan Gylnn, whose plot revolves around the discovery of this type of drugs by an anonymous citizen and illustrates a hypothetical case of possible complications that the consumption of these drugs entails. Subsequently, in 2011, it was adapted as a film under the title *Limitless*, directed by Neil Burger and starring Bradley Cooper and Robert De Niro. Indeed, Hollywood paid attention to this topic in that film, showing Bradley Cooper able to "obtain 100% brain performance" with a magic pill, which turned him into a "superhuman". This situation can obviously be extended to athletes. Some critiques commented that this film makes us reflect on a new type of doping, intellectual doping (Eronia, 2012). In the context of sports performance, we will discuss devices that promise to improve not only physiological aspects but also mental (Davis, 2013) and emotional (Bertollo et al., 2019) ones.

Gene Doping. A Paradigmatic Case

There is no doubt that the sport phenomenon has acquired, during the last decades, a relevance of colossal dimensions and has implied that sporting activities offer numerous perspectives of analysis from: (Bio)Ethics, Sociology, Psychology, Medical Sciences (specifically the speciality of Sports Medicine) or Pharmacology (in relation to the list of doping substances and food supplements used by athletes) and, of course, Law.

In the scenario described above, doping has emerged as one of the most controversial and topical issues in contemporary sport.

Furthermore, in the twenty-first century, we are witnesses of significant advances in the field of biomedical sciences and biotechnologies. Today, the so-called new "BIO" technologies, linked to technical and scientific progress, can play a key role or be a supporting technology with applications in human health. With this spectacular scientific and (bio)medical progress that is opening up before our eyes, in order to improve the physical performance of humans and, particularly, of athletes, new doping techniques have been explored that are increasingly more sophisticated and more difficult to detect.

As a result of the interaction of these two realities -on the one hand, the transcendence and intensity of sporting practice reflected in all areas with a parallel increase in the aspiration of athletes to achieve higher goals and the use of fraudulent methods and, on the other, the spectacular development of biomedicine- the so-called "gene doping" (Miah, 2004), a method that is certainly sophisticated and difficult to detect, is emerging as a protagonist in a sports scenario with a seemingly not too distant horizon. Nevertheless, Thomas H. Murray —expert in Bioethics, President Emeritus of the Hastings Center and for many years chairman of the Ethical Issues

Review Panel at WADA- stated in 2005 that gene doping was not a reality at that time (Murray, 2005). In 2021, the landscape has changed and advances in genetics suggest that gene doping could reach the world of sports imminently. Nowadays, a new concern hangs over sport, which is the real threat of genetic doping and hence the concern of World Antidoping Agency (WADA, 2005).

This new reality will mean that, for the first time, Bioethics and Biolaw will have to position themselves in a field, namely sport, which seemed somewhat remote to these disciplines until now.

Nevertheless, as a prior and unavoidable step in dealing with the numerous ethical and legal implications triggered by the aforementioned "gene doping", it is essential to define correctly the phenomenon under examination given its relevance in the media and on the agendas of political and sporting decision-makers. It is also vital for our society to understand it in order to participate in the debate in which it must necessarily take part, as well as for the sake of the requirements of clarity and taxation in the determination of prohibited conducts and the applicable sanctions derived from the principle of legality.

Conceptual Approach to Gene Doping

Normative Position: The World Anti-Doping Agency (WADA)

The main task of the World Anti-Doping Agency is to set the international framework for the regulation of prohibited substances and methods in the field of sport.

In terms of the background of the World Anti-Doping Code, February 1999 is a key starting date: The first World Conference on Doping in Sport (in response to the 1998 Tour de France scandal that shook the sporting world) was held in the Swiss city of Lausanne under the auspices of the International Olympic Committee, led by the Spaniard Juan Antonio Samaranch, President of this institution at the time. The culmination of the work carried out at this conference was the adoption of the Lausanne Declaration on Doping in Sport, which in turn became the embryo of the World Anti-Doping Agency.

WADA was established on 10 November 1999 in Lausanne with the objective of promoting and coordinating the fight against doping in sport at international level. It is composed, on a parity basis, of representatives of sports, governmental and intergovernmental organisations.

An important milestone was reached in 2003, when WADA developed the World Anti-Doping Code, which led to the gradual emergence of less disparate national rules and undoubted progress in international regulatory harmonisation.

In the same year, at the Second World Conference on Doping in Sport held in Copenhagen (Denmark), more than 100 countries unanimously adopted the World Anti-Doping Code at the Second World Conference on Doping in Sport in Copenhagen (Denmark), under the umbrella of the Copenhagen Declaration.

Indeed, the World Anti-Doping Code was first adopted in October 2003 and entered into force on 1 January 2004. Subsequently, in November 2007, on the occasion of the Third World Conference on Doping in Sport in Madrid, it was revised and amendments to the original version were approved by WADA's Foundation Board on 17 November 2007, entering into force on 1 January 2009. The amended 2015 version of the World Anti-Doping Code incorporates the amendments to the World Anti-Doping Code approved by the WADA Foundation Board in Johannesburg, South Africa on 15 November 2013 and entered into force on 1 January 2015. Strictly speaking, the World Anti-Doping Code was adopted in 2003 and entered into force in 2004. Subsequently, it has been amended three times, first with effect from 1 January 2009, second with effect from 1 January 2015 (Atienza-Macías, 2015) and third with effect from 1 April 2018 (compliance amendments). We now have a new version of the World Anti-Doping Code, the 2021 version, which entered into force on 1 January 2021.

In consequence, it is pertinent to turn to the World Anti-Doping Agency for a definition of the term "gene doping". Thus, in anticipation of this imminent reality, WADA included this technique as early as 2003, as a result of the emblematic Banbury Conference, which would constitute the First Conference on gene doping, held in New York in 2002 and which dealt exclusively with this issue.

For the first time, "gene doping" was defined by the World Anti-Doping Agency and included in the Prohibited List for 2003 as follows: "Gene or cell doping is defined as the non-therapeutic use of genes, genetic elements and/or cells that have the capacity *to enhance athletic performance*".

The pioneering Banbury Conference, organised by WADA and held in March 2002 at the Banbury Center in New York, was followed in 2004 by the creation, also by WADA, of the Expert Group on Genetic Doping. The purpose of this Expert Group is to study the latest developments in the field of genetics, the methods for detecting this method of doping and the research projects funded by WADA in this area. One year later, in December 2005, WADA, in collaboration with the Karolinska Institute and the Swedish Sports Confederation, held the Second Conference on Genetic Doping in Stockholm, which resulted in the Stockholm Declaration, reflecting the recommendations and declarations of the conference participants.

Finally, in June 2008, the Agency organised, in collaboration with the Russian sports authorities, a third expert meeting on genetic enhancement of sport performance in St Petersburg, which was to be the Third Conference on Gene Doping.

With this background, currently, i.e., in *the 2021 List of Prohibited Substances and Methods,* which has entered into force on 1 January 2021 (World Antidoping Agency WADA, 2021) gene doping is now defined as follows:

"The following, with the potential *to enhance sport performance*, are prohibited:

1. The use of nucleic acids or nucleic acid analogues that may alter genome sequences and/or alter gene expression by any mechanism. This includes but is not limited to gene editing, gene silencing and gene transfer technologies.
2. The use of normal or genetically modified cells".

Our Position. Gene Doping and Distinction of Related Figures

From the interpretation of these two definitions —in our opinion (Atienza-Macías, 2020) somewhat imprecise and difficult to understand for those not versed in this subject— it seems to be deduced that we are dealing with a case of genetic manipulation or, at least, genetic intervention. The most authoritative doctrine in Spain (Romeo-Casabona, 2002; Romeo-Malanda, 2006) establishes a clear distinction within genetic manipulations (more properly called genetic modifications) according to their goal: that is, genetic manipulations with a therapeutic purpose and manipulations that do not pursue such an aim.

The first ones are included in what is now known as "gene therapy", which aims to cure or prevent serious diseases or defects due to genetic causes by acting directly on genes, using different theoretical procedures: addition, modification, substitution or suppression.

Relatedly, within the context of genetic manipulations that do not pursue this preventive or restorative goal, there are those with an enhancement purpose, which seek to improve certain socially valued characteristics (Ring et al., 2020), such as physical capacity.

Thus, it seems clear that "gene doping" should be restricted to the field of genetic interventions (or more precisely manipulations) in human beings with the aim of improvement, insofar as they are not intended to cure illnesses, they do not have a therapeutic or restorative purpose, since athletes depart from a state of "normality" and the aim is to achieve records that should obviously exceed normality. This differs greatly from gene therapy. This is a nuance that is very relevant to bring up because it is quite common in the scientific literature on gene doping that both concepts, "gene therapy" and "genetic improvement", are not clearly differentiated.

On the other hand, and beyond the content used, we consider that the very term chosen – genetic doping – is not as rigorous as it should be and responds to somewhat journalistic or sensationalist overtones, as it seems to have been devised more by this group than by the legislator. Moreover, the term "doping" has a pejorative character in that there is a general feeling in society that identifies it with something negative.

Mood Enhancement as a Category Within Human Enhancement or Enhancement Interventions in Sport

We have come to the conclusion that genetic intervention in human beings for the purpose of genetic enhancement in the field of sport would respond more to the reality that we are trying to address with regard to genetic doping. Within these enhancement interventions or human enhancement, "Mood Enhancement" stands out.

Thus, one area of human mental reality that has developed significantly in recent decades is the emotional aspect. The spread of certain mental illnesses that affect

the world of emotions has encouraged the analysis and study of this part of human psychology, which had received less attention.

Mental illnesses such as depression, fear and shyness, which are the subject of modern treatments, are not exactly new and the world of sport has not been exempt from them. Undoubtedly, these symptoms affect notably the athletes' physical performance. An athlete may possess great physical potential, skills and technique in his or her discipline, but may fail in the competition due to an anxiety attack. There are famous cases of athletes who suffer from fear of flying on aeroplanes, a disorder that has made it difficult or impossible for them to travel for important competitions.

On other cases, the athlete may suffer from what is known as an "emotional blockage", which causes performance in competitions to drop considerably. Such an emotional blockage may be caused by stress, pressure from coaches, family or fans. In this sense, modern sports and the media's misguided emphasis on fame, money and success at any cost have inadvertently created a flourishing market for doping substances. These substances, previously consumed only by elite athletes, are clearly invading schools and health clubs around the world. They are being taken up by a whole new generation of young consumers, who, on a daily basis, read newspaper reports of sports figures accused of substance abuse just so they can continue to compete, break records and earn huge amounts of money.

Continuing education programmes developed specifically for these high-risk groups by National Olympic Organisations and sports federations are a key first step in reducing these dangerous behaviours.

The response offered by Medicine to these situations has historically come from Psychology. Multiple psychological methodologies have been developed whose aim has been to solve the emotional states that could disturb the athletes' normal physiological development. However, nowadays, many of these treatment methods are not used for therapeutic purposes, but clearly for improvement. As with other types of enhancement treatments, they were originally intended to treat mental illness, but they have ended up being used not for therapeutic purposes, but for enhancement of individuals who, by a wide margin, were on the borderline of "normality". This is what is now known as "the medicalisation of normality".

The sports field is not on the fringes of this phenomenon and psychological treatments aim to make athletes experience states of optimism, confidence, fullness or, in some cases, aggressiveness in order to achieve maximum sporting performance.

As a result of all of this, it is not uncommon for sports federations to include sports psychologists on their athlete support teams as a means of ongoing contact between qualified psychologists and clubs in the interest of health promotion and performance enhancement support.

No form of psychological support is considered, in the orbit of anti-doping planning, to be a performance enhancing sport that should be prohibited. However, the emergence of performance-enhancing drugs does create dilemmas for anti-doping policy.

Some Ethical & Legal Paradigms of Human Enhancement Interventions in Sport

Among others, we must highlight the problem of health. This phenomenon is still at an experimental stage of development. It is difficult and delicate to predict the risks associated with it, and the precautionary principle is unavoidable in this area.

In particular, with regard to mood enhancers, the fear of collateral damage from these drugs should not be underestimated. Some studies show that Prozac may pose a risk of addiction. Other research has proved a link between some of these drugs and the causation of suicides among adolescents. Similar effects have been shown with paroxitine.

It is also essential to obtain effective informed consent based on the autonomy of the subject in order to grant such consent. In the case of athletes, the principle of autonomy takes on particular characteristics, given the great pressure that they are under throughout their sporting careers. In this sense, athletes' performance is conditioned by overly inflated expectations caused by numerous economic and media interests placed on top-level sport.

Finally, let us address problems related to the principle of equality. There is the question of the inequality that these improvement techniques entail, not only from the point of view of access to them – which is obviously not available to all sportsmen and women – but also those generated *a posteriori* with "improved" or super athletes on the field of play who lack this advantage. Some voices point to the possibility of organising segregated competitions.

Concluding Reflections and Openness to New Questions

In conclusion, we wish to state that, in any analysis of the nature of the problem of doping, it must be clear that its use has, over time, gone beyond the boundaries of the strictly sporting sphere and has reached other social contexts. Thus, drivers, pilots, astronauts, top executives, students and a large number of individuals in a wide variety of professions and activities have used and will most likely continue to use various types of performance-enhancing methods in a kind of "everyday doping" (Douglas, 2007).

Our reflection focuses on the following question: why is doping not allowed in sport as a method or "enhancement" intervention, and why is it allowed in these contexts that we have described throughout this paper (i.e., cosmetic interventions; the case of increasing sexual capacities or the case of students' improvement of intellectual capacity)? The famous philosopher John Harris wonders if it is not cheating to use "smart" what? to pass a competitive exam and if it is indeed cheating for sportsmen to use steroids (Harris, 2010, 2016).

Let us illustrate this question with the case of genetic doping. This subject is included in the field of genetic interventions on human beings for the purpose of

enhancement, widely known by its Anglo-Saxon terminology of human enhancement, which, as we shall see, includes "Mood enhancement".

In sum, why is doping such a hot topic nowadays? is sporting credibility at stake after the controversial doping scandals? what can be said about doping and physical enhancement? what does it mean and imply to increase the athletes' capabilities? are human enhancement treatments ethically acceptable and legally viable in the sporting context? and if so, where do we draw the line between what is legal and what is not? In other words, what should be the criteria for the ethical and legal evaluation of these enhancement treatments?

These are some of the questions that are currently being raised in this area.

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Chapter 15
Arguments Over Life Extension in Contemporary Bioethics

Allen Porter

Abstract In this chapter, I provide a critical exposition of the contemporary bioethics of life extension (LE). First, I provide critical socio-historical contextualization for contemporary bioethics in general by locating it within postmodernity, which discloses crucial implications for what normative claims can possibly be justified within contemporary bioethics and clarifies the typical form that transgression of these limits takes in contemporary bioethics. In the next section, I analyze the structure of the debate over LE into arguments for the necessary desirability (or undesirability) of LE and those for the contingent desirability (or undesirability) of LE, and I provide a survey of the latter. Then, in the next two sections, I critically explicate the main arguments for the necessary desirability and undesirability of LE. I conclude with some final critical remarks on the debate, emphasizing the need for public bioethicists to recognize and be more responsive to the theoretical and empirical pluralism characteristic of the postmodern liberal states in which they typically operate.

Keywords Bioethics · Life Extension · Postmodernity · Transhumanism · Technology

Introduction

It is practically a cliché in the literature on life extension (LE) that significant LE was once considered a fantasy rightly consigned to the realm of science fiction but now looms large as a real and imminent possibility. In recent years, billions of dollars[1]

[1] Consider just the research and development collaboration between Google subsidiary Calico (an acronym for "California Life Company") and AbbVie, which began in 2014 with a $500 million co-investment with the explicitly projected potential for this to grow to $1.5 billion (Calico, 2014).

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have been channeled into LE research as dozens of institutions and corporations have dedicated themselves to the quest for longer life. To get a sense of how rapidly LE research is proceeding, one need only do a Google News search; nowadays, nary a month passes without multiple reports of new initiatives and breakthroughs.

It is urgent that ethical reflection on and public debate over LE be conducted now, before it is too late for them to have any potential impact. Moreover, "[w]e need to think about this now because we *are* making an important policy choice right now: how much to spend on life extension research" (Davis, 2018, 26).

To that end, the goal of this chapter is to critically inform readers about the contemporary bioethics of LE. This is a more complex task than it might seem, requiring me to say a fair bit about contemporary bioethics in general before considering the bioethics of LE in particular. First, however, I must offer a word of caution.

Readers hoping to find decisive normative conclusions in this chapter will be disappointed. Not only do I not offer any conclusions as to the ultimate desirability or undesirability of LE, I do not even try to.[2] Nor do I offer any policy recommendations, such as urging for legislation to slow down, prohibit, protect, or accelerate LE research.[3] Instead, I strive to provide a descriptive yet critical exposition of the chief arguments for the (un)desirability of LE.

Part of what it means for an exposition to be "critical" in this context is that it involve proper socio-historical contextualization of what is being exposited, and that is the purpose of the next section, which delineates fundamental limitations on what can be justified by public bioethical reason operating in a postmodern context.

Bioethics in Postmodernity

In contemporary philosophy, bioethics is considered a particular branch of applied ethics, which alongside moral theory is one of the two branches of normative ethics, which in turn is one of the two main branches of contemporary ethics, the other being metaethics. Metaethics addresses questions *about* morality (e.g., concerning its epistemology or metaphysics), whereas normative ethics addresses questions *of* morality, moral questions about what to do and who to be. Moral theory strives to provide general answers to general moral questions, while applied ethics seeks to apply general moral theory to particular issues so as to deliver determinate answers to concrete moral questions (Timmons, 2002, 19).

[2] In this article, I use "desirable", "undesirable", and their cognates as general and schematic terms for the normative status of LE when I don't want to specify one or another more particular normative status, such as being *morally* (im)permissible, *instrumentally* (ir)rational, etc.

[3] I also do not try to explicate "the science" of LE or detail recent empirical developments in LE research, simply because of the limited scope of this chapter; for those interested in these, see, e.g., Post & Binstock (2004), Davis (2018), and Scott (2018). For those interested in the longer history of LE, see Haber (2004).

Thus, on a conventional understanding of ethics like this, bioethics would be that branch of applied ethics which tries to answer particular ethical questions about "issues that arise in biomedicine and biomedical research" (Resnik, 2021) through the application of general moral theory.

This raises an obvious question for someone seeking to learn about "the" contemporary bioethics of LE, namely: what is the general moral theory that contemporary bioethics should apply to this topic?

"Bioethics as a Plural Noun"[4]

This is where "critical" consideration of contemporary socio-historical context becomes crucial. If we could travel in time and ask this question of medieval Europeans, the answer would essentially be "the moral theory of the (Catholic) Church". In modernity,[5] however, science and rational argument largely replaced faith and appeals to religious dogma as the socially dominant sources of normative authority, if only aspirationally. That is, if we could ask a typical European of the Enlightenment what the true or best moral theory is, the general answer would be "the most rational one", but the particular answer would vary depending on whether one consulted a Kantian, a utilitarian, etc., with each having faith that his preferred moral theory would ultimately emerge from the then-ongoing historical contest as the most rational.

*Post*modernity can perhaps best be described as this modern situation viewed through clear, or at least disillusioned, eyes. There is still a plurality of competing moral theories, but faith in the ability of a universal rationality to resolve this competition has collapsed: "The term *Enlightenment project* [refers to] the endeavor to establish a canonical, content-full morality in secular terms justifiable to persons generally. Postmodernity is the recognition that this project is vain" (Engelhardt, 1996, 23).[6] A full exploration of the reasons for this futility is beyond the scope of this chapter (though see Engelhardt, 1996, 40–65, and Porter, 2020, 260–3), but a few words are necessary given its importance for the LE debate.

[4] This phrase serves as the title of the introductory first chapter of Engelhardt (1996), which I follow in my explanation of the relation between bioethics and postmodernity. For a more optimistic assessment of the epistemological situation of contemporary bioethics, see Beauchamp and Childress (2009) and Mori (2018). For critical discussion of Engelhardt's thought, see Minogue et al. (1997) and Cherry and Rasmussen (2015).

[5] I use this term and cognates in the same sense as Engelhardt (1996, 23): "[M]odernity (as well as terms such as *the modern period*) is characterized by the project of securing by reason the substance of the Judeo-Christian morality, along with an account of moral authority not by faith, but by sound rational argument."

[6] For a critical appraisal of Engelhardt's interpretation of the Enlightenment, see McCullough (2015, 12), which argues that "[t]here was no single Enlightenment but, instead, there were multiple national Enlightenments," and which suggests that one of these may escape Engelhardt's critique.

The normative pluralism of postmodernity is not simply due to the contingent history of a Western Europe characterized by the rise of modern science alongside "the crumbling of the presumed possibility of a uniformity of religious moral viewpoint" (Engelhardt, 1996, 4) in the wake of the Reformation and centuries of internecine religious warfare. Instead, the project of establishing a "canonical, content-full morality in secular terms justifiable to persons generally"—i.e., a morality that would be normatively authoritative ("canonical"), normatively determinate ("content-full"), and free from substantive normative presuppositions ("in secular terms justifiable to persons generally")—was doomed from the start for conceptually necessary reasons.

The project was to derive a concrete morality from analysis of the general form of rationality without presupposing the content of particular reasonings, such that the morality would apply to all rational persons regardless of the particularities that otherwise differentiate them (such as race, ethnicity, and above all religion)—but there was a fundamental problem with the conjunction of these two desiderata, i.e., that the morality be normatively determinate yet presuppose none of the substantive normative commitments that differentiate among ideologies.[7] Specifically, it turns out that these two desiderata cannot be realized simultaneously because there is a conceptually necessary tradeoff between a normative theory's determinacy of content, or its ability to provide determinate answers to concrete normative questions, and its universality of rational form, or its validity for persons in general *qua* rational.

For example, Roman Catholicism has produced a very determinate morality, but its validity depends on the acceptance (on the basis of faith) of premises that cannot be justified to rational persons generally; in contrast, Kant produced a morality that plausibly *did* apply to rational persons generally, but which was also therefore an "empty formalism" incapable of delivering determinate content.[8]

This is why, when inquiring into the limits of postmodern bioethical reason, Engelhardt asks "Can one provide for morality and bioethics more than (1) the formal rational constraints of avoiding contradictions and (2) the conditional constraints of embracing the means to the ends one holds to be obligatory insofar as one holds them to be conditionally or overridingly obligatory?" (1996, 40). In other words, can contemporary bioethics provide more than Kant's "categorical" and "hypothetical" imperatives—i.e., commands that one's practical maxims be logically consistent (avoid contradiction) and instrumentally rational (select the most efficient means for achieving a given end)—without slipping into the endorsement of premises not acceptable to rational persons generally?[9]

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[7] I follow Engelhardt (1996, 19) in using "ideology" to "identify, grosso modo, a concatenation of ideas, images, values, metaphysical assumptions, and epistemological presuppositions that provide a group of people with understandings of morality, justice, proper social structures, [and] legitimate political authority. The term is used to identify the secular equivalent of the nexus of moral, axiological, political, epistemological, and metaphysical understandings such as are provided by a religion." In this sense, an ideology is equivalent to what I call a "substantive normative vision".

[8] A critique first and most famously leveled at Kant by Hegel (see Hegel, 1991, 162).

[9] For Kant on maxims, see Kant (1996a, 73/4:421 [footnote]), (1996b, 380/6:225), and (1996b, 520/6:389); for Kant on imperatives, see Kant (1996a, 66–68/4:413–415) and (1996b, 377–80/6:222–226).

Engelhardt compellingly argued that a normative theory can never achieve determinacy without presupposing the sort of substantive normative commitments that constitute the distinctness of a particular ideology. In "Attempts to justify a content-full secular ethics: Why they all fail" in the second chapter of his seminal *The Foundations of Bioethics*, he considers in some detail "intuitionist accounts, casuistic accounts, consequentialist accounts, hypothetical-choice theoretic accounts" and more, including natural law accounts (1996, 42). Passing over the details, the common result is that all these attempts to secure a determinate secular morality as universally canonical necessarily fail because they either (1) beg the question by presupposing the sort of content-full moral standard they are supposed to establish, or (2) lead to an infinite regress (Engelhardt, 1996, 42).

In short, it turns out that rationality alone cannot justify any of the axiomatic normative commitments constitutive of distinct ideologies, but rather must presuppose one or more of these in order to be able to give determinate answers to concrete normative questions. Put differently: beyond the normatively indeterminate basic principles of logical consistency and instrumental rationality,[10] there are as many "rationalities" and therefore moralities as there are different fundamental normative "priors" (prior commitments). And the problem cannot be circumvented by turning to feeling, such as a putatively universal "moral sense", in place of reason: "the difficulty is to determine *which* reason should guide or *which* sympathy should be canonical" (Engelhardt, 1996, 41; my emphasis).

Postmodern Liberalism and Public Bioethics

Because of the pluralism characteristic of Western postmodernity, it is important to distinguish between what we can call "public" and "private" bioethics. A "private" bioethics is that of some particular "moral community" of "moral friends", defined as such by possession of a particular shared and substantive normative vision that can be applied to reasoning about bioethical matters, while "public" bioethics is that of the larger pluralistic "society" of "moral strangers" characteristic of the typical Western liberal state in postmodernity.[11]

What, then, are the possibilities for contemporary public bioethics in this sense, which is also the sense of my original question about "the contemporary bioethics" of LE? They reduce to two.

[10] Even the universality of rationality in this minimal sense (logical consistency plus instrumental rationality) has been challenged in postmodernity, with increasing frequency and for typically political reasons, by arguments to the effect that logic itself (much less instrumental rationality) is a contingently hegemonic product of historical power dynamics between particular "oppressor" and "oppressed" groups, rather than something with universal scope and necessary validity. See section "Conclusion" below.

[11] See Engelhardt (1996, 7) for further explication of the terms "moral friend", "moral stranger", "community", and "society".

First, public bioethics in a postmodern liberal state can limit itself to claims justifiable within the limits of what Engelhardt names a "general secular ethics" (GSE)—i.e., a conditionally transcendental procedural framework, based in the principle of permission/agreement/consent, for the peaceable collaboration of moral strangers from different moral communities embedded in the same pluralistic society. An Engelhardtian GSE is meant to serve a liberal society as a minimal and procedural "logic or grammar for speaking across a plurality of ideologies, beliefs, and bioethics" (1996, 35), rather than itself being a substantive ideology. It is based in the principle of permission because this is the only available source of normative authority that moral strangers can accept without presupposing substantive normative commitments (see Engelhardt, 1996, 67–72, 122–3). And its only justification is conditionally transcendental: "*If* one is interested in collaborating with moral authority in the face of moral disagreements without fundamental recourse to force, *then* one must accept agreement among members of the controversy or peaceable negotiation as the means for resolving concrete moral controversies" (1996, 68; my emphasis).[12]

The second and more typical possibility is that what proceeds under the guise of public bioethics as a putative product of either rational justification or empirical consensus (or both) is *really* just another private bioethics. This performative universalizing of a particular bioethical vision is generally motivated by either political activism or cultural parochialism, depending on whether the bioethicist in question is cynically projecting or naively presupposing the existence of a rational consensus about a given normative issue over which there is in fact the disagreement characteristic of pluralistic liberal societies more generally.[13] Whether cynical or naïve, such claims of consensus can only be uncritical in light of the normative pluralism empirically characterizing postmodern liberal societies and the impossibility of theoretically resolving this diversity into a unified moral vision through exclusively rational means.

In this light, contemporary bioethics often seems like it is operating within a lingering dream of the Enlightenment, exhibiting a "failure to recognize the depth of the moral diversity that characterizes our context" thanks to a continuing faith in the "presumption that there is a [single] concrete morality available to all through

[12] That is, accepting the minimalistic procedural framework of GSE as the public ethics of the liberal state is a necessary condition of possibility for participation in the liberal state, but this transcendental justification for GSE only holds on the condition that one is in fact committed to this liberal project—and the preferability of that project to incompatible alternatives (e.g., revolutionary Marxism, theocratic Islamism, etc.) cannot in turn be justified by public (bio)ethical reason without begging the question.

[13] As Engelhardt notes: "At times, claims about the existence of a consensus may trade on the failure to note important differences [among the parties to the putative consensus]", but they also "may stem from the way in which politicians seek the *appearance* of a widespread consensus in order to govern" (1996, 61–2; my emphasis). Moreover, even if there were more-or-less widespread (but not universal) empirical consensus about a given bioethical issue, the question would be why this should be viewed as normatively authoritative: "[a]n appeal to a consensus without foundational arguments is an appeal to the orthodoxy of a governing elite in order to legitimate its dominance and to make criticism of its basic assumptions appear immoral or irrational" (Engelhardt, 1996, 63).

rational reflection", a presumption which culminated in the Enlightenment but which "has deep roots in Western history" that extend at least as far back as Plato (Engelhardt, 1996, 3). Not infrequently, contemporary bioethicists even proceed as though the rational resolution of the conflicted normative pluralism, which in modernity came to fill the vacuum left by the collapse of a unified and socio-politically hegemonic Christianity, were something that has *already* taken place—such that bioethicists would merely need to apply "the common morality" (Beauchamp & Childress, 2009, 3) to bioethical dilemmas in order to resolve them:

> Many who work in applied ethics or bioethics seem to disregard these difficulties that lie at the very roots of modern thought. Many proceed with the task of applying ethics as if it were obvious which secular ethic ought to be applied. Many provide bioethics consultations or advice as if there were one content-full bioethics, one canonical content-full bioethical orthodoxy, that should guide all secular moral decisions and justify all health care policy. Such consultations and advice can then lead to imposing a particular moral vision, ideology, or moral orthodoxy as if it were required by reason itself. Such consultants work somewhat as priests, rabbis, or ministers do within a religious context, but without acknowledging their sectarian position. (Engelhardt, 1996, 9).

If this is the situation of contemporary public *bioethics*, then what are the implications for contemporary public[14] *bioethicists*, such as those writing about "the contemporary bioethics" of LE? In general, there are three main roles contemporary bioethicists can ethically perform: activist, expository, and critical.

The ethically activist bioethicist wishes to see a particular "private" ideology become publicly dominant, but only—in contrast to Machiavellians and revolutionaries alike—if this occurs *through* the procedural framework of a GSE, rather than via violations of it. That is, the ethically activist public bioethicist recognizes that his or her preferred ideology cannot be rationally justified without begging the question and that this leaves only establishment by permission and imposition by force as possible means for its achieving public dominance. Because the ethically activist public bioethicist is by stipulation an *ethical*[15] member of the liberal state, he or she necessarily foregoes the option of imposition by force, leaving only establishment by permission. The ethically activist bioethicist's project is then one of persuasion or conversion, consisting in attempts to sway the "hearts and minds" of the public

[14] For a bioethicist self-consciously engaged in *private* bioethics, the context of postmodernity changes nothing fundamental relative to earlier eras. Thus, the same author who argued as a public bioethicist that the limits of postmodern secular reason preclude the possibility of a single substantive bioethics that would be both normatively determinate and justified through purely rational means in *The Foundations of Bioethics* could go on to write, as a *private* bioethicist, a work like *The Foundations of Christian Bioethics* (Engelhardt, 2000)—which offers precisely such a "canonical, content-full" bioethics, just not one articulated "in secular terms justifiable to persons generally".

[15] I mean "ethical" in the Hegelian sense of "ethical life", in which the fundamental normative principle is that "virtue […] is rectitude" (Hegel, 1991, 193)—i.e., according to which ethicality consists in knowing and following the established public norms of a given state and its *Sittlichkeit* (in the case of a postmodern liberal state, this would primarily comprise GSE as well as whatever legal content is produced through empirical exercise of its procedures, such as democratic referenda).

without disguising the partiality of his or her normative vision by presenting it as being justifiable purely rationally or as being something about which there is no significant disagreement empirically.

A contemporary bioethicist can also ethically perform an expository and clarificatory role, namely, by "[a]nalyz[ing] ideas, concepts, and claims cardinal to an understanding of the moral issues raised by health care and the biomedical sciences," "[a]ssess[ing] the soundness of arguments bearing on these issues," and "[p]rovid[ing] geographies of different moral and moral-philosophical positions regarding bioethical issues" (Engelhardt, 2011, 257) from a neutrally descriptive perspective that precludes taking a particular, substantive stand on such issues.

Performing either of these roles ethically requires the bioethicist to be critically aware of the theoretically and empirically postmodern context in which he or she is operating, so as not to inadvertently slide into the uncritical presentation of a private bioethics as public—and the third role contemporary bioethicists can ethically perform focuses on this "critical" dimension, engaging in *critique* of public bioethical reason(ings). This means applying awareness of the limits of postmodern public bioethical reason (i.e., of a GSE) to the critique of texts, policies, practices, and so on insofar as they transgress those limits—most prominently, by exposing uncritical presuppositions, such as when a normative principle (value, claim, theory, vision, etc.) is misleadingly presented as though it were uncontroversially valid thanks to rational requirement and/or factual consensus.

In what follows, I take up the latter two roles. I provide a descriptive survey of the arguments in the debate over LE, and I critically expose some exemplary instances of participants in the debate transgressing the limits of postmodern public bioethical reason.

Arguments for the Contingent Undesirability of LE

There are two types of arguments in the LE debate, namely, those claiming the *contingent* (un)desirability of LE and those claiming its *necessary* (un)desirability. In what follows, my aim is simply to familiarize readers with the basic arguments and counterarguments and to provide representative references for the reader desiring more detailed discussion.[16]

First, a remark on terminology is necessary because of the ambiguity of the term "life extension", which could refer to extension of actual life or lifespan, LE research or LE treatments, intentional or unintentional LE, "moderate" or "radical" LE, and so on. I will withhold from general definition of LE in favor of a contextual approach, specifying whether I mean one or another specific kind of LE if and when relevant. For example, some arguments only apply to what I call "absolute immortality" (i.e.,

[16] It should be noted that these arguments can be grouped in various ways other than the ones I have adopted and that they often interrelate in various ways I don't explicitly flag (e.g., overpopulation issues can exacerbate issues of distributive justice).

complete invulnerability to death), while others apply to what I call "longevital immortality" (i.e., invulnerability to death from "old age"); some only apply to "radical" LE, however this is defined,[17] while others also apply to moderate LE.

One of the most debated class of contingent objections to LE are those involving concerns about overpopulation (see Ackerman, 2009, 334–7; Chapman, 2004, Cutas, 2008; 359; Davis, 2018, 103; Hainz, 2014; More, 2005; Overall, 2003, 55, 134; Solomon, 2006, 181; Wareham, 2012, 203; Wareham, 2015). For example, LE might lead to a "Malthusian crisis" (Davis, 2018, 103) in which population growth exceeds resource growth to the point that quality of life begins decreasing in proportion to the increasing inadequacy of available resources relative to collective need (which can take various concrete forms, from insufficient living space to insufficient food to excessive pollution).

Overpopulation and "graying" populations also have various social and economic implications, such as the potential to create problems for institutions like social security, pensions, incarceration and capital punishment, and more (see Andersen, 2014; Davis, 2018, 97–9; Fukuyama, 2002, 62; Roache, 2013; Wareham 2012, 189). A related debate concerns various forms of social sclerosis, such as the potential for academic and economic innovation to be impaired by the old failing to make way for the new/young (see Bailey, 2007; Davis, 2018, 95–7; Fukuyama, 2002, 66; Pope Benedict, 2010; Schaub, 2007). There are also related concerns about the potential for increasing inter-generational conflict (see Binstock, 2004, 376–7; Fukuyama, 2002, 67). It should be noted that many of these arguments depend upon the extension of mere life being unaccompanied by prolongation of youth, enhancement of cognitive capacities, etc.

Various concerns about quality of life also loom large (see Ackerman, 2009, 326; Fukuyama, 2002, 67; Gems, 2003, 34; Glannon, 2002, 272; Overall, 2003, 190–3). For example, Peter Singer makes a utilitarian argument to the effect that significant LE (even by only 70–80 years) will inevitably result in lower average quality of life because "individuals will enjoy the freshness of youth for a comparatively small portion" of their life and because their average health will be lower than that of those with shorter lives—plus population control would require less reproduction, with the upshot ultimately being that fewer individuals with worthwhile lives would be born" (1991, 139–40; cf. Blackford, 2009). A more typical worry takes its cue from the ancient Greek myth of Tithonus, expressing concern that extended life will not be worth living if LE merely extends life but not also youth/health/etc. (see Fukuyama, 2002, 69; Gems, 2003, 34; Glannon, 2002, 272; Hauskeller, 2011; Lee, 2019, 317).

[17] Many definitions have been attempted (e.g., Häyry, 2011, 22), but there is no general consensus. I will leave the precise line between "moderate" and "radical" LE purposefully indeterminate, treating it as contextual rather than fixed. On this approach, what constitutes "radical" LE in a given case will contextually depend upon at least (a) who is doing the judging of radicality, and (b) what they relevantly care about—in particular, what their relevant "fundamental normative priors" are. For example, if one is committed to a particular content-full conception of human nature (whether Christian, Aristotelian, etc.), then "radical" LE will be that LE which violates or alters this. Similarly, if one cares about personal identity and it turns out that personal identity breaks down if life is extended past a certain threshold, then that threshold will mark the line between "moderate" and "radical" LE in that context.

Like any novel biomedical technology, LE may face various concerns about safety and side-effects. These will derive from the particular type of research or treatment involved; e.g., if germline engineering were necessary for a particular kind of LE, then that sort of LE would inherit the bioethical concerns attending germline engineering (see Petre, 2017).

Other important debates over LE focus on matters of justice. Most prominent is the debate over the likelihood of LE contributing to various kinds of socio-economic inequality and distributive injustice (see Ackerman, 2009, 343; Ardito & d'Errico, 2018, 112; Buchanan, 2011, 102; Chapman, 2004, 350; Harris, 2002, 71; Kass, 2004, 308; Partridge et al., 2009, 74; Pew Research Center, 2013b; Pijnenburg & Leget, 2007, 585; Singer, 2012; Wareham, 2012, 170). Another objection in this area trades on the therapy/enhancement debate, claiming that radical LE is a controversial enhancement that should be deprioritized in terms of resource allocation relative to more uncontroversial medical therapies that increase the quality of unextended life (e.g., Callahan, 1998, 256; cf. Overall, 2003, 55).

Increasing inequality can involve distributive injustice not only in terms of the unfair distribution of goods and access to goods, but also in terms of harms. For example, Agar (2014) argues that approaches to LE like SENS[18] will need healthy middle-aged people for test subjects, but that members of this population are less likely to assume the risks involved than those of other populations, such as elderly people with terminal illnesses (cf. Ackerman, 2009, 327). Agar predicts that, in the face of this need for willing test subjects of good health and middle age, the predictable outcome will be the conscription of the poor for clinical trials (2014, 129–131; cf. Bailey, 2012).

Another set of objections concerns the implications of LE for various kinds of identities and relationships often taken to be important or essential for the worthwhileness of human life. There are debates over how LE might affect workplace relationships, romance, marriage, parenting, and more. Concerns include the potential for LE to undermine the sustainability of romantic relationships, the possibility and/or desirability of having children, and the possibility of authentic love, among others (see Ackerman, 2009, 332–3; Davis, 2018, 94; Fukuyama, 2002, 70–1; Hauskeller, 2013, 8–9; Juengst, 2004, 331–4; Kass, 2004, 267–72; Pew Research Center, 2013a; Schaub, 2007; Wareham, 2012, 87). Arguments in this area can also go in the opposite direction, in the form of claims that LE could extend and even enhance various relationships (Ackerman, 2009, 332; Overall, 2004, 291).

There are also political concerns about LE, with many debating the potential for LE to create immortal tyrants (see Ackerman, 2009, 333; Fukuyama, 2002, 65; Schaub, 2007). Gems (2003, 34) characterizes ageing as "biology's analog of the most successful feature of parliamentary democracy: an effective means to dispose of bad leadership"; noting that "[e]ven under tyranny one can at least wait, and hope to outlive one's oppressor", he argues that this is sufficient basis to conclude that

[18] SENS stands for "strategies for engineered negligible senescence"; it is a program, first defined by Aubrey de Grey, for regenerative medical treatments designed to achieve "longevity escape velocity", i.e., a condition in which the (potentially ineliminable) damages due to diseases of aging are repeatedly or continuously repaired before they can accumulate and cause death (see Agar, 2014, 119).

"anti-aging treatments represent a very serious threat to humanity in the long term." Less frequently noted is the flip side of this objection, which we could call the "immortal slave" concern, i.e., the potential for LE to contribute to extended suffering on the part of various kinds of oppressed peoples, whether literal slaves or unhappy subjects of tyrannical and totalitarian regimes—or criminals, for that matter.[19]

The most prominent response to these arguments in general targets their contingency, arguing that all of the alleged issues are contingent upon factors extrinsic to LE, that they may not eventuate if properly dealt with, and that properly dealing with them need not involve prohibition of LE (see Caplan, 2005, S72–5; Kass, 2004, 309; Overall, 2003, 57). A notable variation on this response is what I call the "technological magic bullet" argument, most often seen deployed by transhumanists in debates over human enhancement, which answers any contingent objection to an enhancement technology by asserting that, by the time the putative problem eventuates, a technological solution for it will also have been developed.

More specific responses tend to consist of proposals for various policies that would solve the putative problems without requiring regulation of LE. For example, overpopulation can be mitigated through various measures, including limiting reproduction (Davis, 2018, 103; Glannon, 2002, 274; Harris, 2000, 59); academic sclerosis can be mitigated by altering tenure policies, and immortal tyrants can be precluded through proper governmental organization (Bailey, 2007; Davis, 2018, 96; Schloendorn, 2006); particular issues of distributive justice can be dealt with through appropriate political and economic policies; and so on.

The reader will note that almost all the arguments so far have been on the anti-LE side. There *are* arguments for the contingent desirability of LE—e.g., claims that LE may lead to "a wiser world", "more appreciation for many things", "better parents", and even "a more peaceful world" (Davis, 2018, 99–101)—but they occupy a miniscule place in the overall LE debate. This is probably because proponents of LE feel confident in their main argument for the necessary desirability of LE and thus devote most of their efforts to countering objections.

Arguments for the Necessary Desirability of LE

There are three main arguments for the necessary desirability of LE.[20] I call them the "more is better" argument, the transcendental argument, and the transhumanist argument.

[19] The 2014 Christmas special ("White Christmas") of the popular techno-dystopian anthology show *Black Mirror* memorably depicts such a scenario.

[20] Prominent debates that don't fit neatly into my schema and which have potential implications for the necessary (un)desirability of LE—though only when combined with a substantive normative vision—include those over whether aging/death is a disease (see Agar, 2014, 115; Callahan, 2003, 74; Caplan, 2005, S73; Davis, 2018, 237; De Winter, 2015; Farrant, 2011, 8; Hauskeller 2016, 136; Hayflick, 2000, 3) and whether LE constitutes "therapy" or "enhancement" (see Agar, 2014; Allhoff et al., 2010; Bess, 2010; Callahan, 2003; Davis, 2018, 219; Farrant, 2011, 12).

The "More Is Better" Argument for LE

The "more is better" argument is the simplest; it simply asserts that life is a good thing, that it's better to have more rather than less of a good thing, and therefore that more/extended life is better than less/unextended life.

The main problem with the "more is better" argument is the question-begging nature of its premises. First, it is obvious that more is *not* always better for all types of goods in all contexts. If one is dying of thirst, a sip of water is good, and several sips are better, but at a certain point drinking too much water becomes unpleasant, then toxic, and finally fatal. Especially given that many prominent anti-LE arguments are of precisely this "more is worse after a certain point" type, applying the "more is better" principle to LE simply begs the question.

Second, it is not indisputable that life is good, much less *a* good of the kind that obeys the "more is better" principle. Some philosophers have argued that life, or at least human life, is *not* good.[21] Others have argued against the intrinsic goodness of life in favor of its instrumental value, the idea being that mere life is only valuable insofar as it is a means for enjoying goods or achieving ends that actually do have intrinsic value, whatever these may be (flourishing, pleasure, etc.)—and that it can even be bad if these goods are absent or overwhelmed by harms.

In both cases, then, the question is begged: *why* is life good and *why* is more of it better? That the argument nevertheless enjoys such widespread deployment and intuitive appeal is best attributed to its serving as a heuristic or parasitic stand-in for what I call the "transcendental argument".

The Transcendental Argument for LE

The transcendental argument for LE gives a single answer to both of the questions begged by the "more is better" argument, and it is the main argument for the necessary desirability of LE in the bioethical literature, though it is more often implicitly presupposed or elliptically alluded to than formally argued for. It says that life is necessarily valuable because being alive is a necessary condition of possibility for experience in general and therefore for the experience of any particular good, and therefore LE is necessarily valuable because it enables potentially experienceable goods in proportion to its extension of life as their condition of their possibility (see Williams, 1973, 87; cf. Chappell, 2007, 36; Farrant, 2011, 29; Overall, 2004, 287). Thus, insofar as all experience of good(s) by a subject depends upon his or her being alive, extending that subject's life is necessarily good for that subject to the extent that that his or her life has experienceable goods.

[21] The most prominent example is probably David Benatar's *Better Never to Have Been: The Harm of Coming into Existence*, which advocates the view known as "antinatalism" (Benatar, 2006). See also Lee (2019, 319) and Knight (2021).

One potential limitation of this argument might seem to be its agent-relativity: it seems not to apply—at least, not directly—in cases of what Williams (1973, 85) calls "non-I desires", e.g., the desire to sacrifice one's life in order to save the life of another. For the good in such a scenario would presumably be the continued life of the other and whatever makes this life worth living for that other, and the sacrificing agent's continuing to live isn't a necessary condition of possibility for the saved agent's ability to experience those goods in general. However, the argument still applies indirectly, insofar as *the other's* life is a transcendental condition of possibility for *his or her* ability to experience good(s), and this fact underpins the motivation to save that life in the first place.

Moreover, this may be viewed as a feature rather than flaw of the argument, which, intuitively, should not be rigidly absolute but instead admit of plausibly reasonable exceptions. Not only does the argument allow for the possibility that achieving certain ends considered to be of ultimate importance, whether egoistic or non-egoistic,[22] could trump the value of preserving one's life as a condition of possibility for the pursuit of *further* ends; because life is a necessary condition of possibility for experience in general (both good and bad), the argument would also not necessarily favor extending life in cases in which the future life will be bereft of experienceable good(s), or promises to contain more harm(s) than good(s), etc.

The transcendental argument is similar to that for the instrumental value of life but is superior in its theorization of the relation between life and the goods it makes possible. Fully explaining this claim is beyond the scope of this chapter, but at least phenomenologically and from a first-person perspective, one's life is not a good like other goods, and the dependency of other goods upon one's being alive does not have the same instrumental form as, say, the way a straw's value depends upon the value of liquid it is a means for conveying or that of the drinking it is a means for facilitating. The relation is rather transcendental: I am not alive "in order to" experience any particular XYZ; rather, being alive is a necessary condition of possibility for experience *as such*.

The transcendental argument is probably so often left implicit[23] because its validity is apt to seem obvious to the typical public bioethicist in a postmodern liberal state. For the argument to work, one need only accept two premises: (1) experienceable goods exist, and (2) humans must be alive to experience. The first is nigh indisputable, even for the most pessimistic and misanthropic person, while the second follows from various views that have enjoyed some degree of cultural dominance among Western academics since the Enlightenment (e.g., the methodological atheism of modern philosophy, the metaphysical materialism of modern science, etc.).

Now, the transcendental argument is not *incompatible* with traditional religious views of the afterlife, nor even with anti-LE arguments based on these. This can be

[22] Williams (1973, 85) notes that "one can want to be dead".

[23] Though see Williams (1973, 87), which actually uses the term "transcendental", as well as Farrant's (2011, 140) distinction between "structural" and "contributory" features of the good life and his argument that longevity is of the former kind.

clarified by wording it more precisely: *worldly* life is a necessary condition of possibility for *worldly* experience as such, and therefore for all *worldly* experience of *worldly* good(s). This phrasing clarifies that the argument does not preclude the possibility of an *afterworldly*[24] existence ("afterlife") as a necessary condition of possibility for the experience of *afterworldly* good(s), nor that these latter could trump all worldly good(s) in importance. If there is an afterlife, and if the highest good(s) can only be experienced in the afterlife, then the transcendental argument would not favor the infinite extension of this life at the expense of the afterlife. Thus, the transcendental argument's validity does not depend upon that of one or more of the theses of atheism, materialism, naturalism, etc.

However, the argument *can* be combined with such theses, in which case it still favors LE, *ceteris paribus*—it's just that this *ceteris paribus* clause covers less; i.e., it covers the possibility that the value of LE is trumped by that of pursuing or satisfying a worldly good or desire which is both of ultimate importance to the agent and incompatible with LE, and the possibility that the value of LE is undermined because the extended life has no experienceable good(s) or has more bad than good—just not the possibility that an *afterworldly* good trumps the value of LE. Since the validity of the argument neither entails nor presupposes these theses denying the afterlife, and since these theses cannot be theoretically justified within the limits of postmodern public bioethical reason, uses of the argument that *do* presuppose them—resulting in the automatic exclusion of divergent views (e.g., traditional religious views on the afterlife) from the debate—can only be uncritical (see section "Conclusion").

The Transhumanist Argument for LE

Transhumanism is a "technoprogressive" intellectual and socio-political movement that advocates for the use of technology to radically transform the human organism in pursuit of the end of overcoming fundamental human limitations, and thereby the "human" as such, in pursuit of becoming "posthuman"—i.e., becoming so radically different from current humans in terms of physical, cognitive, and/or emotional capacities as to be no longer unambiguously of the same species. Immortality through technology is perhaps the most widely shared goal of transhumanists beyond the general one of human enhancement in the direction of the posthuman. Another core feature of transhumanism, advocated by almost all transhumanists, is a claimed continuity with Enlightenment rationalism and humanism. Transhumanism imports humanist values such as rationality, personal autonomy, and so on, claiming that the primary difference between *trans*humanism and traditional humanism is

[24] I have been unable to come up with a truly satisfactory terminology distinguishing "this life" from the afterlife, but the alternatives to "worldly" and "afterworldly" seem even less satisfactory—e.g., "mundane" (vs "arcane"), "mortal" (vs "immortal"), "earthly" (vs "cosmic"), "material" (vs "spiritual"), "natural" (vs "supernatural"), etc.

that the former is not limited to the traditional means employed by the latter to improve the human condition.[25]

As a kind of hyper-modernism, transhumanism has a substantive vision of human nature, just an anti-traditional one, according to which the essence of humanity is a drive to transcend the non-essential aspects of human nature, in the sense of overcoming all limits on human freedom, especially "natural" and biological ones (see Bailey, 2007; Bostrom, 2008; More, 1990). The transhumanist argument for LE is then a familiarly perfectionist one: humans ought to develop LE—and any and all other technologies with the potential to alter "human nature", for that matter—because that is an imperative grounded in the essence of this same human nature.

The main problem with the transhumanist argument for LE is that attending any argument from human nature, namely, that a particular content-full conception of human nature (in this case, an ultra-libertarian one) cannot be justified within the critical limits of public bioethical reason. Whether one views transhumanism as essentially philosophy or theology,[26] its theory of human nature has the same status as any traditionally religious doctrine from the perspective of postmodern public bioethical reason, though more often than not this goes unrecognized or at least unacknowledged by transhumanists.

Arguments for the Necessary Undesirability of LE

There are also three main types of arguments for the necessary undesirability of LE: arguments from religion, secular arguments from human nature, and what can broadly be called arguments from meaninglessness.

Anti-LE Arguments from Religion

Arguments both for and against LE on religious grounds can take various forms, but all suffer from the same problem from the perspective of postmodern bioethical reason—namely, they presuppose the validity of the religion's substantive normative vision, which validity cannot be demonstrated in purely rational terms acceptable by persons generally.

The most prominent form of this type of argument, for historical reasons, is the Western Christian one according to which humans are created *imago dei*, with a divinely dictated human nature that one ought to respect and preserve, including a

[25] For a fuller exposition of transhumanism in relation to bioethics, from which this characterization is adapted, see Porter (2017). For a study of transhumanism in relation to LE specifically, see Wareham (2016).

[26] There are multiple transhumanist religions in existence today, such as Singularitarianism—including ones specifically devoted to LE, such as the Church of Perpetual Life.

"natural" lifespan (see, e.g., Labrecque, 2010, 89–90). Details can diverge as to the limits of this lifespan, but radical LE would clearly be "unnatural" on such views. Moreover, Christianity (among other religions) places an ultimate value upon the afterlife, such that the very meaning of mortal life is teleologically anchored in it. On such a view, preventing death would not only be bad because violating divine commandment, but because it would preclude the possibility of experiencing the highest good(s) in both this life and the next.[27]

From the perspective of public bioethics in a postmodern liberal state, the main significance of anti-LE arguments from religion lies in their existence—i.e., the existence of minoritarian metaphysical views which contribute to the normative pluralism of a postmodern society and thereby ground certain limits for its public bioethical reason vis-à-vis disputed issues like LE.

Secular Anti-LE Arguments from Human Nature

These are essentially the secular equivalent of the sort of religious argument from human nature just mentioned. They argue for some particular conception of human nature on non-religious grounds, such that a determinate "natural" human lifespan can then be fixed as a basis for opposing LE that extends life beyond what is natural (see, e.g., Fukuyama, 2002, 129–33; cf. Caplan, 2005). They face the same problem (presupposing a substantive normative vision unjustifiable within the limits of postmodern public bioethical reason) and have the same significance for public bioethics (contributing to the theoretical and empirical reality of normative pluralism) as arguments from religion. Given the discussion of postmodernity above, it is unsurprising that none of them have gained general acceptance.

Anti-LE Arguments from Meaninglessness

A large and diverse group of arguments is united in arguing for some version of the thesis that radically extended life precludes one or another form of meaningfulness that has plausible claim to a fundamental axiological status, whether as the highest good or as a transcendental condition of possibility for all other goods or simply as a very important good.[28]

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[27] Because the highest good in this life would be living in the manner dictated by the religion, the content of which would be determined by the religion's way of grounding of the meaning and purpose of this life in the afterlife (cf. Engelhardt, 2000, 332).

[28] A few have also ventured the opposite thesis, as *prima facie* absurd as it may seem—namely, that *mortality* threatens meaningfulness, such that unextended life is meaningless because mortal (e.g., Chappell, 2007, 32).

These arguments tend to presuppose a roughly shared view of what makes human life meaningful. The basic view is that this requires that one have and/or be able to pursue and/or be able to achieve a coherent set of life goals through various meaningful projects. For example, Farrant (2011, 44) roughly follows Williams (1973) in arguing that death is bad because "it deprives the deceased of the experiences they derive from the fulfilment of their categorical desires." His view is that the "meaning and value" of a human life comes from "the activities and attachments that we maintain and pursue", which are in turn grounded in a person's "categorical desires", such that a life's being "fulfilling" vis-à-vis these desires is what "makes it worth continuing" (2011, 48–9). Similarly, Bortolotti speaks of "the *coherence of life goals* in the trajectory of an individual life […as] necessary for a life to acquire or preserve meaning via its contribution to an agent's sense of self and purpose" (2010, 41).

For example, Bortolotti considers what she calls "the agency objection",[29] according to which LE would threaten "the development of personal narratives" essential for meaningfulness, the idea being that, over a sufficiently long life, an agent will develop such a large and diverse set of goals that their coherent narrative unification will become difficult or impossible (2010, 40–1). She responds by noting that while "some broad coherence of life goals" may be necessary for meaningfulness, this doesn't rule out their diversity or change, as unextended lives already demonstrate (2010, 41).[30]

A related objection can be called the "life stages" objection (cf. Bortolotti 2010, 47; Kass, 2003; Wareham, 2012, 93; Wareham, 2016, 529). The idea is that some life narratives/goals/projects are indexed to qualitative stages of unextended life such as childhood, youth, middle age, and old age. If life stages disappear thanks to LE, then these goals become impossible to realize. To succeed, this argument requires that LE eliminate life stages and that either all goals/projects/etc. are indexed to life stages or some of essential importance are. It is not obvious that LE, especially moderate LE, would entail the elimination of life stages, which might simply be extended instead, and it's at best unclear how life stages would be affected even by radical LE. On the other hand, it is clear that not all life goals/projects/etc. are indexed to life stages, while it's unclear whether any of indispensable importance are. Moreover, any view positing particular goals/projects/etc. as essential for meaningful life will effectively constitute a substantive vision of human nature which cannot be theoretically justified within the limits of public bioethical reason. Incidentally, the same goes for the view that life stages as such are valuable (e.g., because "natural") rather than not.

[29] She actually covers two separate arguments under this title, the other being a version of the "Romantic paralysis" objection that I consider below.

[30] The logical follow up question, which Bortolotti does not pose, would be *how much* diversity can be tolerated without sacrificing coherence, and whether there is reason to think that radical LE might lead to diversity beyond this tolerable threshold (which may well be an empirical question, rendering the objection contingent rather than necessary).

Next, there is what I call the "Romantic paralysis" objection. The basic idea here is that, without awareness of one's mortality and the constraints it imposes on decision, choices will lack necessity and urgency, resulting in choice paralysis (see Schwartz, 2004) and perhaps other meaning-threatening conditions like boredom, developmental stagnation, etc. (see Callahan, 1998, 131–2; Hauskeller, 2016, 77). The name derives from the fact that the character type of the Romantic avoids the anxiety-inducing prospect of decisive commitment, which entails realizing one possibility at the expense of all alternatives, preferring to withhold from decision and action in favor of entertaining incompatible possibilities in imagination/fantasy: why choose between becoming a doctor or a lawyer today, when you can put the choice off until tomorrow and meanwhile be both in your imagination (see Kass, 2002, 185–6)? As Malpas says, "It is precisely because we cannot play through an endless series of choices, an infinite series of possibilities, that the choices we do make become so important to us; those choices establish the character and identity of our lives; they allow certain things to show up as valuable" (1995, 118; cf. Engelhardt, 1996, 416). A notable version of this argument applies to interpersonal relationships in particular:

> Stanley Hauerwas, a noted author and theologian at Duke University's Divinity School, agrees that the certainty of death makes life more fulfilling. Without death, Hauerwas argues, love as we know it would cease to exist because it is the finite nature of life that prompts people to wholly commit themselves to others. "Death … creates an economy that makes love possible," he said in a 2011 interview with the Pew Research Center. "If you lived forever, there would not be the necessity of loving this one, not that one. You could love them all." (Pew Research Center, 2013a).

A typical response to this kind of objection begins by noting that even if LE were to remove some meaning-grounding constraints on agental finitude, it won't remove them all. First, with regard to life goals, some life goals and their possibilities for achievement are unaffected by variations in lifespan—e.g., the goal of winning a gold medal at the Olympics versus that of winning a gold medal at *the 2016 Summer Olympics*: "Some goals come with their own in-built 'expiry date.' […] Some opportunities are missed and do not come back, no matter how long one lives" (Bortolotti, 2010, 46). This point extends to other kinds of decisions that can contribute to one's sense of self or life narrative—e.g., whether or not to help the old lady who fell down over there just now. The contingency of circumstances entails that some decisions will be required in the here and now, while the irreversibility of time ensures that some decisions cannot be repeated or redone differently. A second response would question whether the proposed scenario is different from that of unextended life, noting that some people suffer from Romantic choice paralysis without LE while others don't; *ceteris paribus*, it's plausible that this will hold under LE as well. At the very least, there doesn't seem to be a logically necessary connection between extended life and Romantic paralysis; more probably, it is contingent upon individual personality and circumstance.

A related but more philosophically sophisticated version of the objection is due to Heidegger. In *Being and Time*, Heidegger uses phenomenology to argue that the self is the ultimate source of meaning/normativity—that is, the radically free and

responsible "fundamental" self that is disclosed through the experience of "existential breakdown", which experience makes possible authenticity, understood as the resolute taking-over of factic grounds as potentially justifying reasons (see Heidegger, 1962; Crowell, 2013, 179). Though explication of the details, or even of Heidegger's neologistic terminology, is beyond the scope of this chapter, his account of subjectivity is of interest because of the role that mortality and an understanding of death play as transcendental conditions of possibility for authentic decision. Basically, "existential breakdown" discloses the free and responsible self as capable of authenticity through the equiprimordial existential structures of "mood", "discourse", and "understanding", which in the case of breakdown take the particular forms of "anxiety", "conscience", and "death", respectively. Roughly, the idea is that "understanding" of "death" discloses that the self both can and must choose not only what to do but who to be—and that this means resolutely committing to one possibility at the expense of the others, among other things.

Nussbaum's (1994, 227) argument that immortality would make courage and other virtues impossible is often mentioned in this context (see also Kass, 2002, 268). While it is an argument for the necessary rather than contingent undesirability of immortality, as Overall (2003, 131) notes, it only applies to absolute immortality (*complete* invulnerability to death), not to longevital immortality (much less any form of finite LE).

Next is an influential objection from personal identity, for which Williams (1973) is typically cited as inspiration, according to which "a substantial increase in longevity would be undesirable because it would undermine the psychological grounds for identity and prudential concern about the distant future" (Glannon, 2002, 268; see also Ackerman, 2009, 330; Bortolotti, 2010, 48; Davis, 2018, 39; Overall, 2003, 155; Schloendorn, 2006, 197). The basic idea is that the more time there is between mental states, the less they are connected, even to the point that they belong to numerically distinct persons—so that, past a certain threshold, LE would entail the pluralization and serialization of the self. The upshot is that, for an agent for whom moderate LE is desirable, LE past the threshold would not necessarily be desirable because the life being extended would no longer be that agent's but someone else's. Challenges to this argument include debating its putative necessity (Smuts, 2009; Overall, 2003,158; 356; Fischer, 2012, 341; Fischer & Mitchell, 2014, 356), debating underlying theories of personal identity (Chappell, 2007, 38; Schloendorn, 2006, 196), questioning whether the pluralization/serialization of the self is necessarily a bad thing (Bortolotti, 2010, 48; Smuts, 2011), arguing that it is actually desirable (Schloendorn, 2006, 195), and alleging that it already occurs in ordinary, unextended life (Bortolotti, 2010, 48; Overall, 2003,158; Smuts, 2011).

Perhaps the most discussed argument from meaninglessness is what is often called the "boredom objection", which really stands for a family[31] of related objections for which Williams (1973) is again the main textual touchstone (see also

[31] As Gorman (2016, 1062) notes, "While Williams' argument has proven elusive to pin down, the paper has spawned a cottage industry".

Ackerman, 2009, 329–31; Altshuler, 2015; Burley, 2009; Davis, 2018, 62–7; Farrant, 2011, 47; Kass, 2004, 312–13; Lee, 2019, 319; Moore, 2006; Overall, 2003, 145–50; Temkin, 2008; Wareham, 2012, 133). The basic idea is that the achievement or even pursuit of life goals will eventually become impossible for someone living a sufficiently long life—whether because the agent satisfies all their goals, because the agent becomes frustrated by repeated failure and gives up on their goals, or because the meaning/satisfaction of activities and achievements simply fades ("diminishing returns").

The overarching theme of responses to the boredom objection, which vary in their details according to how precisely the objection is specified, is to challenge the putative necessity linking radical LE and boredom (see Bailey, 2007; Belshaw, 2015, 329; Bortolotti, 2010, 50; Bruckner, 2012; de Grey, 2007; Fischer, 2009; Galloway, 2012, 1089; Gorman, 2016, 1075; Kekes, 2002, 240–4; Levy, 2005; Quigley & Harris, 2009; Smuts, 2009; Temkin, 2008, 202; Wareham, 2012, 113; Wisnewski, 2005). Other responses tend to be supplementary—such as the observation that, even if extended life inevitably becomes boring eventually, one can always commit suicide or simply end the LE treatment once that occurs, so why die before then? (Davis, 2018, 53)—or hypothetical, such as the "technological magic bullet" argument in the form of a "boredom pill" (Davis, 2018, 44). It has also been claimed that the boredom objection is self-undermining because boredom, were it to eventuate for the person with extended life, would itself simply be another obstacle to be overcome in the pursuit of his or her life goals, thus functioning as a meaning-grounding rather than meaning-threatening constraint (Bortolotti, 2010, 51–2).[32]

Objections from meaninglessness can overlap and interact in various ways. For example, the boredom and personal identity objections are often combined into a dilemma,[33] while Bortolotti (2010, 51–2) argues for a mutually contradictory tension between the boredom objection and the agency objection.

Finally, it should be noted that most of these arguments (and counterarguments) presuppose what is effectively a substantive theory of human nature, according to which the good (human flourishing, meaningful life, etc.) depends exclusively on factors immanent to worldly life. This implicitly excludes substantive views of the good as dependent on factors transcendent to worldly life, such as views grounding the meaning of life teleologically in an afterlife. For example, Farrant (2011) holds that the meaningfulness of life consists in the pursuit and satisfaction of "categorical desires", but he fails to consider the possibility of categorical desires (e.g., stemming from traditional religious faith) that are incompatible with LE.

[32] The problem with this last is that it conflates obstacles to achievement with conditions that render achievement impossible: the whole point of the boredom argument is that, if it is valid, the person would lose the motivation to try to overcome obstacles in the first place, which loss is not itself an obstacle among others but rather precludes the very perspective in which obstacles to life goals are seen *as* obstacles (i.e., as obstacles to be overcome).

[33] This move takes up a parenthetical suggestion by Williams (1973, 92) to the effect that the dilemma might hold if the minimally sufficient conditions for personal identity are stronger than those for mere bodily continuity, "requir[ing], for instance, conditions of memory". See, e.g., Davis (2018, 38) and Fischer (2012, 339).

Conclusion

Because of the postmodern context in which it operates, contemporary public bioethics can justify no definitive conclusions regarding the ultimate desirability or undesirability of LE. Contemporary bioethics does not speak on such issues with the single voice of a universal reason; there are as many bioethics of LE as there are bioethics, as many bioethics as rationalities, and as many rationalities as there are substantive normative visions. This postmodern situation behooves public bioethicists to avoid uncritically presupposing the validity of their preferred private bioethical vision as though it were "the" view of a univocal public bioethics. Frequently, however, bioethicists fail to take sufficient care in this regard, and it is the job of critique to expose when they uncritically transgress the limits of postmodern public bioethical reason.

In contemporary public bioethics, three particular substantive normative visions are most often uncritically presupposed as valid on theoretical and/or empirical grounds. They can overlap and mix in certain ways but are nonetheless conceptually distinct; I call them "liberal cosmopolitanism", "transhumanism", and "postmodernist identitarian leftism".

Liberal cosmopolitans are people who "regard themselves as possessing the canonical, content-full, secular morality (and bioethics) and see it as being ['objectively'] justifiable outside of a particular moral history and tradition" (Engelhardt, 1996, 27), where the morality in question is some substantive version of liberalism (as opposed to the procedural liberalism of an Engelhardtian "general secular ethics"). Liberal cosmopolitanism, in this sense, is a holdover from the Enlightenment, when there was still hope that a concrete morality could be derived from a formal analysis of reason without making or presupposing any substantive normative commitments of the kind that differentiate various ideologies. Liberal cosmopolitanism generally presupposes the validity of secularism and rationalism, and it tends to be characterized by commitments to multiculturalism, internationalism, liberal democracy, and "expansive" positive-rights regimes.

Consider de Grey's (2007) appeal to a putative liberal consensus about identity-based discrimination, framed in the rationalistic terms of Rawlsian liberalism, which he uses to suggest that opposing LE is "ageist"[34] and therefore immoral:

> We lock people up for the same amount of time if they kill people with a gun or with a booby-trap bomb, even though the interval between the murderer's action and the victim's death differs by several orders of magnitude in the two cases. […] Time was when we didn't lock people up for either such crime: we executed them. That tradition has been roundly rejected across almost the entire developed world, as have slavery, sexism, racism, faithism, homophobia—and, with the notable exception of this essay's subject, ageism. Our view of what is and is not repugnant evolves by a process best described by Rawls, with the name "reflective equilibrium", in which logical contradictions between simultaneously held values are progressively highlighted and resolved by the abandonment of the less central one. (de Grey, 2007).

[34] The concept of ageism has been deployed in various ways in the LE debate; see also Ackerman (2009, 328); Beauchamp and Childress (2009, 273); Caplan (2005, S73); Davis (2005, 36); Fukuyama (2002, 65); Juengst (2004, 334); Labrecque (2010, 172); Overall (2003, 42).

The suggestion is that an empirical consensus affirming the liberal view of discrimination has formed through a rational process, that ageism is a form of discrimination, and that opposing LE is ageist. Since this putative consensus is supposedly rooted in rationality, the implication is that those who hesitate to apply it to the issue of LE vis-à-vis ageism must not only be "on the wrong side of history" but be downright irrational. Indeed, de Grey accuses opponents of LE of "irrational rationalization" in support of maintaining their "pro-aging trance" and of being subject to "myths and illogicalities" and a "miasma of arbitrary assumption and distractions" that render them "stunningly irrational from an objective viewpoint" (2007). Nor is he alone in claiming that desiring LE is "rationally required", at least for anyone who can "expect to live on happily" (Schloendorn, 2006, 191).

Of course, neither the theoretical rationality nor the empirical consensus de Grey claims for these views obtains in reality.[35] Rational persons can and do disagree about the ethics of capital punishment, and as of 2018 there were 56 countries practicing legal capital punishment, with another 8 having abolished it only for "ordinary" crimes and another 28 having abolished it only "in practice" (Amnesty International, 2018). Similarly, the view that discrimination against homosexuals is immoral, for example, is only culturally dominant in the postmodern liberal states of the West. Iran not only retains the death penalty but imposes it as a punishment for same-sex sexual acts—and when a German reporter asked Iranian Foreign Minister Mohammed Javad Zarif why "homosexuals [are] executed in Iran because of their sexual orientation", he began his response by saying "Our society has moral principles. And we live according to these principles" (Deutsche, 2019).

In the case of transhumanism, it is typically the aforementioned philosophical anthropology that is presupposed and then deployed in support of a socio-political vision. For example, Bailey (2007) concludes his defense of LE with the assertion that "the highest expression of human nature and dignity is to strive to overcome the limitations imposed on us by our genes, our evolution, and our environment" followed by a prediction that future generations will look back upon this time "with astonishment that some well-meaning and intelligent people actually wanted to stop biomedical research just to protect their cramped and limited vision of human nature". He simply presupposes the validity of the transhumanist conception and the invalidity of traditional conceptions of human nature, presenting the transhumanist conception as though it were an uncontroversial empirical fact, a deduction of pure reason, or the product of a widespread consensus. Finally, like the liberal cosmopolitanism that it often overlaps with in this context, and doubtless due to their shared roots in the Enlightenment, transhumanism's normative vision is typically characterized by commitments to both rationalism and secularism.

Finally, by "postmodernist identitarian leftism" I mean the novel political ideology, resulting from the combination of philosophical postmodernism and political

[35] For Engelhardt's critique of Rawlsian attempts to justify a content-full general secular ethics, see Engelhardt (1996, 59).

leftism, which emerged in the 1960s, came to dominate Western humanities and social science departments in the 1980s, and began to prevail in the larger culture around 2012 (see Porter, 2021). Explicating the details of this ideology, which nowadays is often associated with the term "wokeness", is beyond the scope of this chapter; for present purposes, its most relevant feature is its illiberal approach to so-called "identity politics" (see Porter, 2021, 163).[36]

Specifically, postmodernist identitarian leftists propound "equity" as an identitarian ideal of social justice in explicit opposition to "equality" as part of the liberal ideal of impartial (identity-neutral) justice, where "equity" is defined in terms of either equality of outcome or deconstruction of "hegemonic" identitarian stuctures (Porter, 2021, 207). The basic idea here is that achieving the liberal ideal of legal equality, as advocated by classical civil rights activists like Dr. Martin Luther King, Jr., is not only "not enough" to end identitarian forms of oppression like racism, but in fact functions to perpetuate precisely those forms of oppression by elevating the values (traits, etc.) of a particular, historically dominant identity to a position of putative neutrality and universality (concealing their actual partiality and particularity).[37] The idea is then that illiberal practices of identity-based discrimination are required to achieve "equity"; as one of the more infamous proponents of this ideology puts it, "The only remedy to past discrimination is present discrimination. The only remedy to present discrimination is future discrimination" (Kendi, 2019, 19).

This difference between liberal and identitarian leftist conceptions of discrimination is on display in Overall's (2003) critique of an argument by Callahan (1999, 194), in the course of which she says

> [A]lthough it is true that men who happen to live as long as women would equally suffer under [Callahan's proposed] policy, the fact remains that the large majority of long-living human beings are women, and therefore a practice that denies long-living people life-sustaining medical care does as a matter of fact discriminate against women, even if the intention of the policy is to discriminate "only" against elderly people whatever their sex. (Overall, 2003, 112)

[36] Postmodernist identitarian leftists have the sort of critical, postmodern view of rationality that I have deployed in this chapter, holding rationality to be plural and particular rather than singular and universal. They also affirm a claim about rationality that I have not, namely, that its essential social function is to benefit "hegemonic" identitarian groups by universalizing and valorizing the values/traits/etc. of historically dominant identities (e.g., Western Europeans, whites, etc.) and excluding (marginalizing, pathologizing, etc.) the values/traits/etc. of historically oppressed ones. This also contributes to its incompatibility with liberalism, the critical rejection of which constitutes one of its core tenets.

[37] For example, in 2020 the Smithsonian National Museum of African American History and Culture released guidelines for talking about race that included a graphic, entitled "Aspects and Assumptions of Whiteness in the United States", which claimed that ideas, norms, and practices like the following are oppressive aspects of "whiteness": "the nuclear family", "self-reliance", "hard work [as] the key to success", "work before play", "respect [for] authority", "follow[ing] rigid time schedules", "plan[ning] for the future", "intent counts", "be[ing] polite", and more (Watts 2020).

Overall does not argue for the validity of this conception of discrimination, according to which differential outcomes constitute discrimination regardless of intention, nor for the invalidity of Callahan's traditional liberal conception of discrimination, according to which intention makes all the difference for ethical evaluation. Instead, she simply presupposes these as though they were objectively rational conclusions or uncontroversial empirical "matters of fact". Never mind that, by this logic, the NBA would have to be said to discriminate against white people (because even if the discrimination is supposedly based in consideration of basketball skill rather than race, the outcome is still a vast racial disparity), the police to discriminate against men (because even if men commit more crimes than women, the fact remains that 80% + of arrests in the U.S. are of males), and so on; never mind that conservatives, traditional liberals, and even some traditional leftists (i.e., Marxists) disagree with this view.

The lesson that contemporary bioethicists should draw is clear. In postmodernity, no ideology (or substantive normative element thereof) can be said to "objectively" enjoy the general validity required for public bioethical claims in virtue of sheer rationality, while claims of consensus about bioethical matters inevitably falsify empirical reality—thus, the presupposition of the validity of such views can only be uncritical on the part of contemporary bioethicists (or, if cynically projected despite critical awareness, then unethical).

In this light, what is perhaps the single most prevalent normative presupposition of contemporary bioethics, both in the LE debate and more generally, must be critically reexamined—namely, the assumption of the validity of secularism, manifested through a pervasive failure to consider traditionally religious views as worthy of recognition in public bioethical discourse.[38] Most public bioethicists participating in the LE debate not only do not try to justify this presupposition, they do not even acknowledge making it.

Overall (2003) is one of the very few exceptions in this regard, as she explicitly flags secularism as one of her operative methodological presuppositions and even offers a brief justification for it: "We do not know of any existence beyond death; this life on earth is the only one of which we can be assured. Hence issues of human longevity must be considered within that context: we are dealing with the only life we know that we have. For the sake of this discussion, I therefore adopt a skeptical outlook on religious promises of everlasting life after death" (2003, 14).[39]

[38] The term "secular" and cognates have multiple meanings (at least seven: see Engelhardt, 2011, 89–90). In the sense of Engelhardt's "general secular ethics", the secular is that which is neutral vis-a-vis competing religions. I use "secular*ist*" and cognates in the political theoretical sense of what Engelhardt would call "secular fundamentalism", i.e., an ideology that "seeks to exclude from the public forum and even from public discourse any but a secular ideology" (2011, 76; cf. Iltis 2018).

[39] See also Ackerman (2009, 325), who states "[l]ike other secular philosophers who write on this topic, I will assume there is no afterlife". She provides no justification for this assumption other than that of limiting the scope of her text, but she does critically qualify her language accordingly, carefully speaking of "secular bioethicists" rather than simply "bioethicists" (2009, 326).

Yet even she quickly slides from skepticism about religious metaphysical claims into presupposition of a rational empirical consensus denying them, such as when she explains the "interdiction on anything in modern life that is connected with death" as following from the fact that "people now recognize only too clearly (even if they did not, in medieval times) that death is the end of any possibility of personal happiness" (2003, 33). In the context of a postmodern liberal state like the United States—in which 65% of the population is Christian, with over 40% of Americans affirming that religion is "very important" in their lives (Pew Research Center, 2021)—statements like this uncritically and untenably conceal the reality of normative pluralism.

Such cultural parochialism not only manifests in the assumption of the theoretical unimportance of religious views, but in uncritical presuppositions about the content of those views. In the LE debate, this most often takes the form of conflating the religious view of immortality in the afterlife with the secular view of indefinitely or infinitely extended worldly life.[40] For example, Schloendorn (2006, 195) says that "[a]rguments from indefinite expectable desirability could outweigh finite adverse side effects of life extension and subvert the popular claim that life extension might be superfluous, as we might already be immortal in a religious sense". Similarly, Overall (2003, 23) says it was suggested to her that "one possible drawback of immorality here on earth would be that one would never find out what happens after death—whether, that is, there is life after death. But I am assuming that if eternal life before death is worthwhile, it would obviate any value to or interest in life after death." But as any Christian could tell her, "[e]ternal life in Christian teaching is a very different kind of life than the life whose great extension is being sought by some scientists" because "eternal life is not the infinite extension of life as we know it, but a different kind of life, which we can experience and have to a degree in this life, but can have fully only after death" (Allen, 2004, 388; cf. Kass, 2002, 269–70).

In light of all of the above, if there is one piece of ethical advice I can safely give to the current and future players in the drama of LE without slipping from exposition and critique into activism, it would be not to take anything for granted when it comes to what you think you can expect people to agree to, believe, or desire when it comes to normative matters (even those that seem uncontroversial to you). In the face of the impossibility of objective rational justification for a given substantive normative vision, the only possible sources for its authority are *agreement* and *force*, such that any policy that presupposes an agreement that is actually lacking can have no more authority than the threat of force.

This advice is especially crucial at the current moment, as the pluralism characteristic of the postmodern liberal societies in which most public bioethicists operate is increasingly reflected internally within public bioethics, which will continue to be the case *even if* the secularist assumption continues to screen out traditional religious views from public bioethical discourse—namely, thanks to the ongoing rise of

[40] Ackerman (2009, 325) suggests a distinction between "earthly immortality" and "immortality in a religious sense" but does not elaborate; see also Williams (1973, 94).

postmodernist identitarian leftism and its incompatibility with the sort of Enlightenment liberalism that has been the dominant paradigm for Western bioethics since its inception in the 1970s. Indeed, given that the incompatibility between postmodernist identitarian leftism and liberalism is arguably growing to be the defining political issue of our era, public bioethicists who proceed on the basis of presuppositions of rational consensus lack any legs to stand on, perhaps moreso than at any time since the inception of this field called "bioethics".

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Part III
Biomedical Research: *Research with Human Biological Samples and Health Data*

Chapter 16
Research with Human Biological Samples: Systematization of the Phases and Affected Rights

Pilar Nicolás Jiménez

Abstract The legal nature of human biological samples is complex, which implies that their collection, storage, use and transfer for research purposes affect different rights of the subjects. In particular, this study will address the implications for the right to physical integrity, the right of disposal of body parts and the right to the protection of personal data. On the other hand, the concurrence of other interests and rights justifies the design of governance systems that also guarantee the availability of samples to facilitate research, as well as scientific collaboration. Many countries have adopted specific regulations on the use of biological samples for research purposes, but there are no binding international regulations on the subject. However, certain commonly accepted principles can be identified in this area.

Keywords Human biological samples · Health research · Biological samples · Genetic data · Biobanks

Introduction

General Approach

Availability of human biological samples is essential for the development of biomedical research in general and, in particular, for studies related to the implications of genetics in the predisposition to or development of diseases, or with interindividual differences in drug response. In this sense, there is a scientific interest in accessing samples processed under quality conditions, since they are a very valuable resource for the advancement of science. Therefore, it can be affirmed that the right to research and the interest of society in scientific progress and in the translation of this knowledge to the clinical field are present in this area.

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A sample is a part extracted from a set by methods that allow it to be considered as representative of it. A human biological sample is a cell or tissue extracted or produced by the human body from which the characteristics or status of an individual can be determined. The human biological sample is a part of a person's body, is information support and is a material that can have generative capacity. Taking into account this complex nature, the use of samples in biomedicine has many different facets: transplantation, regenerative medicine, reproductive medicine, population screening, and extraction of information for diagnostic or scientific research purposes, among others.

From each of these dimensions derive different implications for the rights of the source subject, which is the one from which the sample comes: first, its separation from the body has implications for the right to physical integrity and bodily integrity; secondly, its use has implications for the right to decide on one's own body or its parts; thirdly, the generation of individuals has implications for reproductive rights; finally, the collection of information, have implications for privacy and data protection rights. Therefore, ethical and legal implications of using samples for biomedical research may affect different rights of the source subject. To address the analysis of the applicable regulatory framework it is essential to bear in mind this complexity.

As a preliminary point, the concept of scientific research should be defined as the purpose of the use of samples, since the regulation of use is sectoral. This term is not legally defined in the international framework. The interpretation of the General Data Protection Regulation (GDPR) (European Union, 2016) can help, according to which scientific research covers "technological development and demonstration, fundamental research, applied research and research financed by the private sector" (Recital 159). This is such an extensive concept that it welcomes research projects with publishable results and other analytical studies, not excluding those financed by private entities or for commercial purposes, which has been subject to some criticism (Manis, 2017). The European Parliament's Committee on the Environment, Public Health and Consumer Protection is proposing a number of amendments. For this purpose, the following parameters could be taken into consideration in the framework of health research, on which this work focuses:

- The activity should contribute to the increase of knowledge (scientific research in the strict sense) or to the use of knowledge for the production of devices, materials, services, processes or products (technological development and demonstration) (OECD, 2015).
- The activity must be developed under certain quality standards (professional, methodological and institutional).
- The activity should have a benefit (direct or indirect, which would include basic research) for the health of the general population or a particular group (for example, those affected by low prevalence diseases). In other areas of scientific research, the benefit is also due, within the framework of the objectives that are specific to each discipline.

In accordance with this perspective, scientific research covers both the generation and application of knowledge and excludes activities that do not present rigorous guarantees in their development, as well as those that pursue purposes that do not have a potential health benefit for a greater or lesser number of people (for example, the manufacture of biological weapons or illicit reproductive cloning).

On the other hand, it is important to stress that teaching cannot be considered as a scientific activity, even if it is aimed at training professionals in this sector. Nor does the analysis in forensic investigations, whose purpose is the identification of individuals.

An important aspect of the entire sample collection, storage and use process is that it is supervised by an accredited ethics committee (art. 16 of the UNESCO International Declaration on Human Genetic Data, 2003 and art. 22 of Council of Europe Recommendation CM/Rec (2016) 6 on research involving human material). The work of these committees is particularly relevant in the area of international circulation of samples, as will be explained below (Chalmers et al., 2014).

Normative Framework

Many countries have adopted specific regulations on the use of biological samples for research purposes (Romeo Casabona & Simon, 2005; Rothstein et al., 2015; Slokenberga et al., 2021). But there is no binding international regulation that develops a regulation on the matter, beyond the general lines contemplated by Oviedo Convention (1997): prohibition of human beings or their parts, as such, be subject to profit (art. 21) and the requirement of "adequate" information and consent if a part of the human body extracted in the course of an intervention is to be preserved or used for a purpose other than that for which it was extracted (art. 22).

With another character, also in the framework of the Council of Europe, the most specific and developed text, was the Recommendation Rec (2006)4 of the Committee of Ministers to member states on research on biological materials of human origin, which has been replaced by Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin.

It should also be noted that the UNESCO International Declaration on Human Genetic Data of 16 October 2003, states that its objective is to ensure the protection of the rights of individuals and the protection of their rights "to ensure the respect of human dignity and protection of human rights and fundamental freedoms in the collection, processing, use and storage of human genetic data, human proteomic data and of the biological samples from which they are derived, referred to hereinafter as "biological samples" (…)" and that its provisions should apply not only to data, but also to samples. It also incorporated a definition of a biological sample as "any sample of biological substance (for example, blood, skin, bone cells or blood plasma) that harbors nucleic acids and contains a person's characteristic genetic endowment" (art. 2.iv).

Finally, it is also important to remember that the OECD adopted in 2009 the Guidelines on Human Biobanks and Genetic Research Databases, to guide on the creation, governance, access and use of "structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same (…)."

In the following pages I will describe the phases through which research with biological samples passes and to expose in each of them the implications for the rights and interests of those involved. In some points, the Spanish model of 2007, inspired by the referenced normative framework and, in turn, consistent with that of the Recommendation CM/Rec (2016)6 on research on biological materials of human origin, will be proposed as a concrete example.

The Collection and Donation Phase of the Sample

Rights Involved in Sampling: Physical Integrity and Disposition of Body Parts

To obtain samples for research purposes you can go to repositories where this material is stored. In this case, the source subject is not involved at this stage. On the contrary, it may occur that samples are obtained from an interaction with the subject, which may be invasive or not, and may have one or more purposes.

According to the UNESCO Declaration, the invasive method involves "intrusion into the human body, such as obtaining a blood sample by using a needle and syringe (art. 2.vii). The term "intrusion" is used to refer to methods involving "intrusion into anatomical structures", not "bodily intrusion" ("penetrating into the body"), since the mouth swab, which is proposed as an example of a non-invasive method, requires penetrating into a body hole, but does not affect any anatomical structure. The invasive method, therefore, is related to a possible risk to the health of the subject. At other times, the term "intervention" is used to cover any procedure that presents a risk, regardless of which particular method is applied. For example, according to the 2015 Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, the term "intervention" includes: "(i) a physical intervention, and (ii) any other intervention insofar as it involves a risk to the psychological health of the person concerned" (art. 2.3).

In any case, the interaction with the subject implies an impairment to its integrity or bodily integrity, whether it involves a risk (for example, a venous puncture or a surgical intervention) or not (it might be requested, for example, simply to cut the hair) or whether it penetrates the body (into the mouth or another orifice) or not (for example, a device is applied to express breast milk). Only with the consent of the subject can this effect on bodily integrity or bodily integrity be legitimized in the framework of biomedical research. Article 3 of the Charter of Fundamental Rights of the European Union ("Right to the integrity of the person"), links the right to

respect for the physical and mental integrity (paragraph 1) with the respect of the free and informed consent of the person concerned in the fields of medicine and biology (paragraph 2).

In addition, in the event that the method used may pose a risk to the health of the subject (in this case, as we saw, the method is called "invasive method" or "intervention"), an evaluation or weighting should be carried out, because there are limits from which the risk is not admissible, even with the consent of the subject – article 6.2 of the Convention on Human Rights and Biomedicine- (Resnik, 2015). In this case it will be important to know if the intervention is carried out for another purpose that justifies it, and if obtaining the sample for research purposes does not increase the risk assumed for that other purpose (which may be an intervention for therapeutic purposes). If research itself could bring a benefit to the subject, his individual interest should be taken into account in the balancing. Any individual benefit (from intervention or research) for the subject would increase the risk of obtaining the sample.

In short, if collection of samples involves an affectation to the bodily integrity, the rules foreseen to carry out investigations "in subjects" should be applied, prior and added to those corresponding to the investigation of samples "of subjects". As a general rule, exposure to minimum risk is admitted (art. 6.2 of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research), defined as that which "is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned. It is deemed that it bears a minimal burden if it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned" (art. 17 of the same Protocol).

As mentioned above, another possibility is that the samples are available because they were obtained for previous projects or because they are stored in clinical, population, epidemiological repositories, The European Commission has been working closely with the Member States and the Commission.

In all cases, since the sample is a part of the human body, the source subject must be given a decision-making power over its use and, consequently, the power to decide on its destiny through an act of disposition that is usually called "donation". In effect, the will of the source subject determines the possibilities of using his biological samples, although there are different models when configuring this rule, such as admitting presumptions or tacit consent (with option of refusal) or require express consent (usually in writing). Thus, the UNESCO International Declaration on Human Genetic Data states that biological samples should not be used for a different purpose which is incompatible with the original consent, unless free prior consent has been obtained, informed and expressly of the person concerned, or that domestic law provides that the proposed use is in the public interest and is compatible with international human rights law (art. 16). In any case, in order for the subject's will to be valid, it must be freely constituted and informed.

Consent is considered free when it is not conditioned by economic or other circumstances. For this reason, both the absence of a consideration and coercion, direct or indirect (such as linking the donation to the continuity of a treatment) should be

required. As stated in the International Declaration on Human Genetic Data, the decision on the donation of samples should not be affected by economic incentives or other personal benefits (art. 8a). The provision 21 of the Council of Europe Biomedical Convention, according to which parts of the human body should not be subject to profit, also affects this limitation.

Consent is considered to be informed when the subject knows the relevant aspects of the use and destination of the sample: what type of investigations will be carried out; what the conditions of its storage and transfer will be; and what effect revocation of consent will have (art. 10, paragraphs 1 and 2 of Recommendation CM/Rec(2016)6 on research on biological materials of human origin).

Among these points, one of the most controversial has been the area of consent, since the terms in which the sample is reported and agreed determine the possibilities of using it. The requirement of specific consent is generalized when dealing with actions on the body of a person, since they affect differently his right to integrity and safety. In these cases, consent must be given knowing each of the procedures to be carried out. Consent should also be specific when samples are to be used using techniques or procedures that may be controversial, which may be relevant when making a donation decision (e.g., cell line generation or animal research and creation of chimeric entities).

However, when it comes to the delimitation of the purpose of the research, the issue is more complex and the options range from its delimitation for a specific research, for a research area to the admission of broader terms, as scientific research in general. This issue does not only affect the right to dispose parts of the body, but also the right to control the information derived from the analyses carried out, and will therefore be addressed later. However, as will be seen, solutions exist to reconcile the right of subjects to decide on their body parts and the right to control personal information, with flexible sample management systems, through a "mediation instance". In fact, Council of Europe Recommendation CM/Rec (2016) 6 on research involving human material excludes from its scope the use of samples in a specific project (art. 2.2) and proposes governance models along the lines outlined above.

Withdrawal of Consent

As it has been said, participation in biomedical research must always be voluntary. Therefore, the will of the source subject regarding the use of samples must be respected beyond the moment of donation, which is revocable. Article 9 of the International Declaration on Human Genetic Data of UNESCO warns that the person may revoke his consent, unless the sample has been anonymized, that is, the link that relates it to the identity of the subject has been eliminated. Likewise, the freedom of the subject to form his will must be guaranteed throughout the period of participation in the investigation and, therefore, the revocation cannot be subject to conditions or cause harm.

The subject should be able to decide on the scope of the revocation, that is, whether it refers to the use of the sample linked to its identity or refers to the use of the sample under any conditions. In the first case, the sample shall be anonymised and in the second case destroyed. The withdrawal unfolds its effects prospectively, but there may be limitations to its effectiveness retroactively since the previous use of the samples does not lose its legitimacy. This may mean, in fact, that the sample is kept for a certain period of time, if there is a legal obligation (for example, in the framework of a clinical trial) (European Medicine Agency, 2016) or that the data are maintained for scientific interest (consider that they should support a scientific publication resulting from research). What cannot be done in such cases, if consent is revoked, is using the sample or data for future investigations.

The Use of Data Resulting from Sample Analysis and Data Associated with Samples

So far, the biological sample was referred to as a part of the body of a person whose procurement and use as such affects different rights of the source subject. But, in addition, the sample is an information medium and, for this reason, the projection of the rules governing the processing of personal data towards the storage and use of samples can be considered. In any case, it is important to stress that samples and data are different entities, whose collection and use affects different rights, although there may be confluences.

Council of Europe Recommendations 1 (1992) on the use of DNA analysis in criminal justice, and 3 (1992) on genetic analysis and screening for health purposes, state both in principle 8, that samples and body tissues are information carriers that must be treated in the same way as automated medical data.

In the European framework, the General Data Protection Regulation (GDPR) does not apply to samples themselves, but to data obtained once they have been analyzed, insofar as they correspond to an identified or identifiable subject. This is reflected, for example, in the rules governing the donation of samples and the treatment of the data obtained in Spain. Consent to the donation of samples legitimizes their storage in biobanks intended for biomedical research in general, but not for the collection of data in such a broad sense. This second operation requires finding other legal bases for its legitimation, since the GDPR requires that consent to the processing of data be granted on more limited terms.

Another interesting issue is whether anonymization of the samples is a realistic operation, if they harbor the complete genetic information of a single individual. In this respect, it should be borne in mind that the possibility of identifying a subject in legal terms is a relative concept that depends on the context, and that it must be assessed taking into account the reasonableness of the effort that such an operation may entail.

It is relevant to emphasize that anonymization of the sample may be relevant for the purposes of rights deriving from its consideration as an information medium, but not for the purposes of the rights relating to the disposition of the body parts mentioned above.

On the other hand, the anonymization of the sample and its subsequent use affects the right to decide on the use of separate parts of the body and prevents participation in the potential individual benefits of the research -the so-called right to return results- such as, for example, the benefits of the possible discovery of a pathological mutation (Thorogood et al., 2019). Finally, in certain areas, anonymization is not only not advisable, but is contrary to legislation which, for reasons of biosecurity or health protection, requires the confidentiality of the identification codes of the source subjects. The paradigmatic case is the use of the material for implantation in humans (Directive EC, 2004).

When the results of samples' analysis are directly or indirectly linked to the source subject, they shall be subject to the appropriate regulation applicable to personal data (in this case particularly sensitive data as they will include genetic, health or ethnic information). This chapter does not include an analysis on the regulation of the use of data for research purposes, but it should be remembered that this regulatory framework is not encapsulated in data protection legislation (in the European case, the GDPR). It also incorporates rights recognized by legislation regulating biomedical research, such as the right to return results (art. 10 of the UNESCO International Declaration on Human Genetic Data). The management of samples for research purposes should provide guarantees to satisfy the rights of the source subject in its entirety. This will be taken up again in the last paragraph.

International Circulation of Samples

The UNESCO Declaration on Human Genetic Data states that researchers should encourage the free circulation of human genetic data and human proteomic data in order to promote the exchange of scientific knowledge (art. 18c). The international circulation of samples favors research into minority diseases, research in developing countries and, in general, cooperation for scientific progress. It adds that:

> States should regulate, in accordance with their domestic law and international agreements, the cross-border flow of human genetic data, human proteomic data and biological samples so as to foster international medical and scientific cooperation and ensure fair access to this data. Such a system should seek to ensure that the receiving party provides adequate protection in accordance with the principles set out in this Declaration (art. 18 a).

Throughout this circuit, the events take place in two different countries, where it is very likely that the rules on the use of samples are different, even in countries of the same environment.

As is well known, the territorial scope of application of the rules corresponds to that of the State or States they emanate from, by virtue of their territorial

sovereignty. In this way, citizens can know what rule is applicable in each territory where they are. In situations of an international nature, the applicable legal system is determined by rules of private international law (domestic or international rules). There is no international regulation regarding applicable normative in relation to the transfer of samples (except for biosecurity issues) (Directive EC, 2004), so it will have to be in accordance with the regulations of each State.

In the case of Spain, it is provided that:

> Biological samples of human origin from other countries may only be used for biomedical research purposes if, in the course of their collection, storage or storage and transfer, at least, in addition to the requirements laid down in the rules on the entry and exit of samples into Spanish territory, the guarantees provided for in this Royal Decree and other applicable rules, which will be evaluated by the Research Ethics Committee evaluating the research project and, where appropriate, by the external committees of the biobank (art. 31 of Royal Decree, 1716/2011).

These "guarantees" consist of measures proportional to the risks to the rights of the subjects and include, in any case, the supervision of an Ethics Committee or equivalent entity in origin and, in addition, others appropriate to the specific circumstances, such as data pseudonymization. Since the Research Ethics Committee evaluating the research project and, where appropriate, the external committees of the biobank shall be responsible for verifying these conditions, require documentation to prove compliance with the guarantees provided for in the RD and other applicable regulations. For this purpose, the application for project evaluation or for the incorporation of samples into a biobank or collection should be accompanied by the following documentation, in a language accessible to ERC members (documentation in English or accompanied by verification of its contents) (Nicolás et al., 2018):

- Sample transfer agreement, which shall, inter alia, reflect the purpose of the shipment and the conditions of storage and use of the samples, as well as the responsibilities of each party. The exporter should remain an "intermediary" between the source and the importer in the event that samples are transferred linked to an individual's identity.
- Opinion of the Ethics Committee or the competent authority which supervised the collection and dispatch of the sample, where it is established that the procedure has followed the provisions of the regulations applicable in its territory and the minimum international standards relating to respect for fundamental rights. In this sense, the necessary "trust" in the institutions of origin would be reinforced if accredited committees were available in all countries.
- Where storage or use has particular implications (indefinite storage periods, broad research purposes, future transfers, specific and unique methodologies), it must be proven that there is no incompatibility with the terms of the consent and with the legal instrument that supports the transfer. Such accreditation may be included in the opinion or authorization or in the agreement.
- Request for an assessment justifying, inter alia, the need to use such samples in particular for the project or their storage, and the potential benefits in the population of origin.

In the case of samples of vulnerable population (minors, prison population, etc.), verification should be more stringent.

In addition, account will have to be taken of the provisions of the regulations on the import and export of international biological material, in particular biosafety aspects.

Deacesed Persons Samples

We can distinguish three scenarios where the use of samples of deceased persons is proposed: first, death of the person who donated the sample for research purposes; second, death of the source subject of a sample stored in a repository that was not donated for research; third, extraction of samples from a corpse.

In the first case, the death does not imply a modification of the terms of the donation and, therefore, the sample may be used according to the will of the donor. The same happens when the subject expressed in life a will relative to the destination of the parts of his body after death, whether the samples were already stored in some repository, or whether it is necessary to remove them from the corpse. There are situations in which corpse samples can be of particular use for research (e.g., brain extraction).

When the subject did not express his will in life, the rule of the presumption of donation is admissible, both as a projection of a general regime that contemplates it, also for live samples, or as a specific criterion for the case of samples of deceased.

According to the first paragraph of Article 14 of Council of Europe Recommendation CM/Rec (2016) 6 on research involving human material, Samples may be taken from the body if there was consent or if there is legal provision for prior information and the option of refusal. In this regard, the explanatory memorandum to this Recommendation recalls that article 8 of the Recommendation indicates that States take measures to facilitate public access to general information on the conditions for obtaining it, storage and use of biological samples for research purposes, including consent and authorisation aspects. However, this information is not widespread, which makes it difficult to count on the deceased knowing this possibility. This point in the Recommendation should be seen as the best option, since it is the one that guarantees respect for the will of people about the purpose of their body parts. However, the explanatory memorandum itself recognizes the difficulty of recording the living subject wishes and accepts as a reasonable option that the person who should authorize the removal be asked if he knows them. Therefore, according to the second paragraph, the limitation for extracting samples from the corpse is that the opposition of the subject is recorded. It is interesting to note that the Recommendation provides for the removal of samples from the corpse (Article 14 reads “Biological materials removed after death”) but there are no specific rules for the use of samples that were already stored when deceased subjects are involved.

National systems follow these criteria with certain nuances. For example, in the Spanish case there is a specific regime, which refers not only to the collection, but

also to the use of biological samples of deceased persons. Both the obtaining and the use may be made in the case that they had so provided in life or when they had not left express record of their opposition. For this purpose, the existence of previous instructions shall be investigated and, in the absence of such instructions, the next of kin of the deceased and the professionals who treated him in the health centre shall be consulted and the consultations carried out shall be recorded (art. 26.1 of Royal Decree, 1716/2011). It is important to note that, in Spanish law, the donor is the deceased person (also when it comes to organ transplantation) and his will is relevant to these effects. Relatives or relatives do not "authorize" the donation.

Another important issue when it comes to the use of samples of deceased persons is that there is no longer a data subject who is to be obtained and who may also be of relevance to others. In Spanish law, Royal Decree 1716/2011, establishes that persons associated with the deceased person for family or similar reasons may contact the persons responsible for the files or for the treatments containing data of the deceased person in order to notify the death, providing sufficient proof of the death same, and request, justifying the concurrence of a relevant interest, the cancellation of data or anonymization of samples. This provision is related to art. 3 of the Organic Law 3/2018, of 5 December, on Data Protection and Guarantee of Digital Rights (hereinafter LOPDyGDD), which includes this possibility, in similar terms (the GDPR expressly provides for the exclusion of deceased data from its scope and the possibility for States to develop their own legislation in this area).

Minors Samples

In general, biomedical research involving minors must be subject to particular conditions which seek to ensure the protection of a particularly vulnerable population. In particular, the use of samples of minors shall be justified if it is necessary for a specific investigation which cannot be carried out with other samples; if the risk of invasive intervention, if necessary, does not exceed the minimum; and the minor's will shall be taken into account, or even if his maturity is sufficient, he himself shall consent; otherwise his legal representatives shall consent. In any case, the child must be involved in decision-making according to his or her maturity and must be adequately informed of what their participation in the present and in the future entails.

One issue discussed in relation to obtaining data and samples from minors for biomedical research purposes is whether or not it is necessary to contact the subject to request a new consent when he reaches the corresponding age or maturity, especially when their use can be prolonged for long periods, even indefinitely (Berkman et al., 2018).

In favor of this requirement it is argued that it represents the only mechanism to guarantee the right of the subject himself to decide on his participation in the investigation with samples or data, which in the case of genomic data is of particular relevance because it is information that may reveal unexpected information and may

involve higher risks of identification of the subject. The consent given by the representatives is given at a specific time and legitimises the decision-making that affects the minor in this respect (Hens et al., 2009). In the storage of genetic data, such a decision, taken at the time, could affect that already adult child in the future, without his knowledge. The person who would be responsible for providing such information would be the owner of the register or file where it is stored, in order to give the source, the possibility to exercise his rights. Such information would require contacting the data subject, without waiting for the data to be used.

On the contrary, it can be said that from the legal point of view the consent given by the legal representatives in place of the minor is still valid when adulthood is reached. In the case in question, the Commission says that samples or data collection does not mean their effective use in an investigation and that, in any event, when they are to be used, an ethics committee must decide in the particular case whether the specific consent of the subject is necessary. In addition, the use of data and samples should always be subject to the limitations of paediatric investigation.

In any case, the date on which the subject reaches adulthood must be taken into account for future contacts (e.g. to report a finding relevant to health, etc.).

The opinion in favor of reconnecting with the minor when he reaches adulthood is being implanted with increasing force and is the one maintained in the Recommendation of the Council of Europe CM/Rec (2016) 6, on research with human material: where a person without the capacity to consent, whose samples are stored for research, reaches the capacity to consent, reasonable efforts must be made to request that person's consent by himself (art. 12.5).

Governance, Policies and Guarantees: Biobanks

Taking into account the importance of the availability of samples and data for scientific research, it is very desirable to articulate procedures that ensure that the subject maintains his faculties in relation to his biological material and information but, at the same time, allow more flexible options than their use for a specific and specific project. Management by an institution designed for this purpose, with a solid structure and adequate operating protocols, is a very operational solution.

These structures, which Council of Europe Recommendation CM/Rec(2016)6 on the Use of Human Biological Samples for Biomedical Research Purposes calls "collections" (Chap. 5), constitute a mediation forum between the source subject and the researchers, which is solid and sustainable.

According to the Recommendation, "collections" must be subject to a governance system that respects the principles set out in Article 16 and developed in the rest of the chapter (Governance principles) and which can be systematized as follows:

– Responsibility. A responsible person or institution should be designated;
– Transparency. Accessible information on purpose, structure and operation and activity;

- Control and accountability. External supervision for its creation and control of its activity; preparation and publication of activity reports and on the use of samples and project results;
- Quality;
- Respect for the rights of the subjects, in particular the will expressed by the donor, the right to revoke consent; the right to information on the investigations in which their sample was used; confidentiality and the right of return of results;
- Promotion of research. The accessibility of samples by the scientific community should be ensured through predetermined and transparent procedures. The international circulation of samples shall be subject to appropriate safeguards and documented in an agreement.
- Sustainability. in anticipation of the management of decommissioning should it occur.

The concrete model adopted in Spain, which has produced very satisfactory results, is described below.

In Spain, a biobank is a public or private, not-for-profit establishment that houses one or more collections of biological samples of human origin for biomedical research purposes, organized as a technical unit with criteria of quality, order and destination. These establishments are conceived as tools that facilitate the availability of samples for research based on a broad consent and reinforced guarantees in the management of samples. Thus, given the public service vocation of the biobanks, donor consent is given in broader terms than for specific projects or collections dedicated to a line of research, and the samples are made available to any researcher who justifies the interest of his project, approved by a Research Ethics Committee, and who ensures the legitimate use of the samples. These transfers from the biobank do not require specific consent of the donor, who was informed of this management system.

Biobanks' Structure

This flexibility in the transfer and use of samples is developed in a complex structure that operates as a guarantee of the rights of donors and their sustainability: the biobank must be authorized by the relevant administrative authority, be entered in a public register, have an owner (responsible for its operation), a scientific director, a data file manager (which will deal with requests for the exercise of the rights of access to personal data, rectification, cancellation or opposition formulated by the subjects) and with two external committees: one scientific (external scientific committee of the biobank, CCEB) and another ethical (External Ethics Committee of the Biobank, CEEB). These committees shall be composed of persons with sufficient knowledge of the matters related to the functions performed and shall have internal rules of operation, that they shall establish appropriate mechanisms to ensure independence and the absence of conflicts of interest in the decision-making process.

Procedures and Guarantees of the Rights of Subjects

The transfer of samples from a biobank requires a request from the person responsible for the investigation, stating the project to be developed, the favorable opinion of the ERC in relation to it, and the signing of a contract for the transfer of samples, commitments on their use. The transfer agreement shall be formalised in writing in a document signed by the person responsible for the research on the one hand, and the biobank on the other.

Applications must be examined by the External Committees of the Biobank, which will issue the corresponding reports. These reports are mandatory for approval or refusal of application, and binding if negative. The decision on the transfer is made by the holder of the scientific direction of the biobank, who must give reasons if it is rejected.

To carry out its evaluation, the CEEB must verify compliance with the following ethical and legal requirements:

A. The biobank may transfer the samples to the person responsible for an investigation provided that the source subject consents to the transfer. Procedures should be developed to ensure that the terms of such consent coincide with the terms of the assignment. These procedures could involve either a review by the CEEB or another body of the Biobank, or the creation of registers of restrictions on consent or research lines for samples, or other procedures that allow this finding.
B. Samples shall only be made available for applications from scientifically approved research projects. The CEEB should not re-evaluate the project if it has already been approved by the ERC of the research centre. However, it must assess the ethical and legal requirements in order to be able to approve the transfer of the samples and their use in the specific project approved by the CEI and for this purpose the report of the same must be one of the documents provided to the CEEB that assesses the transfer.
C. It shall be verified that there is no disproportion between the project objectives and the number of samples requested. In this sense, the Biobank must establish mechanisms to verify this, one of which could be its review by the CEEB, in all or in some particular cases.
D. Respect for the right to data protection is guaranteed. Samples and associated data should only be released after anonymisation or dissociation, and the request shall indicate the specific measures to be applied to ensure confidentiality and security in the handling of data.
E. The subjects' rights on their data are guaranteed: access to data, return (or not) of results, where appropriate, availability of genetic counseling. This guarantee will be verified by checking that the researcher knows and assumes the obligations foreseen in the biobank's policies in this regard, and that this is reflected in the Master Agreement for Transfer of Material (MTA).

F. If the request comes from abroad, two specific aspects must be taken into account: on the one hand, biosecurity conditions, which must be observed in the transfer and, on the other, those that must be met to ensure respect for the rights of donors.

With regard to the rights of donors, if the samples leave a biobank, the CEEB should review that in the MTA the recipient undertakes to respect the provisions of the biobank sample management system of origin.

Although the essence of the Biobank is to manage donated samples with broad consents that are available to the scientific community, it should be possible to contact the subject before a transfer in certain cases. The meaning of this obligation is to give the subject the opportunity to revoke the consent partially for that purpose.

The following criteria can be taken into account, among others, when making the decision:

– The donor did not consent by himself (minor, incapacitated, exceptional regime).
– The donor was not informed of relevant aspects (for example that complete genome sequencing will be carried out).
– The purpose of the research is unique (e.g. studies providing for the use of human samples together with those of animal origin).
– There is an appreciable and unforeseen risk (e.g. for non-discrimination, loss of confidentiality, risk of identifiability, genetic data will be made available to the scientific community in databases or to be used in third countries).
– Data that may reveal personal information of identified family members who did not consent will be obtained.

Conclusions

The establishment of institutions (biobanks) to facilitate the availability of biological samples for scientific research with guarantees for the rights of source subjects is an initiative that is yielding very satisfactory results. Biobanks have been developed as institutions to coordinate basic studies with clinicians by encouraging the emergence of cooperative models, and have been implemented in many countries with different models adapted to different contexts.

Biobanks should put in place procedures to ensure donor rights with flexibility and agility. The dynamic and active involvement of ethics committees in the whole activity of biobanks is at the core of these institutions.

These structures must be sustainable, have an adequate internal organisation and promote transparency and confidence in their functioning. For this purpose, it is essential to publicize its operating system and generate a public register of biobanks.

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Chapter 17
Biobanks for Biomedical Research: Evolution and Future

Juan Alberto Lecaros

Abstract For more than two decades, in the era of post-genomics and personalized precision medicine, biobanks for biomedical research have successfully fostered the development of basic and translational biomedical research. The expansion of biobanking has brought a wide and intense debate on ethical, legal and social implications (ELSI) when using large numbers of human biological samples and associated personal data. All these challenges are relatyed to the fact that these infrastructures allow several future research projects to be carried out along general lines of research, with the use of samples and sensitive information, such as genetic data, which can be shared internationally, and whose specific purpose the donor cannot know at the time of donation. In this chapter, I will address the challenges that have emerged at the different stages of the evolution of biobanks, from biobanks' governance stage to the sustainability stage, through the harmonization and collaboration networks stage, in order to address the challenges biobanks will deal with in the near future.

Keywords Biobanks · Governance · Sustainability · Ethics · Law

Introduction

Biobanks for biomedical research have been successfully promoting the development of basic and translational biomedical research for more than two decades, in the era of post-genomics and personalized precision medicine (Coppola et al., 2019). In 2009, *Time* magazine included biobanks among the "10 ideas that are changing the world right now". The International Agency for Research on Cancer noted in 2017 that biobanks are on the base of three rapidly expanding fields of

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biomedical science: "(i) molecular and genetic epidemiology (aimed at assessing the genetic and environmental basis of cancer causation in the general population as well as in families), (ii) molecular pathology (aimed at developing molecular-based classification and diagnostic procedures for cancers) and (iii) pharmacogenomics/pharmacoproteomics (aimed at understanding the correlation between an individual patient's genotype or phenotype and response to drug treatment) (Mendy et al., 2017).

However, the expansion of biobanking has also brought with an extensive and intense debate about Ethical, Legal and Social Implications (ELSI) of the use of large numbers of human biological samples and associated personal data, including genetic data, for people who have donated them, as well as for the community and society in general (Chadwick & Cutter, 2007).

In this chapter, I will review the change in biomedical research, from ethical and regulatory perspectives, which resulted from the use of biobanks as platforms for future use of biological samples and associated data for research purposes, available to be requested by any researchers in different research projects. We will analyze this process through three stages of the evolution of biobanks. First stage, which includes the ethical challenges to systematically manage the future use of samples in relation to informed consent for biobanking, the right to withdraw consent, secondary use of biological data and samples, privacy and confidentiality, international sample and data sharing, communication of results and disclosure of incidental findings. Second stage, corresponding to the challenges of regulatory harmonization and the creation of national and international biobank networks as a result of the necessity to share large quantities of quality samples to promote the development of research, by improving access and sustainability. Third stage, addressing the sustainability challenge of biobanks, particularities as compared to other biomedical research infrastructure and the dimensions in which this challenge has to be analyzed for a comprehensive understanding.

Concept and Classification of Biobanks

Since it appeared in scientific journals in the mid-1990s, the term "biobank" has had various definitions in reports, policies and guidelines from national and international organizations without coming to a clear and final consensus (Hewitt & Watson, 2013). However, over time, a broad definition based on three elements has begun to be accepted: (i) they are collections of human biological samples and associated personal data, (ii) organized with technical, ethical and regulatory standards, (iii) that can be used by any researchers in different future research (Vähäkangas et al., 2021). The Organization for Economic Cooperation and Development (OECD) (2010) defined a biobank in a broad sense, using the term "human biobanks and genetic research databases," understood as "structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same; and (b) extensive associated information". Nevertheless, this definition does not refer to one of

the essential characteristics of biobanks, access to the sample by third parties and the way they are managed.

The European Commission, to provide further clarification on the scope of the term, in its *Biobanks for Europe Report. A Challenge for Governance* (2012), defines them as "collect biological samples and associated data for medical-scientific research and diagnostic purposes, and organize these in a systematic way for use by others". The report highlights this last aspect, since what distinguishes biobanks from a collection of samples is the existence of "governance mechanisms in place to allow access to the resource in a systematic way to outsiders." In this sense, the Commission decided to define biobanks based on a set of characteristics that describe their activity through governance that guarantees the rights of donors, transparency and public trust. The report highlights the following aspects: "(a) collect and store biological materials that are registered not only with medical, but often also epidemiological data (eg environmental exposures, lifestyle/occupational information); (b) are not static "projects", since biological materials and data are usually collected on a continuous or long-term basis; (c) are associated with current (defined) and/or future (not yet specified) research projects at the time of biospecimen collection; (d) apply coding or anonymization to assure donor privacy but have, under specific conditions, provisions that participants remain re-identifiable in order to provide clinically relevant information back to the donor; and (e) include established governance structures (e. g. ethics review committees) and procedures (e. g. consent) that serve to protect donors' rights and stakeholder interests" (European Commission, 2012, p. 13).

Biobanks may be classified according to their type, size, purposes, forms of access, controllers, among others. The wide heterogeneity of biobanks has raised, beyond a definition, "the need for a universally-accepted, systematic classification of the different biobank types" (Hewitt & Watson, 2013). One of the most common criteria for classification is size: population-based biobanks versus disease-oriented biobanks. The former are large-scale biobanks that store samples from a general population with the aim of studying the role of individual genetic susceptibility and exposure to external factors in the development of specific diseases by linking molecular data with other associated information; the latter stores biological samples from different sources, generally obtained from patients, which are important for the study of a disease, for example, cancer (Coppola et al., 2019). If the former enable the study of biomarkers of susceptibility and predisposition, and the latter permits the biomarkers of disease, there is a third category, epidemiological biobanks, which allow large-scale cohort studies to search for biomarkers of exposure and biological effects (Harris et al., 2012).

Another traditional approach of classifying biobanks has been according to the type of research carried out with biological samples: (a) population studies, (b) basic research; (c) associated with clinical trials; (d) translational studies; and (e) pathology archives. These latest collections, from diagnostic residual samples, as results of the large amounts of samples stored and the medical data associated with them, have become very attractive for biobanking. But also the secondary use of these samples for research purposes give rise to ethical challenges, since they are

used for a different purpose for which they were obtained and without prior explicit consent for that new purpose.

Since the traditional classification of biobanks are not precise enough to properly delimit the different categories of biobanks (Malsagova et al., 2020), it has been proposed to use functional criteria that allow better systematization and categorization of them, namely, depending on: the type of donor/participant, the collection methods and design (e.g. retrospective or prospective collection, size and scope), the characteristics of the biological samples (e.g. form of preservation of the biological sample, fixed, frozen, fresh, live, and desiccated), and the brand of the biobank based on the leadership of those leading it and the sponsors who support it as well as the intended users (e.g. individuals, often expert researchers and groups, and institutions) (Watson & Barnes, 2011).

This latter criterion is connected to one of the central issues in the ethical discussion about the operation of biobanks, whether they should be considered public goods, whether they are hosted or sponsored by public or private institutions (universities, research centers, hospitals, governments, international consortia). Biobanks as public goods is determined by their vocation to make samples available to the scientific community for all those projects that comply with the scientific and ethical conditions previously established by the biobank, following principles of transparency and public trust that, among other principles, are those that found the governance of biobanks in front of the participants and the community (Gille et al., 2020). Private initiatives of biobanks for commercial purposes, on the other hand, are not aligned with this logic of public good that is claimed for biobanks, and for this reason they have generated a profound ethical debate (Caulfield et al., 2014). An emblematic case of a private biobank is that of the company *23andMe*, whose business model is the sale of samples obtained from the services they provide through direct-to-consumer genetic tests (Caenazzo & Tozzo, 2020; Vähäkangas et al., 2021). Although one of the most sensitive issues in the ethical debate is the distrust in the public perception regarding the commercialization of samples by private biobanks, the increasing difficulty of funding and sustainability of public biobanks leads to the search for public/private alliances (Somiari & Somiari, 2015). Therefore, strategies are proposed to reduce public distrust, clarify the real perceptions of people, propose independent governance (Nicol et al., 2016) and "promote dialogue, both technical-scientific and ethical, essential between the public sector, the private sector and citizens to truly maximize transparency and public trust in both contexts" (Caenazzo & Tozzo, 2020).

Finally, we should refer to another category of biobanks that is becoming more and more significant due to the increase in data from whole genome sequencing (GWS) techniques. They are the so-called virtual biobanks, which are electronic repositories with the information on biological samples and their associated data, independent of the place where the physical biological samples are stored, information that can be shared in networks of national and international biobanks (De Souza & Greenspan, 2013; van Draanen et al., 2017). Because of the increased use of big data for research purposes, some scholars propose that biobanks should move from a sample-centric strategy to a data-centric strategy (Quinlan et al., 2015). To the

virtual biobanks, another recent category should be added, imaging biobanks that store data, metadata and image biomarkers, extracted from computerized tomography, magnetic resonance imaging, and positron emission tomography. This type of biobank allows radiomics, a field of medicine that consists of extracting a large number of features from medical images, using data characterization algorithms, one of whose relevant developments are "image biomarkers (a new class of biomarkers non-invasive) for physiological evaluation or pathological processes and therapeutic treatment" (Malsagova et al., 2020).

Each biobank categories have ELSI challenges, which we will examine throughout the different stage of biobank evolution, from the governance challenge stage to challenges for sustainable biobanking, passing through the stage of harmonization and collaboration networks. The ELSI aspects of biobanking comprises four broad topics: (1) Topics related to how biological materials are incorporated into the biobank and their use: samples donated directly to the biobank for research purposes or residual samples from clinical care for future use in research, as well as issues related to the informed consent of the donor (types of consent, information provided, right of withdrawal, participation of minors and use of samples of deceased persons, opt-in or opt-out policies, etc.). (2) Issues related to biobanks as institutions, such as authorization, registration, governance principles, management and quality standards, etc. (3) Issues related to the conditions of access by researchers to the samples and associated data of the biobank, which implies, for example, impartiality in access, commitments and responsibilities assumed in the material transfer agreement; and issues related to the ownership of biological materials and intellectual property derived from such materials, including custody issues, conflicts of interest, review committee, and regulation of intellectual property over human biological material. (4) Finally, issues related to the information collected and stored, as well as the rights of the donor to know the results of the research, access their data and be informed of the results relevant to their health (including an incidental findings policy), disclosure of results, confidentiality, data security measures and data protection –anonymization, pseudoanonymization, risks of re-identification, discrimination and stigmatization (Solbakk et al., 2004; Vähäkangas et al., 2021; Nicholas, 2022).

First Stage of Biobanks' Evolution: Governance's Challenges

The evolution of biobanks has been characterized by a constant challenge to traditional ethical principles and criteria of scientific research with human beings and their regulation. ELSI challenges of biobanks are related to the fact that these infrastructures enable the realization of multiple future research projects and in wide-ranging lines of research, with the use of samples and especially sensitive information, such as genetic data, which can be shared internationally, and whose specific purpose may not be known to the donor at the time of donation. The challenge is, then, to balance the enormous social value that biological material and

associated information has for research and the benefits for human health on a large scale, enhancing the quality of science and international collaboration, with the risks each individual donor in the samples is exposed to (Bledsoe, 2017).

This challenge is not an easy task, at least for two reasons making management and governance of biobanks provoke so much ethical and legal concern in the last two decades. First, they are infrastructure aimed at the future use of samples, stored indefinitely, which significantly increases the donor's loss of control. Second, with the digitalization of biological data, biobanks become custodians and responsible for large volumes of future genetic data, whose relevance, risk and impact are very difficult to predict if we consider the growing increase in interoperability between different databases worldwide (Vähäkangas et al., 2021; Akyüz et al., 2021). Under these circumstances, being able to guarantee and protect the basic ethical and legal principle in relation to research with human beings becomes much more complex and difficult, compared to the ethical review of research by specific projects: the interests of the individual (the so-called principle of moral primacy of the human being) –its autonomy, integrity, privacy, etc.– should prevail over the interests of science, (Różyńska, 2021).

If biobanking escapes the traditional logic of biomedical research governance –"one researcher, one project, one jurisdiction" (Kaye, 2011), which is subject to the prior supervision of an ethics committee that evaluates the requirements ethics to be met a priori by a specific project, as detailed in the protocol and informed consent–, the question arising is how the governance of biomedical research is reconfigured when the rights of the participants must be protected against future projects, not yet specified or determined, in relation to the use of biological samples and associated personal data, as well as their destination and the results that will be obtained from them. It is these new conditions of biomedical research with biobanks that have made us rethink the rights of the participating subjects and adapt them for the prospective use of their data and biological material. This includes right to participate in science and access to its benefits, right to consent, right to withdraw, rights of informational self-determination, privacy and confidentiality, and the right to know and not to know about genetic information, right to genetic non-discrimination and non-stigmatization, and even intellectual property rights.

The first stage of evolution of biobanks was oriented to take care of these moral and legal interests and the need for a new governance for biomedical research, and how to provide it with an ethical justification and an adequate regulatory framework. The foregoing included, mainly, an intense discussion on the modality of informed consent for biobanks, along with other topics such as the secondary use of samples and associated data, the effects to withdrawal of consent, privacy and confidentiality of data, the access to the results of the research and the return of the "incidental findings", the international data and samples sharing, as well as the ownership of the biological material.

Of all the topics, without a doubt the most discussed has been informed consent, because the traditional standard, namely the specific consent given for a specific project with a specific researcher, limits the practical possibility of authorizing the future use of samples in projects not yet specified with access for all those

researchers who request them. But, on the other hand, the ethical question arises to an open consent to indeterminate future uses that ends up blurring an essential element for free and voluntary participation: specific and adequate information about the objectives, scope, benefits and risks of the research in which the subject participates.

Informed Consent for Biobanking: Broad and Dynamic Consent

During the first decade of the 2000s, an intense debate began among experts in bioethics and regulation in biomedicine about the legitimacy of using broad consent instead of specific consent in biobank practice, with clear positions for (Hansson, 2005; Cambon Thomsen et al., 2007; Haga & Beskow, 2008; Helgesson, 2012) and against (Árnason, 2004; Caulfield, 2007; Greely, 2007; Caulfield & Kaye, 2009). Those who argued against claimed that broad consent is not valid consent because it does not allow informed autonomy to be exercised, since neither the objectives nor the risks of the research are specified. Those who argued in favor said that in order to justify research, the principle of autonomy of the participating subjects is not enough, it is necessary to appeal to other ethical principles. Both arguments answered the question of how to balance the public interest represented by the use of human biological material with the rights of donors.

In a very influential article in this debate, Hansson et al. (2006) argued that "broad consent and consent to future research studies are valid ethically and should be recommended for biobank research" as long as the following conditions are met: "personal information related to the research is handled safely, that donors of biological samples are granted the right to withdraw consent, and that every new study is approved by the ethics-review board" (p. 266). This last condition is important to reject the argument that broad consent is equivalent to blanket consent or open consent. If each investigation that uses samples from a biobank must go through the review of an ethics committee, then it is granted that it is not a blanket consent, that is, a consent that the donor grants only once authorizing future use and open of your samples and data without any supervision. Nor would broad consent consist of an open-ended permission without any limitation, nor would it be an open consent in which the donor authorizes their data to be made available to the world scientific community, anonymized or not (as in the initiatives HapMap, 1000 Genomes, and Personal Genome Project) (Rothstein et al., 2016). In addition, those who have argued in favor of broad consent add that biobanks operate under the logic of public good, following principles of equity and solidarity, therefore, in this context, the ethical framework of scientific research cannot be reduced to the individualistic view based on the principle of autonomy as argued by those who oppose broad consent (Knoppers, 2005; Chadwick & Berg, 2001).

In summary, the arguments to justify broad consent were based on three reasons: (i) practical reasons, since it would be impracticable to re-consent thousands of donors each time their samples are used in a specific research; (ii) biobanks are

intermediary tools at the service of the scientific community and the good of society that function as a public good, with open access to third parties to the samples they store; (iii) biobanks allow non-interventional studies of minimal risk. However, these same reasons have been criticized by those who questioning broad consent, considering its fragility to operate as a definitive ethical justification (Caulfield & Kaye, 2009).

After years of debate, the regulatory bodies and international guides were accepting the legitimacy of a broad consent that would allow a system of access and use of samples by any researcher, as long as this system is maintained under organizational measures that granted the rights of donors. In this sense it can be called a consent for the governance of the biobank. This was the policy that followed Council of Europe, in its Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin, that considered a good practice to request broad consent when collecting material whose future use is not specified, but it should not be so broad that it becomes an "unconditional, blanket consent", for the same reason it suggests being as explicit as possible regarding future uses (Explanatory Memorandum 48). In the United States, the discussion and adoption of broad consent by experts and the regulator took longer. Scholars in 2015 reached a consensus that broad consent is ethically acceptable as long as it has ethical oversight from a committee for future projects that will use the samples and, where possible, mechanisms for maintaining contact and sharing communication with donors (Grady et al., 2015). Finally, Congress modified the Common Rule in 2018 incorporating an express rule on broad consent and the basic elements it must contain (45 CFR 46.116(d)).

The need to maintain contact with the donor, as a condition that legitimizes the consent for future use of the samples and associated data, justifies another form of consent that has been proposed for biobanks: dynamic consent. This form of consent uses digital tools to facilitate two-way communication between the participant and researchers, placing the participant at the center of decision-making. Those who promote this type of consent consider that this interface has an advantage over the broad consent model because: (i) allows participant to be consulted each time their samples and data are used; (ii) facilitates giving and withdrawal consent when circumstances change; (iii) provides a single record of the transactions and interactions that are maintained; (iv) allows participant to give different types of consent or ask for their opinion as new research projects are initiated or new ethical issues arise; (v) and, finally, the decisions made in the initial consent can be modified over time through this interface (Kaye et al., 2015; Budin-Ljøsne et al., 2017).

However, before the idea of this form of consent became widespread, empirical evidence showed that people preferred a single initial consent instead of expressing their will in successive instances (Lipworth et al., 2011). In another study, which compares broad consent with dynamic consent, the latter is criticized for the overload that implies in time, both for the participants and for the researchers, granting a new consent for each project, as well as criticizing due to the negative effect that it could have on participation by repeatedly exposing people in each consent to the complexities of research and the need for them to have an opinion and make a

decision about it (Steinsbekk et al., 2013). Dynamic consent has also been criticized because it can jeopardize the logic of public, collective and long-term good of biobanks, to the extent that the individual decisions of each participant for each project, by replacing the decision criteria of the committees of the biobank, could weaken its governance, which could be a risk, in turn, for the participants themselves. In addition, there is a risk that the research policy of a biobank is replaced by the sum of informed consents that were only given for a particular project; and, finally, if the dynamic consents include granting a broad consent within their options, it is contradictory, because precisely the latter was the ethical problem to be avoided (Soulier, 2019).

Secondary Use of Data and Biological Samples

There has also been discussion in the literature about what are the appropriate mechanisms to incorporate residual tissue collections obtained primarily for clinical care purposes into biobanks. These collections are of interest to biobanks because to the large number of samples they accumulate and the associated health data. The focus of the discussion has been on evaluating which is the most appropriate method to consent to the entry of residual samples into the biobank: opting-out (procedure under which the non-expression of will is treated as a sign of consent) or opting-out. in (procedure under which a person explicitly expresses his consent). While the consensus is that the opt-in method is preferable for research participation, both methods should be evaluated based on the kind of tissue and research in which they are to be used. Thus, it has been suggested that in certain situations the opt-in method is necessary: "(1) research with higher risks or increased burdens, (2) the use of controversial or high-impact techniques, (3) research on sensitive tissue, and (4) research involving vulnerable patients" (Giesbertz et al., 2012). These same authors have argued that the opt-out method is justifiable if it is used under certain conditions that give more guarantees to the potential donor, in which case the dichotomy between the two methods is less strong. The conditions they propose to be able to implement an opt-out system are: "(1) awareness has to be raised, (2) sufficient information has to be provided, and (3) a genuine possibility to object has to be offered" (Giesbertz et al., 2012). This system was adopted in the latest CIOMS Guidelines version of 2016 in guideline 11 collection, storage and use of biological materials and related data, which operates with the same conditions and restrictions indicated above for the opt-out.

The Right to Withdraw Consent

Other interest of the research participants whose exercise must be adapted to the biobank is the withdrawal of consent. The biobank should balance the conservation interest of its collections with the participant's right to withdraw their authorization to use their samples and associated data at any time. In fact, the nature of the operation of the biobank makes the exercise of the right of withdrawal different from what is done in traditional biomedical research, because, of course, the withdrawal can only be applied to future research, not to those in which they are being used samples and data or those that have already been used. When the data are entered to other data sets cannot be deleted, nor the withdrawal be extended to the data that is the result of research carried out. For the same reason, the way in which this option is communicated to the donor and how he can exercise it is relevant. One communication strategy is to signal to the donor their option to request the destruction or anonymization of the sample and associated data. In case of anonymization, the samples may be used without the possibility of linking them to the identity of the donor, to the extent that the code that could identify them has been eliminated. Another strategy is the staggered one, different from the previous "all or nothing" (Melham et al., 2014), which offers more options to the participant, and which has been the strategy adopted by the UK Biobank: (i) "no more contact" with the participant, but that their samples and associated data, and information from their clinical record, can continue to be used; (ii) "no further access" to the information in the clinical record, nor the possibility of contacting the participant, but authorizing the use of samples and data that were previously donated; (iii) "no more use" of the previously obtained samples and data, along with no contact or obtaining more information from the participant, therefore, the samples are destroyed and only the participant's information necessary for auditing is kept. Undoubtedly, a dynamic and continuous consent over time can facilitate the exercise of the right to withdrawal in a staggered manner.

Privacy and Confidentiality

The risks associated with the privacy of the subjects participating in a biobank, with the confidentiality and protection of their personal data associated with the samples, are one of the most sensitive and discussed ethical issues within the governance of a biobank, especially when the risk is associated with genetic data. The potential risk of malicious or improper use of personal data or the eventual risk of re-identification of the owner arises a set of obligations both for the data controller or data processor in the biobank and for the researchers who request them (Akyüz et al., 2021). The challenge for biobanks, when defining personal data protection duties, should be able to balance the collection and exchange of data and samples on a large scale with the way sensitive information is obtained and safeguarded, such

as genetic data and health data, respect the consent of the owner and his legal rights to data protection and non-genetic discrimination (Rothstein et al., 2016).

Although the irreversible anonymization of samples and data can be considered the safest way to protect privacy, this mechanism seriously limits the usefulness of biobanks. Because the research carried out with the samples will not be able to link a person's genetic and biological data with their health and epidemiological information associated with their samples, and thus be able to contact them again to update that information, request new consent or provide clinically relevant information. Therefore, irreversible anonymization does not guarantee the rights of the participants –to the return of results and relevant information, and to the withdrawal of consent, since it makes it impracticable– nor does it allow the operating logic of research with biobanks. (Eriksson & Helgesson, 2005). For these reasons, some legislations (e.g. Brazil and Mexico) does not allow the total de-identification of the samples, unless expressly authorized (Rothstein et al., 2016). So the way to properly guarantee the rights of the donor is to pseudo-anonymize their identified or identifiable data.

The terms to refer to the degrees of identification of personal data and the rules for their protection, their secondary use and international exchange, have been very varied among the different jurisdictions. This situation, in addition to confusion there are those who think that it has affected the international collaboration between biobanks (Knoppers et al., 2007). Hence the relevance of international standards to promote regulatory harmonization.

An example of international standards is the UNESCO International Declaration on Human Genetic Data (2003), which recognizes that human biological samples, to the extent that they are a data medium (genetic and proteomic) that can identify a person, must be treated under the same principles of personal data protection, for which it distinguishes the following categories: (i) data linked to an identifiable person (contain information, such as name, birth date and address, by which the person from whom the data were derived can be identified), (ii) data unlinked to an identifiable person (are not linked to an identifiable person, through the replacement of, or separation from, all identifying information about that person by use of a code) and (iii) data irretrievably unlinked to an identifiable person (cannot be linked to an identifiable person, through destruction of the link to any identifying information about the person who provided the sample), which cease to be personal data, unlike the first two that, according to the Declaration, "should be dealt with in accordance with the wishes of the person", that is, respecting their right to informational self-determination.

Another example is the Recommendation CM/ Rec(2016)6 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin that distinguishes data associated and dissociated from an identifiable person from irreversibly dissociated data, using the terms "identifiable biological materials" and "non-identifiable biological materials", respectively (article 3). Identifiable biological materials "are those biological materials which, alone or in combination with data, allow the identification of the persons from whom the materials have been removed, either directly or through the use of code(s)"; and in the latter case, that of

coding –or also called pseudonymization–, the Recommendation distinguishes between two situations: if the user of the biological materials may have direct access to the code(s) (coded sample) or if the code(s) may be under the control of a third party (reversibly anonymized samples). In contrast, non-identifiable or irreversibly dissociated samples "are those biological materials which, alone or in combination with data, do not allow, with reasonable efforts, the identification of the persons from whom the materials have been removed". In the latter situation, the reasonableness criterion means that "if the identification is not foreseen or expected in any case, and the appropriate technical measures (for example, encryption, irreversible random verification, etc.) have been adopted to prevent that happens, the information processed by the original data controller cannot be considered to refer to identified or identifiable natural persons" (Nicholas, 2022).

International Data Sharing

The protection of the privacy and confidentiality of the data associated with biological samples that are shared internationally has been one of the aspects of continuous ethical observation by international guidelines and by the regulation of the different jurisdictions. It is essential for biobanking to be able to enhance their stored biological resources through governance policies that ensure the international exchange of samples and associated data with adequate levels of security and data protection. However, the regulatory dispersion that exists in this issue and the lack of legal harmonization constitute one of the main difficulties that the international community of researchers faces (Rothstein et al., 2016).

The international recommendations of different organizations related to genomic research have tried to reduce this lack of harmonization with guidelines that support regulatory policies in this area. Along these lines, for example, the P3G-IPAC organization for international genomic research suggests introducing clauses in the informed consent in relation to international data sharing like that: "Data will be made available to other researchers around the world and used in unspecified future biomedical research in universities, hospitals, non-profit groups, companies, and government laboratories after approval. All researchers will have to respect the laws and ethical guidelines that apply to biomedical research" (Thorogood & Zawati, 2015). In addition, it suggests specifying in the consent the guarantees of privacy and access governance.

Another international organization that has promoted the culture of sharing genomic data is the Global Alliance for Genomic and Health (GA4GH), whose "Framework for Responsible Sharing of Genomic and Health-Related Data" requires researchers to provide transparent information on "data transfer to third parties; international transfer of data; terms of access; duration of data storage; identifiability of individuals and data and limits to anonymity or confidentiality of data; communication of results to individuals and/or groups; oversight of downstream uses of data; commercial involvement; proprietary claims; and processes of

withdrawal from data sharing" (https://www.ga4gh.org/). The logic of this framework is that privacy requirements are proportional to the types of data (identifiable, encrypted or anonymized) and the use that will be given, without prejudice to the fact that other kinds of risks and benefits are also considered for participants, researchers and society in general. In addition, given the impossibility of guaranteeing the absolute anonymity of data –especially, genomic data–, it is necessary for reasonable governance of international data exchange "a commitment by researchers to forgo any attempt to re-identify not expressly authorized by law" (Thorogood & Zawati, 2015). These same authors add that "addressing re-identification risk requires ongoing risk assessment, adaptive privacy safeguards, and more concerted oversight of access".

Communication of Results and Disclosure of Incidental Findings

Donor subjects have a right to information related to the biological samples and associated data. Within these information rights, the most sensitive to manage, as the literature has highlighted for some time (Clayton, 2008; Wolf et al., 2012; Clayton et al., 2013; Black et al., 2013; Appelbaum et al., 2014; Zawati & Knoppers, 2012) is that of the incidental findings that are found from the analyzes that are carried out on the samples, especially when techniques such as whole genome sequencing and whole exome sequencing are used, which allow obtaining information that goes beyond the primary objectives of the investigation. This right must be distinguished from other rights to information, namely, the right to know the general results of the research in which their samples are used, which is justified by the right to science and to enjoy the benefits of scientific progress and its applications, and the right of access to personal data, the latter emanates from their right to informational self-determination.

Donors are entitled to health information obtained from the analysis of samples consisting of the following aspects: (i) they refer to health data in a broad sense, including those that are relevant for taking reproductive decisions, (ii) the subject can choose whether or not to receive this information (right not to know), and (iii) the information may also be relevant to third parties. The foregoing leads to ethical and legal problems: first, the subject must receive information in the consent process that allows them to adequately exercise these rights; second, to eventually be able to rely on genetic counseling to communicate this health information; third, the need to communicate the information when it is relevant to health and determine who should communicate it; fourth, to determine the relevance of the information according to some criteria, such as the severity of the disease that is predicted with the information, if there is a possibility of intervention, and its analytical validity and clinical relevance.

One of the ethical problems that the literature addresses regarding incidental findings is the risk that the research purpose of biobanks will be confused by the participants with therapeutic or clinical purposes, which in the research ethics literature is has called therapeutic misconception. Another confusion that arise in the practice of managing these issues in biobanks is between the general return of research results and the delivery of individual results. For this reason, the literature recommends that there be clear definitions in this regard in biobank policies and well-established criteria for the return of incidental findings (Zawati & Knoppers, 2012). An example of governance policy in this area is the UK Biobank, which in its protocol establishes that "there may be occasions when staff consider there to be a professional or ethical obligation to draw attention to abnormal measurements (such as elevated blood pressure) or incidental findings (such as possible melanoma). In such circumstances, participants will be encouraged to contact a relevant health professional". In addition, it provides that participants will be given the results of reference laboratory tests prior to storage of a sample when this may indicate a serious disease for which intervention is possible. However, its policy states that no information, whether genetic or not, will be provided as a result of the analyses that are carried out after the registration of the subject in the biobank (Johnston & Kaye, 2014).

In comparative law, the criteria are not entirely clear and uniform regarding this communication obligation. Black et al., in a study addressing 23 laws, policies and guidelines of international, regional and national organizations that provide guidance or identify the need to disseminate the incidental findings to research participants, found little reference to how biobanks and researchers should bear the costs and funding of communicating incidental results. They therefore call on the research community and policy makers to reflect on the financial implications of ethical imposition of communicating incidental findings. International recommendations can help to promote better harmonization of the criteria for reporting incidental findings in biobank policies.

In the latest version of the CIOMS/WHO Guidelines (2016) a new recommendation is included in Guideline 11 collection, storage and use of biological materials and related data, which specifically proposes criteria for the return of results and disclosure of (un)solicited findings, which is a way of delimiting the ethical obligation and its costs, noting that: "In general, the three guiding principles for return of results need to be followed: results must have analytical validity, clinical significance and actionability to qualify for being returned. This implies that life-saving information and data of immediate clinical utility involving a significant health problem must be offered for disclosure, whereas information of uncertain scientific validity or clinical significance would not qualify for communication to the participant. The research ethics committee should also evaluate whether individual counseling is necessary when returning particular genetic findings. Some cases may require making an ethically responsible management plan for returning (un)solicited fndings".

However, this is still a widely debated topic in the different jurisdictions and biobank policies (De Clercq et al., 2017). It has been argued that, if the policy for

returning results in biobanks is not addressed clearly and specifically, establishing when, how and what type of results must be returned, the trust of donors may be compromised and thus affect the sustainability of biobanks (Cadigan et al., 2017). Although the debate about policies for returning results and, in particular, incidental findings, continues to evolve, there is at least consensus on the ethical obligation to return results that are clinically relevant and to promote better international harmonization and clear and specific policies for each biobank that guarantee transparency and trust in the community.

Second Stage of Evolution: Harmonization and Collaborative Networks

Biobanks are collaboration platforms that enhance and optimize their work through collaboration networks, which requires efforts to harmonization of technical, ethical and regulatory standards. Indeed, the development of biobanks, especially population biobanks, in recent decades has required greater global coordination and international harmonization of ethical and legal standards for the protection of donors, especially in privacy of genetic data, basically because this activity has been challenged by three trends: "1. Biobanks are storing and sharing more information as molecular sequencing becomes more affordable, researchers collect more clinical and epidemiological data on participants, and digital networks expand. 2. Biobanks are increasingly being used as "universal research infrastructures" accessed for broad, future uses by researchers from various fields, sectors, and nations. 3. The scale of biobanks and linkage between them is expanding to achieve the sample sizes needed to explore the complex causes of common diseases." (Thorogood & Zawati, 2015). However, this international collaborative effort to share samples and data from large populations, considered a scientific and ethical imperative aimed at promoting the common good of knowledge and people's health (Zawati et al., 2014), is hampered by the lack of common legal criteria, especially with regard to access to samples and data.

Although the regulatory strategies for the establish, organization and operation of biobanks are very different from one jurisdiction to another, two main can be found: (i) countries that opt for special legislation for biobanks; and (ii) countries that apply general legislation to the activity of biobanks, such as laws related to the use of tissues, data protection laws, among others, and complement the legal regulation with specific national guidelines for biobanks. Compared with national legislation, regional and international guides have the mission of establishing common criteria that, although they are not legally binding (soft law), can guide national legislation. However, and despite the enormous proliferation of this type of international guides related to good practices in biobanks, in practice they have not been able to promote regulatory harmonization due to the particularities of each national

legislation and local ethical practices regarding the use of human biological material, the culture of data protection, confidentiality and privacy.

Below we present the analysis of the two regulatory strategies at the level of national law for the governance of biobanks, as well as the international instruments aimed at harmonizing legislation and the challenges they have entailed, ending with the initiatives of international collaboration networks of biobanks, which develop their own methods and guidelines of good practices for their operation as a mechanism to improve interoperability between biobanks.

Countries with Specific Legislation on Biobanks

The strategy of establishing a specific legal for biobanks was adopted early by some European countries that initiated a national population biobank policy (Zika et al., 2010; Zawati et al., 2014; Beier & Lenk, 2015; Chalmers, 2015). The first countries to enact special laws to regulate the activity of biobanks with special laws and regulations were: Iceland (The Biobanks and Health Databanks Act No. 110/2000; Regulations on the Keeping and Utilization of Biological Samples in Biobanks. No. 134/2001), Estonia (Human Genes Research Act, 2000), Sweden (Biomedical in Medical Care Act No. 297/2002), Norway (Act Relating to Biobanks No. 12/2003, replaced by Act on medical and health research, No. 44, 2008), Spain (Law 14/2007 on Biomedical Research, 2007; Regulations N° 1716/2011 which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and for the treatment of biological samples of human origin, and regulates the operation and organization of the National Registry of Biobanks for biomedical research), Belgium (Loi relative à l'obtention et à l'utilisation de materiel corporel humain destiné à des applications Médicales humaines ou à des fins de recherché scientifique, No. 18385, 2008). Just after, are added Finland (Biobank Act No. 688/2012) and Singapore (Human Biomedical Research Act No. 29/2015).

In the legislation of these countries there are some common elements such as the regulatory control of the activity of biobanks, the protection of personal data, the rules of international samples and data sharing, rules of informed consent, among others. Regarding the establish of biobanks, these countries, in general, set regulated and detailed procedures for the authorization and establishment of biobanks, with an authorization and registration procedure before the competent authorities in health, which, therefore, in general, it is also a supervisory authority. In addition, the sponsorship of the biobank belongs to the government or public bodies and entities linked or dependent on it (Spain), or a public university (Estonia).

One of the essential issues that regulate these laws is informed consent, establishing as essential elements of consent the purpose of the biobank and the express declaration of the granting of samples. However, when specifying in the law the requirements that consent must satisfy, some countries assume extremely rigorous models, while other countries simply establish the general requirements that must be met in its granting. In general, regarding the waiver to informed consent, the

cases covered by the legislation are associated with hypotheses of an excessive effort to re-contact or obtain consent to obtain the sample. Another exception to informed consent is established in the event that the new use of the sample is not suitable for the purpose for which it was obtained. In this case, the data that allows identifying the donor of the sample is dissociated, in such a way that the use of the sample is possible without being associated with the donor whose consent could not be obtained or obtained again. In these exceptional cases, it is necessary to have authorization from the Scientific Committee associated with the biobank or from the corresponding authority.

The option of withdrawal of consent is considered in all these laws. Some legislations have rules that require the destruction of samples after withdrawal consent (e.g. Iceland and Sweden). An important exception to the destruction of the samples that would proceed after the withdrawal of consent is the case of Norway, which requires that the corresponding sample has been previously anonymized (Zawati et al., 2014).

In general, the laws require the need to adopt adequate security measures for the protection of biological samples and associated data that are stored in the biobank and usually refer to data protection law. A general duty of codification of the information related to the samples is required, and the data and information obtained from the samples must be safeguarded. In addition, in certain cases, the drawing up of a reference to the administrative or technical regulations issued by a competent body is verified (e.g., Spain and Iceland).

Although these biobank laws regarding international sharing of data and samples have features in common, not all laws set identical criteria in this regard. In some cases, it is necessary to request a transfer authorization from the health authority that supervises the country's biobanks (Iceland, Sweden, Norway); in other cases, the authorization of the corresponding IRB is required (Spain, Finland). Not only is the authorization of the corresponding supervisor required, in other cases the sponsorship of a national institution is also required. In addition, conditions are established for the return or destruction of samples that have been transferred abroad (Sweden).

In relation to the communication of incidental findings, few countries consider legal regulations that require their communication. These legislations opt for the will expressed in the consent (Spain), that is, consent or not of the donor to communicate them in case they appear, or they opt to require a communication protocol for these cases (Singapore).

The regulatory strategy based on a special law, although it can produce legal certainty in the operation of biobanks and express guarantees of the rights of donors, has its limitations. First, because the particularities of the legislative tradition of each country make it more difficult international regulatory harmonization. Second, it is not enough to generate transparency and public trust. Third, adaptive capacity of the legislation to changes is weaker, therefore, it is crucial that regulator does not produce very exhaustive rules, restricting space for recommendations.

Countries with General Legislation Applicable to Biobanks

These countries choose to resolve the regulatory issues of biobanks through guides or orientations (soft law) that complement the general legislation applicable to these matters, for example, relating to biomedical research, use of tissues and data protection. The common law countries that opt for this regulatory strategy are the United Kingdom, the United States and Australia.

In the case of the United Kingdom, once the UK Biobank was created in 2002, a law of general application was enacted (Human Tissue Act [2004]), which contemplates the establishment of the Human Tissue Authority, an institution in charge of authorizing, through licenses to the different biobanks, the collection, storage and use of human tissues. Other laws applicable to biobanking are the Data Protection Act (1998), the Human Rights Act 1998, the Mental Capacity Act (2005), the National Health Service Act (2006), the Freedom of Information Act (2000), among others. For lack of specific legislation, there are many guidelines. In the case of the UK Biobank, its sponsors, the Wellcome Trust and Medical Research Council, have developed an "Ethics and Governance Framework (EGF) and established their own internal monitoring body, the Ethics and Governance Council (EGC), to legitimize and communicate the governance of UK Biobank to ensure it is managed in the public interest" (Kaye et al., 2016). Regarding data sharing policy, Wellcome Trust has issued its own Policy on Data Management and Sharing (updated 2017).

In the United States, the regulatory strategy was also not along the lines of a federal law that regulates biobanks, but through the application of different general laws that are extended to biobanking, such as the Common Rule, 45 CFR § 46, Health Insurance Portability and Accountability Act (1996), Standards for Privacy of Individually Identifiable Health Information (referred to as the 'Privacy Rule'), and the personal data law, Privacy Act (1974). Other laws that apply to biobank activity in the United States are the Stem Cell Therapeutic and Research Act (2005) and the Genetic Information Nondiscrimination Act (2008). However, the lack of specific legislation for biobanks has been criticized because it is cumbersome to apply the general rules for biobanking and also because they do not adequately protect personal data associated with samples through de-identification as required by the standard of European countries (Rothstein et al., 2016; Harrell & Rothstein, 2016). The most widely supported guideline is the National Cancer Institute's Best Practices for Biospecimens Resources (2007, 2011).

Although Australia does not have formal biobanking legislation, the main national funding agency, the National Health and Medical Research Council, has issued different guidelines and policies in this area. Most Australian biobanks are part of the Australasian Biospecimens Network, which has issued its own guidelines, the ABN Network Biorepository Protocols (Chalmers, 2015). Among the most outstanding particular aspects of the Australian regulatory standard are the considerations related to the protection of its original peoples. These are based on the fact that in its population it is possible to find genetic heritage of native peoples of about 40,000 years old. As an example, can be mentioned the report published by

the NHMRC entitled *Ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities: Guidelines for researchers and stakeholders* (2018). An analogous case is New Zealand. Indeed, the Māori & Indigenous Governance Center of the University of Waikato, New Zealand, has published the *Guidelines for Biobanking with Māori* (2016), which establish special considerations aimed at protecting the population of Māori origin.

International and Regional Guidelines on Biobanking

At the international level, the first documents dealing with consensus standards for the management and transfer of biological material and genomic data were those issued by the Human Genome Organization's (HUGO): Principles Agreed at the First International Strategy Meeting on Human Genome Sequencing (1996) (Bermuda Principles); Statement on DNA Sampling: Control and Access (1998); Statement on Human Genomic Databases (2002); Sharing Data from Large-Scale Biological Research Projects: A System of Tripartite Responsibility (2003).

Around those same years, UNESCO was especially concerned with developing international human rights law relating to the human genome and genetic data, first with the Universal Declaration on the Human Genome and Human Rights (1997), and then with a more specific instrument that came to complement the previous one, the International Declaration on Human Genetic Data (2003), which regulates biological samples understood as support for personal data (genetic and proteomic data) and with the condition of personal data. This statement, along with protecting the privacy and security of donor subjects, provides that the principle of free, prior and informed consent allows national legislation to establish exceptions based on the relevance of the data that may be obtained for medical research or scientific, or for public health. And regarding the international exchange of samples and data, it establishes that "in accordance with their domestic law and international agreements, the crossborder flow of human genetic data, human proteomic data and biological samples so as to foster international medical and scientific cooperation and ensure fair access to these data".

Without a doubt, the recommendations of international organizations that have had the greatest impact are the Guidelines on Human Biobanks and Genetic Research Databases (HBGRD) published in 2009 by the Organization for Economic Co-operation and Development (OECD), which among its general recommendations is to promote that data access policies are fair, transparent and do not limit research. Likewise, a broad expert consensus has had a more recent guideline, that of the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition (2016), which in its guideline 11, storage and use of biological materials and related data, highlights substantive issues of biobank governance. First of all, this guideline highlights that broad consent in research is acceptable, which, although it allows

different future uses of the sample, requires certain restrictions for use, differentiating from blanket consent. Also, the guidelines highlight the need for institutions that collect biological samples and related data to have a governance system that allows them to request authorizations for the future use of materials for research purposes. Governance systems must safeguard the confidentiality of the link between samples and personal identifiers of donors. Likewise, they must comply with principles of transparency and accountability within which the participation of patient groups and the community in general must be enabled, as well as having appropriate mechanisms to keep participants informed of the results of the investigation. Other relevant aspects of this guideline point to the transfer of samples abroad, indicating that it must be done through a Material Transfer Agreement (MTA), which specifies the variety and duration of use, and what must happen at the end of the period usage, among other things.

At the European level, the Council of Europe has issued two recommendations, in order to harmonize the legislation of the member countries, the first was Recommendation Rec(2006)4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin (2006), which was superseded by the Recommendation CM/Rec(2016)6 that establishes the conditions for obtaining and storing materials for future research, as well as for their use in specific research projects, in particular as regards regarding adequate information and the consent of interested parties, with its own chapter for the governance of collections.

The World Medical Association (WMA), for its part, in 2002 adopted a declaration on this subject, which was revised in 2016, at the 67th WMA General Assembly, Taipei, Taiwan, entitled Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks. The specific statement, within its ethical principles, what information is necessary to be able to request a broad consent, in addition to establishing the basic principles for the governance of biobanks: protection of individuals, transparency, participation and inclusion and accountability, and these principles adds the necessary elements for a governance regime.

Although the binding force of international or regional guidelines depends on the issuing agency, they are all soft law, therefore, they cannot be used in case of conflict with local legal provisions, which, eventually, can be very restrictive for biobanking. Another limitation is the diversity of sources from which these guidelines come, which can often contradict each other. For this reason, other regulatory strategies that depend on the initiatives of the biobanks themselves to create national or international collaboration networks that have their own operating standards are gaining strength.

Biobanks Networks

Biobank networks began to form to address the difficulties of operating biobanks unconnectedly. Difficulties include "insufficient samples to conduct research on rarer diseases; inadequate infrastructure to process, store and retrieve samples to meet the necessary quality standards for research; cost of establishing and maintaining a large enough resource over the long term, and satisfying legal, ethics and governance requirements" (Shickle et al., 2010).

Although biobank networks are a way to promote and enhance the greater use of samples to reach a size necessary for the validity of the research and avoid bias, they maintain regulatory challenges such as having standardized technical procedures, a common quality control programs; homogeneous ethical requirements and an open policy for sharing. Therefore, biobank networks manage to harmonize their operation, rather than with a regulation strategy like the ones we saw in the previous paragraphs –special legislation or guidelines or national or international policies–, agreeing on common criteria of methods, approaches and tools for functionality.

One of the first collaboration strategies between biobanks was through the European initiative Promoting Harmonization of Epidemiological Biobanks in Europe (PHOEBE), which lasted until 2009. Until today, there is another collaboration initiative at European level, implemented as of 2013, Biomolecular Resources Research Infrastructure (BBMRI), whose main objective "was to develop an information technology concept for the exchange of data between biobanks (at national and European levels) and strategies for biobank material quality management, and also to present a positive and transparent image of biobanking" (Chalmers et al., 2016). It is currently a pan-European infrastructure of national biobank networks that is part of the European Research Infrastructure Consortium (ERIC), defined as a federated research infrastructure of biobanks and biomolecular resources that provides expertise and services –management services, support with ethical, legal and societal issues, and a number of online tools and software solutions for biobankers and researchers– in order to facilitate the use of European sample collections and data for the benefit of human health. Another federated initiative of European biobanks, dedicated to scientists conducting research on rare diseases, is EuroBioBank, a biobank network of RD-Connect.

There are also other international organizations that have played an important role in standardizing preservation and storage material from biobank. One of them is the International Society for Biological and Environmental Repositories (ISBER), whose mission is providing training and governance resources for human specimen repositories, through the ISBER Best Practices: Recommendations for Repositories, which provides standardized terminology describing the level of identifiability of samples. Another standardization initiative was the Public Population Project in Genomics and Society (P3G), an international consortium made up of not-for-profit organizations that conduct, use or collaborate with health studies, biobanks, and research databases.

At the level of national biobank networks, it is worth highlighting the Canadian Tumor Repository Network (CTRNet), the Australasian Biospecimen Network Association (ABNA), which includes biobanks across Australia and New Zealand, and Confederation of Cancer Biobanks (CCB), UK, all federated biobank networks. Other national networks instead follow a centralized model such as Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConfab, Australia), onCore UK (UK), Singapore Tissue Network, UK Biobank (Vaught et al., 2009). The review of international biobanks and networks carried out by Vaught et al. was repeated 10 years later, in which 12 of the 16 biobanks and networks reviewed were maintained, concluding that, despite "changes to their operation models or through diversification of their activities", in his opinion "one thing remains certain: our biomedical research community will still require the systematic collection and distribution of human tissue specimen from donors to scientists if we are going to continue to build knowledge about human disease and its consequences" (Devereux et al., 2019).

Third Stage of Evolution: Challenges for Sustainable Biobanking

Sustainability in the field of biobanks is a highly debated issue as a result to the implications that this activity has, from an ethical, legal and social point of view, since very relevant public interests are at stake, such as the health of the population and the generation of knowledge with high quality standards. In addition, the particularity of how biobanks work makes them very different from other research support structures, to the extent that they must take on many challenges, such as the ever-increasing complexity of sample storage and recovery, the management and integration of data and the establishment of common platforms in a global context (Karimi-Busheri & Rasouli-Nia, 2015).

Sustainability Problems

As Watson et al. have pointed out, "the topic of sustainability is challenging for the discipline of biobanking for several major reasons: the diversity in the biobanking landscape, the different purposes of biobanks, the fact that biobanks are dissimilar to other research infrastructures and the absence of universally understood or applicable value metrics for funders and other stakeholders" (2014). Without a doubt, it is essential to consider that the different types of biobanks (population versus specific pathologies or clinical study cohorts versus biomedical study cohorts) differ with respect to their sustainability plan as consequence to certain particular characteristics of each one (types of strategic collections, informed consent, participants,

samples and associated data, infrastructure, services, associated users, case monitoring, etc.) that are often not considered by stakeholders (Husedzinovic et al., 2015).

In this operating scenario of biobanks, the concept of sustainability applied to them cannot be reduced only to self-financing, other dimensions must be considered beyond the financial one, such as the operational and social dimension (Watson et al., 2014). Without question, the financial aspect of biobanking is very relevant, but at the same time complex. There is evidence that shows that the recovery of costs for the transfer of samples or the commercialization of products or services are not enough to achieve and maintain sustainability (Chalmers et al., 2016). This situation has led biobanks or biobank networks to seek new sources of long-term sustainability, which has apparently achieved a balance between public and private contributions (Doucet et al., 2017).

However, the debate continues about whether biobanks should be self-sustaining infrastructures through the strategy of giving impetus to market priorities (commercial patents) that seek to quickly bring out medical products and therapies. But it is clear that, during all this time of evolution of biobanks, these are platforms with a social value that goes beyond the exclusive purposes of profit. There are initiatives carried out by biobanks that are of interest to society as a whole, for example, if we think about the usefulness of generating anonymized health data sets to create virtual populations on which treatments and interventions can be modeled by computer of different types, as well as the usefulness of promoting the interoperability of data sets and sample collections for research purposes, or integrated in health care that require longitudinal samples of patients for permanent monitoring (Doucet et al., 2017). Therefore, the challenge is not only to have metrics to measure the sustainability of biobanks adjusted to the type of biobank (i.e., user, size, type) and taking into account the value to society, but also to continually evaluate new metrics that integrates apparently incompatible interests between sponsors, researchers, participants and the community in general, to approach a more real and adequate measure of the value of biobanks (Chalmers et al., 2016).

Dimensions of Biobank Sustainability

The sustainability of a biobank requires a balance between the social, operational and financial dimensions in the context of its own work (Watson et al., 2014). These dimensions have a close interaction and dependence on each other. For example, operational aspects are directly related to trust and acceptability by stakeholders, which means that following international biobank regulations and accreditations has an impact both technically and socially (Luna Puerta et al., 2020).

The operational dimension (efficiency) includes aspects of operational and organizational management, definition of policies and structure of a biobank. In turn, this dimension includes three points: (1) Entry efficiency means defining a participant enrollment program and a sample capture and storage system. (2) Internal efficiency has to do with operational harmonization according to good international

biobanking practices. Some examples of harmonization are: (i) sample exchange and quality: SPREC (Lehmann et al., 2012) and/or BRISQ (Moore et al., 2012) standard quality indicators for biospecimens that allow interoperability and standard *College of American Pathologists* (CAP) (Hainaut et al., 2009) that allows determining quality control in tissue samples; (ii) data exchange and transmission: adoption of integrative interoperable systems in accordance with The FAIR guides principles (Findable, Accessible, Interoperable, Reusable) (Wilkinson et al., 2016). (3) Output efficiency points to two actions: evaluating response capacity, for example, measuring user satisfaction, and having a broad catalog of services, biospecimens, and biomaterials.

The social dimension (stakeholder) refers to the relationship and interaction that a biobank establishes with the different stakeholders and also involves all aspects related to the ethical, legal and social implications (ELSI) that are the responsibility of the activity of biobanks (Bjugn & Casati, 2012). This dimension includes acceptability and assurance of standards. The first includes (i) guaranteeing compliance with the ethical-legal approvals for the biobank and associated projects, and (ii) engagement of people: transparent and participatory governance, generating dissemination and education activities, involving the patient in their follow-up, etc. (Mitchell et al., 2015). The second includes (i) adherence to good biobanking practices, obtaining certifications and accreditations (CAP, ISO, ISBER, etc.), quality program, etc., and (ii) training and education in biobanking, using local capacities, internships and international courses (Kinkorová, 2021).

The financial dimension (value) is related to the availability of resources and how these resources are obtained and used, which includes the business plan and model, the offer of services and products, and the sources of financing. This dimension includes the following points: (i) brand strategy that includes preparing an academic, marketing, business development plan, etc., constantly re-evaluating the development plan, and establishing a user rate (stratified or differentiated); (ii) stakeholder need includes, first, recognizing interests and needs of the community, scientific world, biotechnology and health industry, and second, defining strategic collections according to country and regional needs, according to the type of biobank that make up the Network and to associate researchers, etc.; brand recognition includes, first, disseminating the value of the biobank with all stakeholders, and second, measuring the value and impact of the biobank: generation of collaborations, publications, number of master's and doctoral theses, associated awarded projects, patents, etc.

Final Remarks

After more than 20 years of operation of research biobanks, despite constant ethical, legal and social challenges, the recognition of social value that these infrastructures have for the generation of knowledge applied to the field of genomic, post-genomic, and personalized medicine, as well as global or planetary health challenges, has not

declined. Likewise, biobanking is promoting a culture of international collaborative research that leads to a new paradigm regarding the assessment of risks and benefits of people's participation in research, community engagement, and the role of the association of public and private actors in promoting science.

I have stated that the shift from the logic of biomedical research "one researcher, one project, one jurisdiction" to a logic of research using future samples for many lines of research and shared internationally, has not only meant reconfiguring the mechanisms for protecting the interests of research subjects (informed consent, protection of privacy, access to information, etc.) focused on their individual decisions, but also to introduce the idea of governance of long-term research infrastructures, which should take into account broader health needs of the population. The latter highlights that biobanks are intermediary tools at the service of the scientific community and the good of society that function as a public good.

At the same time, the evolution of biobanking as a consequence of the increased use of genome-wide sequencing techniques and the importance the use of large amounts of data gains, shows that it is crucial to constantly review governance criteria to address new risks. The potential of these risks affecting the privacy control dimensions and the growing importance of international sample and data sharing, further stresses the demand for international regulatory harmonization criteria and commonly accepted good practices. Finally, I affirm that the ability of the global research ecosystem to adapt to these new risks depends on a systemic approach that understands the viability of the public value that biobanks have for society with an always renewed view of the three dimensions of sustainability.

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Chapter 18
Biobanking in Global Health & Research

J. W. Ashcroft and C. C. Macpherson

Abstract Biobanking of patient-derived materials is routine in health care, research, and public health emergencies. Ethical guidelines for biobanking address concerns including some about genetic materials, informed consent, confidentiality, regulatory environments, and standards of governance. This chapter identifies some limitations of existing guidelines that were apparent to one author during an Ebola outbreak, and specifies five ethical concerns about biobanking that warrant additional attention: misconceptions about biobanking, unknown consequences for donors, socioeconomic inequities that compound vulnerabilities, lasting and proportional benefits in North-South research, and contextual challenges to disclosure and understanding. These affect patients, donors, health systems, research, and policy, and are amplified during public health emergencies.

Keywords Biobanking · Ethical guidelines · International Guidance · Bioethics · Biobanked materials

Biobanking & Ethics

Attention to ethical and regulatory concerns involving biobanks emerged once it became possible to store stem cells and genetically identifiable materials for future research and patient care. Advances in genetics continue to elicit attention in peer reviewed literature given the implications for confidentiality, informed consent, and benefit sharing of genetic materials and information (Ashcroft & Macpherson,

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2019; Hansson, 2009). Scientific, technological, and medical developments enable the storage, sharing, use, and sale of digital and other types of materials and information which also constitute biobanking, although such activities with blood, cell lines, and other biological materials preceded the concept of biobanking.

Today, collection of human and nonhuman materials and information is routine in medicine, research, agriculture, and beyond. Ethics of biobanking extends from human genetic and biological materials to humans and non-human materials and data. Its scope includes related processes such as collection, storage, sale, data management and sharing, benefit sharing, regulatory environments, governance, and informed consent processes. Conceptual and practical research on biobank ethics and policy is needed (Langhof et al., 2019). A special issue of the journal *Health Care Analysis* addresses ethical concerns about biobanking of human genetic materials and information including informed and broad consent; withdrawal of materials; confidentiality and the potential of genetic materials to reveal information about relatives who had no opportunity to give or refuse informed consent; commercialization of materials and information donated for diagnostic or public health purposes; and contacting donors with incidental findings or for other reasons (Widdows & Cordell, 2011).

The word 'biobanking' itself is so expansive as to be misunderstood by many including health professionals and policy makers, who may also misunderstand or discount potential implications for donor confidentiality. This chapter describes the range of activities that constitute biobanking and the limitations of ethical and regulatory guidance, describes examples from JA's experiences during an Ebola outbreak, and identifies five specific concerns amplified during public health emergencies. These are misconceptions about biobanking, unknown consequences for donors, socioeconomic inequities that compound vulnerabilities, lasting and proportional benefits in North-South research, and contextual challenges for disclosure, understanding, and informed consent.

What Is Biobanking?

A *biobank* is popularly defined as a repository of human biological samples for research (Merriam-Webster Dictionary, 2018; Wikipedia, 2018). A more precise definition of *biobanking* is the collection and storage of cells, tissues, bodily fluids, and biodata including digital images, genetic and demographic information, and electronic medical records. These materials are collected and stored routinely in healthcare, research, and during public health emergencies. They are widely shared for research and occasionally commercialized. Biobanking of non-human materials including plants advances human and veterinary medicine and research. Ethical concerns thus involve interconnections between human, veterinary, environmental,

and ecosystem health in what many call "One Health[1] (Pang, 2013; Brankovic et al., 2014; Capps & Lederman, 2015; CDC, 2018). Current definitions of the word *biobank* are inaccurate and imprecise. They imply that all biobanks are the same when in fact they differ significantly with institution and jurisdiction. The words biobank and biobanking are easily misunderstood by everyone. As used in this chapter, they encompass this variation and breadth.

Sharing biobanked materials across institutions and borders is vital to understanding, preventing, controlling, and treating infectious diseases. Biobanking of materials and information from pre-SARS-CoV-2 helped elucidate relationships between multimorbidity, polypharmacy, sociodemographic, lifestyle and COVID-19, and thereby improve risk stratification and protect those most vulnerable (McQueenie et al., 2020).

Biobanks are typically stored in governmental, commercial, or academic repositories that may focus on type/s of material stored (blood, DNA, and others) or a single specialty (infertility, genetics, a specific disease or disorder, etc). The 'U.K. Biobank' stores a range of materials from biological and genetic samples to biochemical markers, electronic health records, physical activity data, and survey responses (BiobankUK, 2021). Its website builds trust in its activities and outputs by providing transparency for the public, researchers, and health professionals. Not all biobanks are as transparent, and institutional and national resources influence their policies and practices.

Biobank policies and practices determine how materials are collected; the transparency, security, and circumstances in which materials are stored, shared, and transported; and adherence to ethical and regulatory guidance. Differences in biobank governance, policies, materials, and specialty reflect socioeconomic and other considerations, and may contribute to unanticipated risks, harms, or violations of ethical or regulatory guidance. In practice, this means that assumptions about the uniformity of biobank practices and policies in different jurisdictions are erroneous. This widespread but erroneous assumption is compounded (often unintentionally) by other assumptions and misinformation. For example, a study of informed consent processes found that biobanks are thought to be a type of research rather than a resource for research or healthcare (Widdows & Cordell, 2011).

Biobanking & International Guidance

Widely respected international ethical guidance for human research exists but relatively little explicitly addresses biobanking and the language used is not standardized. A search of the comprehensive *International Compilation of Human Research*

[1] The United States CDC describes One Health as "a collaborative, multisectoral, and transdisciplinary approach — working at the local, regional, national, and global levels — with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment."

Standards for the words ‘biobanks’, ‘repositories’, ‘specimens’, and ‘fluids’ found only 17 countries and five organizations with any such guidance.[2] A more exhaustive search of its legislation, regulations, and guidelines using other words would likely reveal more.

The most prominent international guidance documents that reference ethics surrounding the use of stored biological data/materials (including outbreak-derived items) have limitations. These include The Nagoya Protocol (2014), WHO’s Guidance for Managing Ethical Issues in Infectious Disease Outbreaks (2016), The Declaration of Helsinki (2013) and The World Medical Association (WMA) Taipei Declaration (2016). The content and limitations of this guidance are outlined here and discussed in light of experiences during the Ebola outbreak of 2014.

The Nagoya Protocol

Institutional, national, and international research ethics guidelines vary considerably in what they say about biobanking. Although the word *biobank* is not explicitly employed, the non-retrospective (i.e. materials and data collected prior to adoption are not covered) Nagoya Protocol[2] came into force in October 2014 and was signed by over 50 countries. The protocol applies to genetic resources[3] and traditional knowledge associated with these resources. In addition, the protocol stipulates that any benefits that might arise from the utilization of genetic resources and knowledge must be shared equitability with those who provide them, hence, the country of origin. Critically, the protocol does not apply to human genetic resources and genetic resources covered by specialised ‘Access and Benefit Sharing’ (ABS) treaties that are supportive of the Convention on Biological Diversity (CBD) for which no international equivalent exists.[4]

Although this protocol represents a significant step forward as a legal instrument specific to the sharing of biobank-related resources and subsequent benefits, it has limitations. Benefits that arise from the use of a genetic resource are not necessarily easily identifiable. For example, publishing data on a genetic resource in a reputable journal can lead to an increase in prestige (a gain in reputation), research grants, and employment. As such, every institution sourcing material needs to ‘exercise diligence’ by ensuring that the material has been accessed in accordance with ABS laws implemented by the provider country. While the Nagoya Protocol is a

[2] The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity.

[3] Any material of plant, animal, microbial or other origin containing functional units of hereditary is considered as genetic material in this context.

[4] Although no international equivalent exists, there are professional bodies which seek to provide their membership with guidance in this area (e.g. International Society for Biological and Environmental Repositories).

multilateral agreement, each country implements their own guidelines and laws so the requirements to comply can differ substantially between countries.

Of further consideration is the reality that not all countries rank implementation of the protocol in the same way or possess the same level resources to implement and regulate. This later concern is catered for in Article 22 protocol but no stipulation is made with respect to enforcement:

Article 22(1): The Parties shall cooperate in the capacity-building, capacity development and strengthening of human resources and institutional capacities to effectively implement this Protocol in developing country Parties and Parties with economies in transition.

In the context of emergency situations (e.g. infectious disease outbreaks), the protocol urges signatories to be "mindful" of the International Health Regulations (IHR) and Article 8(b) raises the importance of ensuring expedited access to human pathogens for public health preparedness and responses:

Article 8b: Pay due regard to cases of present or imminent emergencies that threaten or damage human, animal or plant health, as determined nationally or internationally. Parties may take into consideration the need for expeditious access to genetic resources and expeditious fair and equitable sharing of benefits arising out of the use of such genetic resources, including access to affordable treatments by those in need, especially in developing countries.

What is exactly meant by "mindful" leaves significant room for interpretation potentially complicating the relationship(s) that exist between parties. In addition, not all countries are currently signatories of the protocol (nor have the current 50 signatories all ratified the protocol) raising the issue of how researchers, industry and outbreak responders should apply (including proactively) the protocol in these countries. Low- and middle- income countries (LMICs) are the epicentre for many emerging and re-emerging infectious disease outbreaks and comprise many non-signatories. As such, LMICs may be more vulnerable than others with respect to equitable benefit sharing and least likely to be protected by the protocols (due to lack of implementation). Despite laudable intentions, Nagoya is ideal in aim but non-specific and unenforceable. Accurately or not, some perceive such declarations as "ethics in a vacuum".

WHO: Guidance for Managing Ethical Issues in Infectious Disease Outbreaks

This World Health Organization (WHO) guidance arose out of lessons identified in the wake of the 2014–2016 Ebola outbreak in West Africa (*see further discussion below*) (WHO, 2016).

The WHO recognises that responses to epidemics, emergencies and disasters raise many ethical issues for the countries, organisations and people involved (including public health specialists and policy makers). This guideline is intended to

outline "ethical principles that should guide communication planning and implementation at every level from frontline workers to policy-makers." Its breadth does indeed cover an impressive array of topics including "Long-term storage of biological specimens collected during infectious disease outbreak" (Guideline 11). However, its depth (especially Guideline 11) is limited to large brush strokes typical of guidance of this type.

For example, when discussing the need for appropriate Material Transfer Agreements (MTAs) to enable the sharing of samples, this guidance specifies that end users must "guarantee that the benefits of any subsequent use of the specimens will be shared with the communities from which the samples were obtained." This statement is well supported and reflects the ethical principle of reciprocity however, without any guidance on HOW this is to be achieved by parties in real terms allows for potential abuse and neglect. Furthermore, the editing committee did not directly reference any existent declarations or protocols currently used, missing an opportunity to solidify and unify various schools of thought. Whilst high-level documents such as this represent a useful foundation upon which to build, there is nothing novel about its content nor does it offer practical guidance for implementing the processes and frameworks suggested.

The Declaration of Helsinki and CIOMS International Ethical Guidelines for Health-related Research

The *Declaration of Helsinki* addresses biobanks in item #32 with only a few lines on informed consent and research ethics review (World Medical Association, 2013). CIOMS' *International Ethical Guidelines for Health-related Research Involving Humans* offers significantly more breadth and depth on biobanking (CIOMS, 2016). Designed for a wide range of researchers and stakeholders, these comprise 25 guidelines with commentary on each. Guideline #11 *Collection, Storage, and Use of Biological Materials and Related Data* and #12 *Collection, Storage, and Use of Data in Health-related Research* offer several paragraphs each, plus commentary describing requirements for related governance, research ethics committees (RECs), informed consent and its withdrawal, opt out procedures, residual tissues, return of results and disclosure of unsolicited findings, storage and use of 'material from low-resource settings', and more. Commentary on #12 adds secondary use of stored data, archived data, data mining, mandatory population-based registries, and others.

Guidelines #11 and 12 both require that: (i) collection and storage of materials and data occur in "collaboration with local health authorities"; (ii) local representatives be part of the governance system; and (iii) all materials be returned to their original setting and results and benefits shared with the hosts. How these are interpreted and applied and the extent to which their intent is met are influenced by institutional, national, and other considerations as described above. Adoption of and compliance with these guidelines varies with location, resources, and over time, and

may often be ignored or abused. This is a particular concern because international researchers may be tempted to exploit unfamiliarity of host LMICs with CIOMS guidelines and their limited regulatory human subjects protections including data-sharing and benefit-sharing.

Disease outbreaks and other public health emergencies often cross national boundaries and involve North-South and South-South populations and responses. This contributes to practical and ethical challenges for healthcare workers (HCW), researchers, institutions, governments, and other stakeholders. *How* to resolve or minimize these challenges is not clear in any existing ethics guidance, particularly given that effective responses will of necessity differ in different contexts, circumstances, and jurisdictions. For example, while biobanking was essential to local and international responses during the 2014 Ebola outbreak in Sierra Leone (which is classified as an LMIC by the World Bank), its practice demonstrated the differing resources and capacity between institutions and countries (*see below*).

The Taipei Declaration

Cognisant of limitations in the Declaration of Helsinki, the World Medical Association (WMA) updated its 2002 Taipei Declaration to address collection, storage and use of identifiable human data and biological material within and beyond clinical practice and patient care (WMA, 2016). The 2016 revision provides additional guidance for Health Databases and Biobanks. It recognises the potential benefit of biobanking in accelerating understanding of disease and the effectiveness, efficiency, safety and quality of preventive, diagnostic and therapeutic interventions but stipulates that these benefits cannot negate the need to protect patient or donor autonomy and confidentiality. Material and information stored in a database or biobank for multiple and indefinite uses must only be used if informed consent is obtained. Section 12 stipulates that informed consent must include disclosure of associated risks, privacy safeguards, access controls, results, benefit sharing, and how samples will be stored and used in the short and long term.

The declaration calls on parties to ensure that the interests and rights of the communities concerned are protected, particularly for populations considered to be LMIC or otherwise vulnerable. It promotes benefit sharing and protection from exploitation with attention to the need for contractual approaches to data collection and sharing including future uses and intellectual property rights biobanked materials. Before sharing or using materials, it calls for reasonable efforts to seek consent from donors (or surrogates) who were incapacitated when their diagnostic samples were collected and stored. This practice is routine during infectious disease outbreaks and raises questions about consent and ownership of materials derived from patients who died or never regained capacity. It bears noting that the Taipei Declaration primarily targets physicians (consistent with the WMA aims) rather than researchers or public health professionals.

In summary, no existing guideline encompasses the breadth of biobanking or its aims, uses, or practices in different locations and contexts around the world. If a patient or research participant lacks understanding about biobanking of their materials then, in many situations, their informed consent is incomplete. Physicians, researchers, and public health professionals have a responsibility to disclose this information, but many have their own faulty assumptions and misconceptions about the biobanks, biobanking processes, and ethical concerns. Some overestimate potential benefit or underestimate potential harm to a patient or donor, thereby hindering disclosure. Others feel unnecessarily uncertain or conflicted about collecting materials or obtaining informed consent. Moreover, instead of policies influenced by science, evidence, and ethics, government biobank policies may be unduly influenced by politics, and private biobanks by potential commercial gain.

Case Study: Biobanking During the 2014 Ebola Outbreak in Sierra Leone

This section describes experiences of JA in Sierra Leone during the Ebola outbreak and provides a practical illustration of the limitations highlighted above. It is followed by discussion of our previous work on ethical concerns about biobanking (Ashcroft & Macpherson, 2019).

Sierra Leone (SL) is a vibrant country that has overcome obstacles from Cholera and Ebola to military coups and a prolonged and vicious civil war during which countless atrocities took place. Roughly the size of Ireland and with a population of over five million, its geography includes beaches, rainforest, mountains, mangroves, and savanna grasslands (Sesay, 2020). Its official language is English but it has over 16 different tribal or ethnic groups and 24 languages; and traditional leaders remain influential in communities, healthcare, and government (Lewis et al., 2014; Albrecht, 2017; Sierra Leone Information System, 2006). Despite vast wealth in natural resources such as diamonds, gold, and bauxite, poverty affects the majority of the population and life expectancy is 49.5 years (Seisay & Kamara, 2017).

Prior to the 2014 Ebola outbreak, the healthcare system in Sierra Leone was in a fragile, perhaps perilous, state due to chronic underfunding, limited supplies of essential equipment and medicines, and a dearth of adequately trained HCW. The population density of doctors in Sierra Leone was, in 2010, roughly 2: 100,000 – well short of WHO's recommended minimum level – 23: 100,000 (WHO, 2010). At last reporting, there were only four hospital beds per 10,000 populations, and government expenditure on healthcare is US$12 per capita (Shoman et al., 2017).

Before the outbreak, only one hospital had a functional infectious disease unit (the Kenema Government Hospital's Lassa Fever Unit). When its head, Dr. Sheik Umar Khan, succumbed to the Ebola virus early in the outbreak, this further deflated capacity to cope and respond. An unprecedented number of HCWs became infected during the outbreak and an estimated 221 died, equivalent to 21% of the HCW force

then in Sierra Leone (Government of Sierra Leon, 2015; WHO, 2010). The commitment of so many HCWs in SL to their profession, despite lack of Personal Protective Equipment and other resources necessary to provide care safely, is admirable, more so because many also faced discrimination and stigmatization from their communities and families as a result of their efforts (McMahon et al., 2016; The Guardian, 2014).

The socioeconomic, cultural, and physical environments in which the outbreak began were typical of LMICs in hindering access to economic and other resources essential to effective public health interventions. Undeveloped infrastructure, staffing shortages and low levels of education coupled with miscommunications impeded all aspects of care and diagnosis. With respect to diagnostic samples, problems including collection, packaging, transportation and subsequent storage of samples for potential re-testing and research purposes were prevalent. This, combined with the high pathogenicity and transmissibility of the Ebola virus, limited knowledge about effective treatment or control, and rapid and highly visible morbidity and mortality in communities and institutions, meant that all HCWs and researchers in SL were at high risk of Ebola infection when the outbreak began including international partners on site.

Initial international responses had little impact because they failed to understand and address the complex social dynamics including the importance of traditional beliefs about health and illness. Communities in SL distrusted and resisted international responses because these conflicted with traditional practices, for example, regarding burial. Real progress began to occur when efforts were undertaken in partnership with sociologists, anthropologists, and others to respectfully engage local communities, and to understand relevant belief systems and their importance in everyday life.

This may have contributed to the subsequent development of literature in peer reviewed journals that documents the value of community engagement in public health responses.

In SL, the public was also distrustful and suspicious of local responses due to widespread perceptions regarding historical injustices and corruption (Pieterse & Lodge, 2015). Indeed, Ebola wasn't mentioned publicly by SL's President until 2 months after the outbreak began due, in part, to concern about how the public would react (Shoman et al., 2017). Rumors included the idea that the outbreak was fabricated as a front for nefarious activities like stealing organs or eliciting gifts from wealthy donors, or a government conspiracy to undermine certain tribal groups (The Guardian, 2014). This distrust may explain the lack of public information about the biobanking of patient samples during the early part of the outbreak when community engagement was not seen as a priority in SL and its value was less understood around the world.

Diagnostics were conducted primarily by externally run laboratories operating under memoranda of understandings or Material Transfer Agreements (MTAs). Over the course of the outbreak, patient diagnostic samples were either: destroyed, exported out of the country through an official government agreement, exported out of the country without an agreement, or stored and archived in country (Saxena &

Gomes, 2016; Hannigan et al., 2019). Each organisation that was supporting Ebola diagnostics in country had their own agendas and approach to how they treated the samples placed in their care. The lack of a standardised approach and comprehensive oversight resulted in an untold number of Ebola biological samples that are unaccounted for. This inadequacy was broadly highlighted during an International Health Regulations (IHR) evaluation (October, 2015) of functional core capacity (WHO, 2015) which determined national capacities were not able to keep pace with national needs to manage these emergencies (e.g. Ebola) efficiently and effectively. Consequently, Ebola diagnostic samples were often stored in facilities that did not have appropriate levels of biosafety and biosecurity[5] (McLaughlin & Nixdorff, 2009).

With support from the Canadian Government as part of the Global Partnership biosecurity agenda, SL's Ministry of Health and Sanitation took steps to establish a central biobank and consolidate all related materials (HCCG, 2018). A series of delays in the process contributed to several freeze-thaw incidents and undoubtedly led to some degradation of samples, especially RNA extracts. The high costs of space and electricity to maintain samples at temperatures of −80 Celsius were wasted because the samples were likely degraded leaving them with no scientific value. This situation was worsened by misconceptions that the degraded samples would generate new treatments and income for SL. Whether to preserve samples that were not maintained at adequate temperatures and their unlikely but uncertain scientific value was a decision that troubled researchers, government officials, and international partners, as did the question of what grounds to use to make this decision.

In addition to uncertainty about the biosafety and biosecurity aspects of biobanking or sharing biological samples, the ethical standards remain regarding the consent of patients and communities whose samples were stored and about the entities that expressed interest in using these samples for research-related purposes (UNEP's Dakar Declaration, 2015) (AVLM, 2014). Ebola-related biobanking during the 2014–2016 outbreak contributed significantly to knowledge about the disease and improvements in its control, especially with respect to ring-vaccination strategies (as is evident in the use of rVSV-ZEBOV Ebola vaccine during the two 2018 Ebola outbreaks in DRC) (Huttner et al., 2018; Lévy et al., 2018; WHO, 2018). These positive outcomes do not negate the concern noted by Saxena and Gomes (2016) regarding the absence of a "complete inventory of the samples collected during the past 18 months [of the 2014 outbreak], their location, conditions of storage, 'ownership', and participant authorization for future use," nor do these outcomes currently provide tangible, real-term, benefits to the donor communities. The next section discusses some ethical implications of these practical challenges.

[5] Defined as the: "protection, control and accountability measures implemented to prevent the loss, theft, misuse, diversion or intentional release of biological agents and toxins and related resources as well as unauthorised access to, retention or transfer of such material".

Bioethics & Biobanking

Five ethical challenges for biobanking emerge from this chapter and encompass but are not limited to human genetics or technological advances. These challenges are particularly relevant in public health emergencies and in North-South and South-South partnerships in clinical or research. The challenges are (i) misconceptions about biobanking; (ii) unknown consequences for donors of demographic or other information that may be inferred or extracted from their original donation; (iii) socioeconomic inequities that increase donor vulnerabilities; (iv) provision of lasting and proportional benefits; and (v) contextual challenges to disclosure, understanding, and informed consent. Recent ethical guidance developed in response to public health emergencies (PAHO, 2017; Kass et al., 2019; Emanuel et al., 2020; WHO, 2020b) does not adequately address these challenges.

Misconceptions About Biobanking

Popular and scientific definitions of biobanking are inconsistent. Even in academic publications these oversimplify and may omit information such as the primary aims of a given biobank or its implementation of regulatory policies. Consequent assumptions and misunderstandings compound therapeutic misconception (even among researchers, physicians, and healthcare workers about distinctions between patient care, public health intervention, and research. Therapeutic misunderstanding and misrepresentation were visible in news coverage (and literature) about the demand for potential Covid-19 treatments and emergency use authorization before any evidence of their efficacy or safety.

Distinctions between research, patient care, and public health are easily blurred. Public health emergencies obscure these distinctions in that those collecting samples are likely to feel urgency about patient care and less attentive to research or future use. This has implications for policy and bears on the responsibilities of governments, institutions, researchers, funders, health authorities, and others.

Unknown Consequences for Donors

Biobanked materials or information derived from individuals is sometimes generalized to their wider community or population. This may influence their individual or collective access to care, how others perceive them, and the extent to which they are treated respectfully in healthcare and research settings. The conditions under which samples are obtained vary with institutional practices and regulatory environments and provide different levels of varied protection from potential harms like bias or misdiagnosis. Whether inadvertent or intentional, misuse or exposure of biobanked

information may have profound consequences for donor wellbeing and for families and communities. A review of 15 Ebola studies found that only eight even mentioned confidentiality (Richardson et al., 2017). Without well-maintained data collection and management systems and regulatory environments, patient and donor rights are easily overlooked in the rush to put systems in place for a public health emergency.

Inadvertent or intentional mishandling of biobanked materials and related information can have profound repercussions for patients and others as during the 2014 Ebola outbreak when many patients and families were stigmatized, ostracized, or subjected to psychological or physical violence. Outrage in Liberia followed the public disclosure by national and international media of the name of a 17-year-old Ebola victim and his family members, and of photographs of children being tested for Ebola and their homes (Internews, 2015). Related fear can impact health-seeking behaviours and hamper response efforts (James et al., 2020; Nuriddin et al., 2018). Serious harms to individuals, families, and communities results from inadvertent or intentional misuse of biobanked materials.

Socioeconomic Inequities That Increase Vulnerability

Public health emergencies with rapid or severe morbidity or mortality may render everyone more vulnerable than they would otherwise be. In low resource communities and countries where socioeconomic determinants of health undermine access to health-promoting resources and even healthy processes of early child development (Macpherson, 2019). Such vulnerabilities are specific to health and form one of the many layers of vulnerabilities reflecting socioeconomic, geographic, and psychological features of individuals and populations (Luna, 2018). Public health interventions and policies are part of the context in which biobanking occurs and must acknowledge and respond to these vulnerabilities if they are to be effective in a given jurisdiction. This bears on all countries but those most vulnerable to the associated failures or harms are LMICs and those with the fewest resources.

In West Africa, trust in research and public health responses are undermined by "decades of social and personal risk, vulnerability and powerlessness" that extend beyond Ebola (Smith & Upshur, 2015). Compounded by fear and violence, this mistrust complicated Ebola responses in the region when patients refused transfer to treatment centres or were "violently freed out of isolation units by their worried families" (Sissoko et al., 2016; Schuklenk, 2014). This was at least in part precipitated by the "profound mistrust and failure to communicate with a frightened public" (Thompson, 2016) and accentuated by the difficulty of translating words and concepts across dialects and cultures (Doe-Anderson et al., 2016). Trust building, community dialogue, and transparency reduce misunderstanding and mistrust (Folayan et al., 2016). The coherence of guidelines and policies are strengthened by attention to such contextual vulnerabilities and adoption of responsive protections (Potter, 1988).

Lasting and Proportional Benefits

CIOMS guidelines (, 2016, note 6) urge wealthy country sponsors, institutions, and researchers to consult and design research priorities, aims, and practice with their LMIC hosts. Early in the 2014 Ebola outbreak, the primary research aim was likely to improve knowledge about patient care and prevention. While benefit sharing with host countries is inherent to this aim, as the outbreak progressed and more was learned, other aims emerged (perhaps of necessity). Successful development and testing of promising medications, vaccines, and other products for prevention or clinical care have commercial benefits for some stakeholders but LMIC host countries tend to receive little or none of these commercial benefits.

Potential commercial benefits to sponsors of such products include lucrative products that may increase revenue for decades. Disclosing these benefits in consultations with host LMICs and institutions about research priorities and design, and in informed consent processes, would enhance transparency that is essential to trust and communication. Failing to disclose them reinforces power differentials between wealthy partners and low resource hosts, facilitates diversion of host resources to research needs without providing fair or proportionate benefits to hosts (employment, infrastructure, education, etc), and undermines trust in public health, medicine, and research (Macpherson, 2019).

Biobanking during the 2014 Ebola outbreak aimed to benefit everyone but commercial and other aims emerged for varied stakeholder groups including research partnerships, grants, and publications. For Sierra Leone, the extent to which these aims may lead to equitable short- or long-term benefits depends greatly on whether the aims reflect their context and priorities. Decisions about whether to preserve samples of scientifically uncertain quality and usefulness might best be resolved through practices and policies that are responsive to contextual vulnerabilities and have the trust and buy in of host stakeholders including communities.

Benefit sharing is challenged by geographic and temporal separation. The sale, sharing, and exportation of biobanked materials or information may benefit some without benefiting host countries, institutions, or individual donors. Ebola vaccines provided to affected communities during the resurgence of Ebola in the Democratic Republic of the Congo (2017, 2018, 2021) and Guinea (2021) are a significant benefit (Henao-Restrapo et al., 2017; WHO, 2020a, 2021; Maxmen, 2020) but such commercialisable products emerge relatively infrequently from research, and their transparent and equitable provision is unusual in North-South research. Another potential benefit is the provision of results to hosts and participants, but such information may not be conclusive for years and, if provided at all, may take the form of academic publications or technical reports with meaning only to specialists.

Contextual Challenges to Disclosure and Understanding

Misconceptions about biobanking and distinctions between research and treatment hinder disclosure and understanding even in wealthy countries. One review found that few patients recruited to research understand the risks of donating materials for biobanking (D'Abramo et al., 2015). Despite establishing a national ethics committee and IRB in SL before the 2014 Ebola outbreak (Ashcroft, 2018), misunderstandings of ethics guidance challenged informed consent processes.

Even during public health emergencies, WHO stipulates that prior to sample collection "*[the patient] should be given access to information about the purpose of the collection, whether their sample will be stored and, if so, the ways in which their specimens might be used in the future…[and]…should be asked to provide informed consent or be given the opportunity to opt out of the long-term storage of their samples*" (WHO, 2016). Whether and how to do this compassionately in the context of an acute Ebola outbreak when collecting materials from patients who are near death and urgently need medical help is unclear. In this context, relatively few may want or understand such information and their surrogates, if available, may be more concerned with helping their loved one or preventing their own infection than with the potential harms of donating. Disclosure and assessment of patient or donor understanding in such conditions is more challenging than otherwise.

The communitarian tradition in many African countries contributes to the resistance of some to informed consent. During the 2009 H1N1 pandemic, benefits to critically ill patients of participating in related research at times justified overriding consent requirements for biobanking (Biros, 2003; Burns et al., 2009; Cook et al., 2010). Ethical uncertainty about this issue led WHO's Ethics Research Committee to request clarifications or amendments to some research protocols it reviewed during the 2014 outbreak (Alirol et al., 2017). CIOMS (2016) permits modifications to and waivers of informed consent for some research in some contexts and much research during the 2014 outbreak likely met these requirements. Many LMICs, however, lack RECs that adhere to internationally accepted procedures as week as resources and training for REC infrastructure and training (Saenz et al., 2014).

CIOMS Guideline #11 (2016) says "When biological materials and related data, such as health or employment records, are collected and stored, institutions must have a governance system to obtain authorization for future use of these materials in research" noting that the "ethical acceptability of broad informed consent relies on proper governance". Commentary adds that "some low-resource settings may be inexperienced in storing and using biological materials. … requirements for community engagement, capacity-building and equitable distribution of burdens and benefits of research as described in other guidelines also apply to biobank research in low-resource settings". Meeting these standards requires resources and knowledge that may be unavailable in LMICs particularly during public health emergencies. Strengthening research capacity and infrastructure in LMICs is essential before another emergency occurs.

Guideline #20 states that research during public health emergencies should be integral to responses, competing priorities and interests should be weighed and balanced, and scientific validity should be ensured and ethical principles upheld. It calls on "researchers, sponsors, international organizations", RECs, and other stakeholders to ensure that research upholds each CIOMS guideline and does not unduly impact the local public health response. It reiterates the need for responsivity to health needs of those affected; equitable distribution of potential burdens and benefits; community engagement in design, planning, and implementation; and data-sharing, dissemination of results, and making effective interventions available to affected communities. It adds that "health officials and research ethics committees should develop expedient and flexible mechanisms and procedures for ethical review and oversight"; holds sponsors responsible for providing protocol and budget to mitigate adverse events; and holds sponsors and RECs responsible for evaluating whether risks to participants during public health emergencies are adequately minimized. Even in wealthy countries, few REC members have knowledge or skills essential to such evaluations. As noted above, biobanking is misunderstood by many in the absence of a public health emergency, and more so during one. Without a clear definition of biobanking, providing disclosure and obtaining informed consent to donate samples, images, or other types of information will remain problematic.

Conclusion

A considerable amount of work and energy has been dedicated to examining the ethics surrounding clinical trials during infectious disease outbreaks. Comparatively little has been done with respect to the ethics of collecting, storing, and sharing diagnostic samples in research during and after public health emergencies. While diagnostic materials are routinely collected during public health emergencies and stored, biobanking is imprecisely defined and understood and this bears on transparency of information essential to communication and trust.

Local context, material transfer agreements, and other factors determine whether materials and biodata remain in the host country, are transported across borders (and to what countries and institutions) or destroyed. Ownership of and access to biobanked materials may benefit some while harming others. Transparency about what will and may be done with materials and information collected is essential to obtaining informed consent from donors and participants. Benefit sharing plans should be negotiated transparently and fairly, recognize and minimize power imbalances between parties, transparently, and agreed before a study is undertaken. What party will provide resources for implementation of biobank data collection and sharing practice and policies must be determined. To negotiate meaningfully and effectively, resources for research and research ethics must be provided to LMIC hosts and this may itself constitute a research benefit. Each disease outbreak and public health emergency reaffirms the need to improve research capacity and influence in

negotiations and the importance of better understanding, transparency, and trust for all stakeholders in biobanking.

Notes

1. *These numbers reflect a search using key words 'biobank, repositories, specimens, and fluids' of the International Compilation of Human Research Standards from the U.S. Department for Health and Human Services, Office of Human Research Protections. 2018. Available at: https://www.hhs.gov/ohrp/international/compilation-human-research-standards/index.html. Accessed Nov 29, 2018.*
2. *An Ebola Treatment Centre (ETC) can be described as a self-contained medical facility where patients positive for the Ebola virus can be isolated and treated appropriately. These facilities often include: isolation wards, a pharmacy, diagnostic laboratory, waste management systems for highly contaminated items, specially designed decontamination stations and strict demarcation of containment areas/levels.*

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Chapter 19
Ethical and Legal Considerations in Genomic Data Sharing: Evolution of the Discourse and the Road Ahead

Adrian Thorogood and Davit Chokoshvili

Abstract The importance of genomic data sharing has long been recognized across a range of contexts, from community resource projects to biomedical research seeking insights into diseases, to the provision of personalized healthcare. However, so far, the opportunities of genomic data sharing at scale have not been fully realized. This chapter explores some of the main ethical and legal issues posed by genomic data sharing among institutions and across jurisdictions. The most vexing issues stem from concerns over data privacy and security, consent, and protection of data subjects' fundamental rights. Additional challenges relate to meeting legal consent and transparency requirements in some jurisdictions (including the European Union) where the recipients and uses of data cannot be fully specified in advance. Ethical and legal data governance frameworks play an important role in addressing these concerns and enabling responsible data sharing. Divergence between regulatory frameworks, privacy protection, consent models, and governance frameworks across contexts and countries remain a barrier to scale data sharing across networks, but can be addressed through a combination of institutional coordination and creative infrastructure design.

Keywords Genomic data sharing · Responsibility · Open science · Governance · Data sharing networks

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Introduction

In the two decades following the completion of the Human Genome Project, the field of human genetics has seen remarkable progress. Rapidly diminishing costs of genome sequencing, coupled with continued improvements in next generation sequencing technologies, have resulted in a wealth of genomic data (Birney et al., 2017; Narayanasamy et al., 2020).

Genomic data are routinely generated in both clinical and research contexts and are increasingly linked with rich related health data to better understand health and disease (Birney, 2019, Rehm et al. 2021). In this respect, large-scale genomic data resources offer unprecedented opportunities to accelerate progress in genomic medicine, especially if they can be connected across institutions and countries (Byrd et al. 2020). To realize the full potential of genomic research and precision medicine, it is essential to widely share genomic data with researchers and health professionals who can effectively use it (Knoppers & Joly, 2018). However, accomplishing large-scale genomic data sharing remains a challenge due to a range of ethical, legal, technical and incentives barriers.

This chapter explores the history and the current landscape of genomic data sharing, and then moves on to discuss key ethical and legal issues. The most pressing of these issues relate to the privacy, autonomy, and fundamental rights of sequenced individuals, whether they be research participants or patients. Nevertheless, the genomics community continues a long tradition of effective and responsible data sharing, and continues to innovate along both of these dimensions.

History and Rationale for Genomic Data Sharing

Over the past decades, genomic data sharing has expanded in scope and across contexts, in line with the general progress made in the fields of human genetics and genomics, bioinformatics, and database technologies in research and healthcare. Data sharing played a prominent role during the Human Genome Project (1990–2003), and continues to expand to encompass broader data types. This includes data from any genome-wide assay, most prominently whole-exome sequencing (WES) and whole genome sequencing (WGS). These assays are now delivered on the scale of thousands if not millions of individuals (Birney et al., 2017; Narayanasamy, et al., 2020). Genomics also encompasses data beyond the human germline, including sequencing of tumor cell mutations, RNA sequences and proteomic data (Boycott et al., 2017). Molecular sequencing can now even be pursued at the resolution of tissues, or even single cells (Regev et al., 2018).

Genomic sequencing is adopted in increasingly diverse contexts. Genomics platforms are now common in numerous areas of clinical and translational research, and are also gradually entering healthcare, for example, to facilitate rare disease diagnosis and targeted cancer treatment (Birney et al., 2017). Genomic data sharing is

therefore no longer confined to the creation of reference maps and community resources between research laboratories. It is also increasingly discussed in connection with general debates over the transparency and reproducibility of biomedical research, and the appropriate secondary use of healthcare data (ACMG Board of Directors, 2017). The policy rationales commonly deployed in support of genomic data sharing can therefore differ slightly depending on the context.

Building Publicly-Funded Community Resources

Genomic data sharing naturally emerged in the context of the Human Genome Project. This seminal global collaborative effort aimed at creating the first human genomic reference map (Collins et al. 2003). The Bermuda Principles in 1996 famously established an agreement between the world's major publicly funded sequencing centers to release newly obtained fragments of genome sequence data publicly within 24 h. The common understanding was that no single lab could sequence the entire genome alone (especially not faster than private-sector initiatives); that coordination between labs was needed to avoid duplication of effort; that waiting for sequences to be published would make these issues worse; and that the human reference genome was a common good (and the labs paid to generate it with public funds had an obligation to make it available) (Contreras, 2011).

Following the success of the Human Genome Project, a consensus view emerged that rapidly sharing genomic data after its generation should be an aspiration under all publicly funded research endeavours that qualified as community resource projects. Accordingly, the Bermuda Principles were subsequently reaffirmed by members of the biomedical research community, notably at the Wellcome Trust-sponsored meeting in Fort Lauderdale, US (2003) and the Data Release Workshop held in Toronto, Canada (2009). However, these subsequent discussions also introduced more nuanced views concerning the mutual responsibilities of data generating organizations, funding agencies, and data users benefiting from the availability of the community resource. A common understanding emerged that data-generating organizations required incentives and recognition, in the form of data embargo periods that allowed closed consortia to publish first results before the resource was made open to the wider research community. It was recognized that much of the data collection activities within publicly-funded research projects tend to be hypothesis-driven, which is qualitatively different from open-ended data collection for its broad utility. This provides further justification for delaying release of data to the scientific community, granting data generating researchers an exclusivity period to perform their planned analyses (Contreras, 2011; Birney et al., 2009; Cook-Deegan et al., 2017).

This more nuanced understanding of potentially conflicting objectives and interests of the key stakeholders has resulted in genomic data sharing policies aimed at striking a balance between the interests of different stakeholders involved in publicly funded research. For example, it has become common for public funding

agencies to allow for specified embargo or exclusivity periods before requiring funding beneficiaries to deposit their data in databases accessible to external users. Furthermore, data-generating organizations often remain the "owners" of the shared data, thus retaining some degree of control over whether or not, and under what conditions, external researchers can use their data (Doshi et al., 2016). These measures are viewed as a necessary compromise to incentivize and reward researchers performing primary data collection. The general principle that data generated through publicly funded projects should be shared with the research community remains strong. The policy debate focusing on how to strike an ideal balance between competing interests of the key stakeholders is still ongoing, including the rights and interests of sequenced individuals, their families and their communities (Cook-Deegan et al., 2017).

Open Science

A narrative in the broader scientific context closely related to genomic data sharing is open science. The fundamental idea behind the open science narrative is that once new scientific knowledge is generated, it should be widely shared as early as practically feasible (Friesike et al., 2015). This encompasses a range of practices across the scientific lifecycle, from study registration, to open access publications, to sharing research data alongside publications (or even in real time) (Carroll, 2018). The open science ethos holds that data sharing helps advance science by enhancing the reliability and reproducibility of research findings, while at the same time promoting a collaborative culture within the scientific community (Friesike et al., 2015; Carroll, 2018; Woelfle et al., 2011).

The main arguments at the heart of the open science narrative can be readily applied to support the sharing of genomic data generated as part of health research projects. Sharing the original data used to perform a study is essential for the reproducibility of research (Cook-Deegan et al., 2017; Stodden, 2011). Reproducibility, and hence verifiability, of research findings is growing in importance with the emergence of genomic medicine, as novel insights obtained through genomic studies are more commonly used to advance healthcare. For example, many clinical trials routinely rely on genomic data to gain a more accurate understanding of a drug's safety and efficacy profile in a specific patient population (Patrinos, 2018). Similarly, genomic data is increasingly utilized to help personalize the prevention, diagnosis, and treatment of diseases with a genetic component (Nardini et al., 2021). As the medical utility of genomics grows, so does the importance of sharing genomic data among researchers to aid translational medicine efforts.

Sharing data can also accelerate scientific research by making data available to a community of researchers able to use data effectively and creatively (Woelfle et al., 2011). Combining diverse datasets allows researchers to test their research questions and hypotheses across many different populations, linking genomic data with other forms of data to help derive new insights (Boycott et al., 2017). Accelerating

scientific research by removing barriers to data sharing is also arguably a moral imperative, embedded in the human right of everyone to benefit from scientific advancement (Knoppers et al., 2014). As such, making genomic data widely available for research should be seen as a prima facie duty of biomedical researchers and an aspirational goal of the scientific community (Schickhardt et al., 2016; Yotova & Knoppers, 2020).

Open science faces numerous ethical, legal, and policy barriers. In particular, meaningful integration and re-use of scientific datasets essentially depends on their quality and standardization. Responsible data management has been encouraged by the Findable, Accessible, Interoperable, and Reusable (FAIR) principles (Wilkinson et al., 2016). Implementation of the FAIR principles in genomics has been a topic of major interest for the biomedical research community. In recent years, significant progress has been made towards FAIRifying genomic data and associated clinical data, through the adoption of common data standards, emergence of dedicated genomic data infrastructures, and improvements to data provenance methods (Harrow et al., 2021). This has helped create networks of interconnected research institutions who can meaningfully share and re-use genomic data. Examples of such networks include large international research platforms, notably European initiatives such as the European Genome-phenome Archive (EGA) and the European Life Science Infrastructure (ELIXIR) (Harrow et al., 2021; Fernández-Orth et al., 2019).

Improving Patient Care in Clinical Genomics

With the emergence of genomic medicine, another narrative is emerging about sharing clinical genomic data. This is a special case of a broader debate over the appropriate sharing and secondary use of healthcare data for purposes such as research and quality control (Jungkunz et al., 2021). In genomics, there are calls for clinical laboratories to make data available to other laboratories in order to improve patient care. There are two scenarios in which medical benefits of genomic data sharing are particularly conspicuous: (i) establishing medical diagnosis in patients with a suspected rare disease and (ii) improving the clinical validity of genetic tests routinely utilized in the healthcare context.

The field of rare diseases has long been riddled with challenges associated with establishing accurate medical diagnoses. Due to the paucity of clinical cases in many rare diseases, medical professionals have traditionally lacked the insight to recognize disease symptoms and diagnose the condition. This often leads to lengthy diagnostic odysseys during which rare disease patients and their family members unsuccessfully seek answers to their medical questions (Carmichael et al., 2015). With genetic and genomic data sharing, it has become possible for clinical geneticists to resolve many cases of diagnostic odysseys. For example, when the presence of a rare disease is suspected, the geneticist may order broad genetic analysis such as WES/WGS. The analysis may identify one or more candidate mutations

responsible for the patient's medical condition. However, in the absence of similar clinical cases, it may not be possible to determine if the mutation is causative of the condition. In this respect, it is critically important for clinicians to access information on other patients with similar clinical symptoms and/or genotypes. In response to this need, numerous data sharing initiatives have been established where clinicians from participating institutions can securely share details of their patients, allowing for accurate clinical case comparison essential for diagnosis. In recent years, there have been numerous reports of successful diagnoses of rare diseases facilitated by clinical data sharing platforms (Taruscio et al., 2020).

As genomics enters clinical care, a growing number of medical diagnostic laboratories are performing genetic analysis. Genetic tests carried out by clinical laboratories tend to be highly accurate analytically, meaning they can correctly identify the presence of genomic sequence variants. However, genetic testing laboratories often diverge significantly in the interpretation of these variants. Clinical interpretation of a particular genetic variant can vary considerably across laboratories, ranging from benign to pathogenic (Pepin et al., 2016; Chokoshvili et al., 2018). This discrepancy is concerning, as it may have significant implications for the quality of subsequent medical care of patients informed by genetic test results. Systematic data sharing between clinical genetics laboratories helps to address this problem by allowing the aggregation and comparison of interpretations, as a form of quality control and assurance. Such sharing is supported by databases like ClinVar, a prominent, publicly available resource for sharing variant interpretations and supporting evidence, providing the clinical genomics community with guidance on consensus interpretations (National Library of Medicine – National Center for Biotechnology Information, 2021). Additionally, multiple countries have established national networks of healthcare institutions and diagnostic laboratories operating within national health systems who securely share genomic and associated clinical data, building a shared knowledge base of clinical evidence for the interpretation of genetic test results. Examples of such networks include national health registries in the Nordic countries (Bakken et al., 2020; Ameur et al., 2017) and the Canadian Open Genetics Repository (Lerner-Ellis et al., 2015). In the US, professional societies such as the American College of Medical Genetics and Genomics (ACMG) have called for extensive sharing of laboratory and clinical data from genetic testing to improve patient care and to advance test development (ACMG Board of Directors, 2017).

Barriers to clinical genomic data sharing still remain. Privacy and confidentiality are an issue, especially where there is uncertainty over the identifiability of variants or the associated evidence. Curation and quality control of variant annotations may require significant expertise and resources. Addressing this challenge will require greater investment in infrastructure and standardization of clinical evidence-reporting (Association for Molecular Pathology, 2021). Despite vocal moral appeals for laboratory data sharing, financial incentives are lacking (Denton et al., 2021). Private laboratories in particular may be unwilling to share their data. Some private laboratories specialized in a particular clinical domain may build proprietary databases superior to those of their competitors. This was the case with Myriad Genetics,

whose early dominance in the market for breast cancer genetic testing allowed the company to build the most reliable variant annotation database for hereditary breast cancer (Conley et al., 2014). The shift of genomics into healthcare has also highlighted the limited diversity of populations addressed by genomic science. Disease risk variants more specific to under-represented populations may be missed, and polygenic risk scoring for common and complex disease will be less accurate (Hindorff et al., 2018). A range of international and national projects are seeking to improve representation in genomic reference databases and studies, including the US-based All of Us Initiative (Devaney et al., 2020), the H3Africa Consortium (Mulder et al., 2018), and the Human Pangenome Reference Consortium (Miga & Wang, 2021).

Some of the most vexing challenges for genomic data sharing across contexts are those stemming from the need to safeguard the privacy and autonomy of sequenced individuals, as well as their family members and communities, the focus of the remaining sections of the present chapter.

Privacy Risks

Genomic data - particularly WES/WGS data, and to a lesser extent smaller-scale sequence or genotype data - has two defining characteristics. First, genomic data is deemed highly sensitive, owing to the fact that it conveys substantial information about important aspects of the data subject's life, including information about disease predispositions, family relationships, and ancestry. Second, genomic data is a unique barcode, stable over time, which can be potentially used to infer the identity of the data subject (Jones et al., 2020). Given these two characteristics, genomic data has been increasingly viewed as a special form of data, with some authors embracing genetic exceptionalism, a view that genomic data is so unique that it necessitates a distinct governance and regulatory framework (Green & Botkin, 2003). The notion of genetic exceptionalism is contentious, with dissenters highlighting ways in which genomic data is similar to other forms of medical data (Martani et al., 2019). There is, however, a general agreement that the sensitive and potentially identifying nature of genomic data calls for a responsible approach to its processing. This is also reflected in the European General Data Protection Regulation (GDPR), which regulates the processing of personal data, i.e., data about an identified or identifiable individual (Shabani & Marelli, 2019). The GDPR explicitly defines genetic data as a special category of data (Article 9(1)), which can only be processed under exceptional conditions (Article 9 (2)). While the GDPR provides an avenue for processing special category data for research purposes, processing must be subject to adequate technical and institutional measures (Article 89 (1)). In view of these considerations, it is worthwhile to explore the main factors that make genomic data special, that is, its sensitive nature and potential identifiability of data subjects.

Genomic Data Is Sensitive There are several factors accounting for the sensitive nature of genomic data. First, genomic data contains information pertaining to an individual's current and future health, including predisposition to diseases. The majority of this information is probabilistic and should be interpreted as one of many factors contributing to health outcomes, particularly for common complex diseases (Franks et al., 2021). However, for certain conditions, particularly those following the monogenic mode of inheritance, genetic information can be highly deterministic, conveying greater certainty as to the current or future health status of an individual (Cassidy et al., 2008). Furthermore, with the advent of polygenic risk scores, which aggregate the effect of many genetic variants across the genome, it is expected that the reliability of medical insights obtained from genomic, especially WGS, data will continue to increase in the future (Lambert et al., 2019). The growing medical relevance of genomic data exacerbates the concern that the disclosure of genomic data to third parties could lead to discrimination and stigmatization of individuals. Some of the commonly discussed forms of discrimination include a potential impact of an individual's access to employment and health insurance (Adjin-Tettey, 2012). Although many jurisdictions have laws to prevent employment and insurance discrimination based on genetics, evidence is accumulating that such practices persist (Tiller et al., 2020). Moreover, genetic discrimination should be conceptualized in a broader manner, encompassing subtler forms of stigmatization and exclusion typically falling beyond the scope of anti-discrimination laws. For example, evidence suggests that many individuals with a known genetic predisposition for life-limiting diseases experience social stigmatization and often report unfair treatment by peers (Wauters & Van Hoyweghen, 2018). Importantly, some of the issues arising from the sensitive nature of genomic data are further amplified by the fact that genomic data contains information about health risks that may be shared by family members and biological relatives of an individual. Therefore, unauthorized access or misuse of an individual's genomic data may result in harms for multiple persons. In certain cases, harms may extend to larger groups of genetically related individuals, such as members of a particular ethnic group, whose shared unique genetic markers render them readily distinguishable from the general population (Jackson et al., 2019).

Genomic Data Is Potentially Identifiable Genomic data constitutes a unique blueprint of an individual, which remains largely unchanged over the lifetime. This renders the information contained within genomic data potentially identifiable – i.e., it can be used to infer the identity of the individual whose genomic data is being analyzed. Early evidence that genomes carry unique variants that can be used to potentially re-identify individuals came in 2004, where authors demonstrated that human genomes can be uniquely identified from as few as 30–80 statistically independent single nucleotide polymorphisms (SNPs) (Lin et al., 2004). Since then, numerous re-identifiability methods have been described that utilize genomic data, often in conjunction with other forms of personal, medical, or genealogy information (Shabani & Marelli, 2019). This has led to the general view that genomic (and

particularly WGS) data are inherently identifiable and cannot be irreversibly anonymized (Jones et al., 2020; Mascalzoni et al., 2019).

Practically speaking, identifiability is often viewed as context-dependent (PHG Foundation, 2020). For example, although genomic data can be used to infer important physical and medical attributes of the data subject, in many cases, this information in isolation will be insufficient for establishing the data subject's identity. The party attempting to identify the data subject will require access to additional information, such as electronic health records, biometric data, or personal identifiers like the data subject's name. The relevant contextual factors include on the one hand, the availability and cost of technical measures for re-identification, access to cross-referenceable databases, and incentives for re-identifying data subjects, and on the other hand, appropriate safeguards aimed at protecting the privacy and confidentiality of genomic data subjects (Shabani & Marelli, 2019).

A complete anonymization of genomic data is not only difficult but may often be undesirable. Anonymization tends to undermine the utility of data for research or clinical purposes. An inability to re-identify a sequenced individual would also prevent recontact about clinically actionable findings (Lysaght et al., 2020). In genomic data sharing contexts, the focus tends therefore to be on ensuring privacy and confidentiality of data subjects while also maintaining a link between data subjects and genomic data.

A central privacy safeguard employed to minimize privacy risks in research contexts is coding. Coding can be broadly defined as the practice of (reversibly) separating identifiers from a dataset so that it is no longer directly attributable to the data subject without additional information (for example, a key code) (Shabani & Marelli, 2019). Pseudonymization is a similar legal concept under the GDPR of separating identifying information from a dataset. The additional information required for re-identification must be subject to appropriate technical and organizational safeguards (Article 4(5)). Under the GDPR, pseudonymized data is considered personal data and, therefore, is within the scope of the Regulation. Pseudonymization does reduce the compliance burden, and is an important data protection safeguard in its own right that reduces legal risks.

Robust de-identification and coding/pseudonymization are especially important where genomic data is broadly shared with external researchers. Organizations providing access to data have central responsibility to adequately protect data subjects from the risks of re-identification. The NIH as part of its Genomic Data Sharing Policy (GDS) mandates that institutions are required to broadly share genomic data for research purposes, but also that they must adhere to both data de-identification requirements under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, and broader data protection standards set forth by the Health and Human Services (HHS) Regulations for Protection of Human Subjects (The National Institutes of Health, 2014). Importantly, the GDS emphasizes that institutions should adopt a proactive and continuous approach to evaluating privacy and re-identifiability risks, as opposed to merely passively implementing prescribed

data de-identification techniques, taking into account relevant recent developments in the domain of data privacy and security (Office for Human Research Protections, 2017). The necessity of this approach is becoming increasingly evident with the emergence and rapid evolution of privacy-preserving technologies, such as secure multiparty computation, homomorphic encryption, and differential privacy techniques. While all of these methods offer distinct privacy advantages in genomic data sharing, they typically come at the expense of diminished data accuracy or increased computational costs, significantly affecting the utility of genomic data to researchers. As a consequence, substantial improvements to existing privacy-preserving methods are being continuously proposed (Froelicher et al., 2021), resulting in a constantly changing landscape. Given the rapid pace of evolution of privacy-preserving technologies, institutions engaged in genomic data sharing need to continuously monitor the field for new developments.

The identifiability and potential insights contained in genomic data present important risks of misuse. Genomic data is of considerable value in forensics, where it can be used for the purposes of law enforcement, including criminal investigations. Consequently, access to genomic databases is of great interest to public authorities and law enforcement agencies, raising concerns over potential violations of data subjects' privacy rights and possible misuses of genetic information by authorities (Skeva et al., 2020). These concerns are particularly pronounced in relation to less democratic societies, where authoritarian governments could use genomic data to systematically target and persecute certain groups of the population, such as ethnic minorities. An often cited example in this regard is the use of genomic data by the Chinese government in its oppressive policies against the Muslim Uyghur population (Moreau, 2019). However, even in the Western countries, where genetics-based discrimination by governments is currently uncommon, there is a growing public awareness that genomic data can be misused by government and law enforcement authorities. If left unaddressed, these worries may erode public trust in both genomic research and clinical genomics (Curtis et al., 2019). Moreover, genomic datasets constitute a highly valuable resource for commercial research purposes such as drug development and biomarker discovery by pharmaceutical companies. This creates strong financial incentives for institutions holding genomic data to monetize this resource by entering in commercial data-sharing agreements with for-profit entities. However, this raises fairness and transparency issues, particularly where data subjects are not aware that their data is used for commercial research purposes. Studies with the general public indicate that members of the public tend to distrust commercial research entities and may not be willing to have their genomic data shared for for-profit research purposes (Milne et al., 2019; Critchley et al., 2015). Consequently, attempts to monetize WGS data in the absence of data subjects' express permission are likely to hurt genomic research on the whole and discourage public participation.

Data Access Governance

Given the sensitivity and identifiability concerns relating to genomic data, genomic databases cannot generally be made publicly available. Institutions seeking to share rich genomic and related health data must be supported by appropriate organizational and technical safeguards aimed at ensuring genomic data privacy and confidentiality. Data access governance frameworks play a key role to safeguard the rights of the data subjects while at the same time enabling sharing of genomic data with parties who can effectively use it (Shabani et al., 2021a, b). Access governance for data sharing goes beyond security policies and procedures. Besides cybersecurity threats and resultant data breaches associated with external data sharing, additional data misuse risks are introduced by the uncertainty as to the intentions of external parties accessing the data.

Early forms of access governance in genomics emerged in the mid-2000s, shortly after it became clear that genomic data could be used to infer personal information about data subjects. Recognition of these privacy concerns stimulated several major research organizations and data-storing platforms to adopt controlled access mechanisms, whereby access to data is only provided to authorized researchers through secure means (Contreras, 2011). Although public access to genomic data has continued to exist alongside controlled access models, the type of data available publicly is typically of lower scope and utility, often limited to aggregate allele frequencies and descriptive characteristics of large patient cohorts. By contrast, more granular and record-level data is typically subject to controlled access procedures (Villanueva et al., 2019). In recent years, introducing a tiered approach to data access models has been increasingly discussed, whereby different levels of data access are provided, seeking to better balance openness and privacy (Broes et al., 2018).

Access governance frameworks include policies, processes, and enforcement mechanisms (Kaye et al., 2016, 2018). Access policies define the eligibility criteria for data access, as well as the procedures and specific conditions under which data can be accessed. Having a clear access policy supports procedural fairness and facilitates communication with parties interested in gaining data access, helping them understand whether they are eligible and how to submit an access request. Governance also includes access processes where data access requests are evaluated by a Data Access Committee (DAC). DACs are typically composed of members whose collective expertise spans the fields of medicine, biomedical research, data science, law and biomedical ethics (Shabani et al., 2016). DACs have a dual-purpose nature: i) to protect the rights and interests of data subjects, ensuring that data access and use conforms to their reasonable expectations, and ii) to help make data effectively available for use by researchers to advance scientific knowledge. DACs are a particularly valuable component of governance frameworks where data is made available outside institutions or close consortia to diverse research communities for

broad research purposes. Such non-discriminatory data sharing often requires careful deliberation. To support this delicate balancing act between openness and privacy, the Global Alliance for Genomics and Health (GA4GH), an international standards body, has articulated international standards for DACs, emphasizing the transparency and consistency of DACs in their decision-making process (Voisin et al., 2021). Standardization of access processes can also facilitate coordination between DACs, facilitating access to integrated networks of genomic databases.

Finally, access governance frameworks typically incorporate contractual safeguards in order to reduce the likelihood of data misuse by external researchers after access has been granted (Shabani et al., 2021b). In practice, this is commonly accomplished by embedding specific contractual clauses in legally binding data access agreements (DAAs, also referred to as data use agreements and data transfer agreements) which clearly delineate the obligations of researchers and spell out what constitutes unacceptable use of the data (Joly et al., 2011). DAAs can be an important communication tool for ensuring accountability on the part of researchers. Potential weaknesses of existing DAAs are a lack of enforceability and standardization. This can lead to reluctance to share, or prolonged negotiation over terms (Mello et al., 2020). Consequently, as with other components of access governance frameworks, it has been recommended to standardize DAAs such that they can better meet the needs of research institutions operating in the context of cross-border data sharing (Saulnier et al., 2019).

In recent years, there has been considerable interest in actively engaging communities of data subjects in designing access governance frameworks and participating in access processes. This reflects broader trends towards more participatory scientific research, epitomized by the emerging paradigms of patient empowerment and citizen science. Engagement can help to ensure access governance more accurately reflects the rights and best interests of data subjects. Data sharing initiatives may establish a dedicated advisory board of community representatives (Milne et al., 2021). This is best done early in the project's development so engagement can meaningfully shape governance. Community representatives may even directly advise or participate on DACs. Community engagement in access governance may be especially useful where data subjects belong to a special or vulnerable group requiring additional protection (Ogunrin et al., 2021). Mechanisms to involve smaller groups or even individual data subjects are currently being explored (Milne et al., 2021; Largent et al., 2018).

Governance of Genomic Data Sharing Networks

A major factor shaping the evolution of access governance models is the proliferation of databases and associated importance of data sharing networks established and coordinated by multiple resources. Data sharing networks enable aggregation of datasets from different sources in a manner that conforms to the FAIR principles, thus transforming heterogeneous datasets into a valuable common pool resource for

research. These networks may be supported by common data access infrastructure as well as governance of varying complexity. In their simplest form, data repository networks can be fully centralized, with data from the participating institutions being directly deposited in a common storage repository. Access to this repository by third-party researchers may also be governed by a common access policy and central DAC (though data providers may also retain control over access to their own data). A notable example of a centralized approach is the controlled access database of the International Cancer Genome Consortium (ICGC), which was implemented in 2011 (Joly et al., 2012). Given the sensitivity and perceived value of rich genomic and related health data, legal and institutional barriers may restrict data transfers to central repositories. In a distributed network, datasets – as well as control over who access them – remain with the individual data providers. Distributed networks may still be integrated by some level of shared central infrastructure and coordinated access processes. The network could allow for a common access process to facilitate user access to, and linkage across multiple databases, such as a common (meta) data catalogue, central access portal for launching requests, and even a standard access request form (Harrow et al., 2021). In general, there are efficiency trade-offs associated with data networks where access decisions are made locally. Fragmented access to databases can increase the administrative challenge for researchers seeking access to data, who may also encounter a patchwork of rules, as well as inconsistent decisions from different DACs operating independently (Devriendt et al., 2021).

Federated data networks are a flexible alternative in which data providing organizations retain control over their data in secure repositories, while users are still able to draw insights across the network (Thorogood et al., 2021). Genomic datasets remain under the control of contributing organizations or countries, and users are typically granted only remote access to the data within secure repositories or processing environments. Though the data does not leave the local site, data and technical standards enable the possibility for users to run an analysis at each site, receive a result, which can then be combined into an aggregate result (Suver et al., 2020). Data providers can agree to coordinate access governance to varying degrees, though the insistence on physical control over data is likely to translate into local control over who accesses data. Federated data networks offer the benefit of security and control, and may allow the sharing of some data that would not otherwise be shared. Data utility is dependent on data providers' ability to implement common data and technical standards and to sustain data availability over time. In terms of ethics and data protection, federated approaches offer the advantage of limiting data copying and strengthening local accountability, but do not obviate requirements for consent, ethics approval, or compliance with data protection principles. Given the high costs of standardization and local secure hosting, federation is most appropriate between large-scale genomic databases with the mandate and resources to share in this manner (Thorogood et al., 2021).

International networks can present practical problems for coordinating the ethical oversight of research. It is a basic ethical principle that biomedical research involving human subjects that protocols be subject to review and approval by a

competent research ethics committee (REC). Research projects only involving secondary use of genomic and related health data may or may not be required to obtain such an approval, depending on the country. Different requirements and standards for research ethics review can lead to coordination challenges where data are shared across borders. Another problem is that projects seeking to integrate data across multiple institutions and countries may require multiple, potentially duplicative research ethics reviews, leading to administrative delays and costs without necessarily improving protection of human subjects. Many jurisdictions are already moving to coordinate research ethics review of multi-site health research. Research ethics oversight could be coordinated internationally through mutual recognition, delegation, or federation between RECs (Dove et al., 2016). Given the common objectives and heritage of national health research regulatory frameworks, recognition of equivalence may even be possible at the level of national norms, rather than individual decisions (Thorogood & Beauvais, 2021). Coordinated review is more justifiable for data-intensive research that tends to involve different types of risks than clinical studies that can arguably be managed through responsible governance. Any such proposals will depend on improved standards and transparency of REC processes to promote trust in these processes and offer equivalent protections (Voisin et al., 2021).

Informed Consent for Genomic Data Sharing and Research Use

It is imperative for any ethically sound research involving human subjects to ensure that the research is conducted in a manner that respects the fundamental rights of the participants. Individuals must not be enrolled against their will, either through coercion, deception, or lack of transparency. This fundamental ethical principle is typically operationalized through the notion of informed consent. Informed consent is commonly defined as the process whereby individuals can voluntarily choose to participate in a research study after being adequately informed on the purposes, methods, and risks associated with the participation (Manti & Licari, 2018).

Informed consent is a basic ethical and legal requirement in biomedical research. It remains unclear, however, how to apply this principle in contexts where samples and/or data are stored and shared for broad research purposes. Many authors have questioned whether consent for long-term storage and subsequent research use of genomic data can be truly informed. Given considerable uncertainty surrounding future research applications of genomic data, it is not feasible to provide detailed information to the consenting individual at the time of recruitment about the specific projects for which their data may be used in the future, or the future implications and risks of genomic data sharing (Hallinan, 2020; McGuire & Beskow, 2010; Porteri & Borry, 2008).

Consent to participate in genomic research and to share data is even more fraught in clinical contexts, where patients may be vulnerable due to illness or power imbalances with physicians, and may fail to distinguish between standard care and research interventions (therapeutic misconception) (Hiller & Vears, 2016; Byrjalsen et al., 2020). Although these issues do not necessarily invalidate hospital-based recruitment, they highlight the need for additional organizational measures to enable voluntary and sufficiently informed consent, such as separate consent processes and choices. Barriers to a freely given consent to processing of personal data in health research is also seen as problematic in the context of the GDPR in Europe (European Data Protection Board, 2019). These challenges have prompted decades of proposals and debate over how to improve consent models for genomic data sharing (Greenwood & Crowden, 2021; Henderson, 2011).

Presumed Consent

The argument that informed consent for genomic data sharing has major limitations raises the question of whether informed consent, in its current form, is absolutely necessary to enable ethically appropriate sharing and reuse of genomic data.

Despite the centrality of informed consent in the bioethics discourse, it appears that under certain circumstances, ethically responsible research can be carried out on previously collected genomic data in the absence of explicit informed consent. In this respect, valuable insights can be drawn from the experience around legacy datasets, i.e. collections of genomic and related health data for which consent from data subjects is either missing or does not fully address re-use of genomic data for broader research purposes, and associated data sharing. In many countries, research ethics committees can authorize re-use and sharing of valuable, previously collected health research data, considering scientific merit, the impracticability of renewed consent, lack of objection, and minimal risk of adverse effects on individuals (Thorogood, 2020; Wallace et al., 2020; Parker et al., 2019).

The reality that informed consent can be waived for at least some secondary research purposes could be used as an argument to support prospective collection and storage of genomic data and/or patient samples without an explicit consent for secondary use or sharing. Crucially, this does not mean that the consenting process is completely abolished, depriving data subjects of any possibility to learn about, or withdraw from future research. Rather, proposed solutions embracing this approach can be best thought of as presumed consent models: while they do not rely on a data subject's explicit stated permission, they inform the data subject about the intended sharing and secondary use of data and explain how they can opt out of future research. While under this model opting out requires greater effort than answering a question on the consent form, it is critical that an opt-out procedure exists and is clearly explained to the data subject (Chen et al., 2017; Dankar et al., 2019). The principal advantage of presumed consent is that it is conducive to high rates of

research participation. Concerns about individual autonomy are largely offset by transparency and a possibility to subsequently withdraw participation. At the same time, by introducing additional barriers to withdrawal, presumed consent models ensure that the option is only exercised by those data subjects who strongly oppose being enrolled in research.

An implicit ethical rationale behind presumed consent is that the risks to physical integrity posed by clinical research are of a much higher magnitude than the informational risks of data-intensive research, especially where those informational risks are managed through appropriate data privacy and security measures. However, this argument can be challenged in view of the uncertainty regarding risks of harm associated with future applications of genomic data. Privacy concerns with genomics research and particularly international data sharing mean that the availability of exceptional waivers may very much depend on contextual factors including robust privacy and security measures (Gainotti et al., 2016; Ballantyne et al., 2020). Moreover, presumed consent models may not be legally appropriate tools for genomic data sharing at an international scale. In jurisdictions where informed consent is a legal prerequisite for processing genomic and other personal data, presumed consent models may be insufficient for data access and research use. For example, under the GDPR, consent can only be valid if it is obtained through a "clear affirmative act" by the data subject (Recital 32), essentially rendering presumed consent inadequate. This means that research institutions required to use consent as the legal basis for data processing under the GDPR, cannot legally access genomic data that had been collected based on presumed consent.

Broad Consent

Broad consent is a popular approach where informed consent is solicited for future research of certain types under a defined governance framework, as opposed to consenting to a particular study (Steinsbekk et al., 2013). Broad consent seeks to strike an ethically acceptable balance between two important objectives. On the one hand, broad consent aims to ensure respect for data subjects by informing them about the key aspects of the research framework and allowing them to decline participation in secondary research if they so choose. On the other hand, broad consent recognizes that the practical challenge of obtaining a specific consent to each study may stymy scientific advancement and improvement in human health (Grady et al., 2015; Richter et al., 2018). Critics of broad consent point out persistent uncertainty over future uses of genomic data and risks of sharing (Stein & Terry, 2013). There is a real possibility that some data subjects will end up participating in a study that they would not have consented to (Mikkelsen et al., 2019). Tension between these objectives can be greatly reduced, however, through an appropriate governance framework that offers robust privacy and security safeguards, appropriate oversight of secondary use, ongoing transparency, and options to withdraw participation (Courbier et al., 2019). There is also concern about the ongoing validity of broad

consent over time. Individual's values and preferences are likely to evolve, alongside changing scientific and political realities. Changes in an individual's legal consenting capacity may also threaten the legitimacy of broad consent, for example, where minor participants reach the age of majority. This concern is addressed to some degree by ongoing transparency and opt-outs, but (periodic) recontact to reaffirm consent may also be needed in some contexts (Mikkelsen et al., 2019; Pacyna et al., 2020).

While the GDPR generally insists that consent to the processing of personal data be informed and specific, it is not incompatible with the ethical notion of broad consent (Zenker, 2021). First of all, consent need not be used as the legal basis for sharing and re-using genomic and related health data, in which case an ethical broad consent combined with ongoing transparency may be sufficient to satisfy GDPR principles. Where consent is used as the legal basis for data processing, the GDPR recognizes the practical need for a broad consent, with Recital 33 acknowledging that "it is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection." Consequently, Recital 33 states that data subjects should be allowed to "consent to certain areas of scientific research", in a manner compatible with broad consent. Especially where broad consent concerns special category health and genetic data, the scope of the consent must still be limited to certain "areas of research", and provide data subjects with meaningful choices (e.g., to consent to the primary study only, re-use in a disease area, and perhaps finally re-use for broader biomedical research purposes) (European Data Protection Board, 2019). A legal and practical challenge is the difficulty of meaningfully delineating different types of research areas for consent purposes (Kalkman et al., 2019). Moreover, the identity of a data controller is a recommended core information element of consent (and is required for transparency) (Recital 42; Article 13). In the context of genomic data sharing, institutions and researchers requesting access to genomic data are likely to be controllers for the processing within their research projects. Intermediary databases may also qualify as controllers in some contexts. A narrow interpretation of this recital would require the consent to specifically name all these parties (though this may conflict with the permissive recital on broad consent). Where the identities of the future data users are not fully known at the time of data collection, this requirement may significantly limit genomic data sharing for broader research purposes across institutions.

Dynamic Consent

The challenges associated with broad consent for genomic data storage and sharing have spurred discussions about a possible need to revert back to the traditional model of study-specific informed consent. This would entail recontacting research participants for a new (specific) consent upon each instance of genomic data re-use (Stein & Terry, 2013). Whereas in the past recontacting research participants for a "fresh consent" was a highly resource-intensive process requiring a significant

amount of researchers' time (Vermeulen et al., 2009), nowadays participant recontact (at scale) can be streamlined using digital consent tools. Dynamic consent approaches employ digital tools to engage participants about specific studies seeking to use their data. Individuals can insist on consenting to each study specifically. In a participant-centric approach, individuals can alternatively choose to set their own granular or broad data sharing preferences, and update these over time. Owing to their scalability and patient-centric appeal, dynamic consent solutions have gained considerable attention in the policy discussion in recent years (Kaye et al., 2015; Budin-Ljøsne et al., 2017; Prictor et al., 2020). Dynamic consent is, arguably, the most GDPR-compliant approach where consent is used as the legal basis for data processing, providing transparent communication and an affirmative opt-in to specific research projects. This consideration has been partly responsible for the proliferation of both research-based and commercial dynamic consent solutions in recent years, particularly in the European Union (Mamo et al., 2020; DNV GL, Group Research and Development, Precision Medicine Program, 2021).

Dynamic consent for genomic data sharing is associated with its own unique set of challenges and limitations. Critics argue that dynamic consent places undue responsibility on the data subject, creating information overload and resulting in consent fatigue. This, in turn, may either lead to thoughtless participation in future studies, or discourage data subjects from reviewing consent requests altogether, thus effectively opting out of ongoing research (Steinsbekk et al., 2013; Mikkelsen et al., 2019; Teare et al., 2021). Furthermore, by placing the data subject at the heart of the decision-making process, dynamic consent solutions may de-emphasize the institutional review process, potentially resulting in weaker ethical oversight (Steinsbekk et al., 2013). Some evidence suggests that the perceived utility of dynamic consent will vary significantly among data subjects. Some individuals prefer to have a direct control over what studies use their data, whereas others feel no need to provide study-specific consent and are willing to delegate these decisions to the data-owning research institution (Sutton et al., 2019; Wallace & Miola, 2021). Unequal access to, or comfort with digital technologies may mean that dynamic consent tools will not be actively used by all eligible data subjects (Prictor et al., 2018). These considerations suggest that even where dynamic informed consent is implemented, its use by data subjects should be optional. That is, data subjects who do not wish to be recontacted for each study-specific consent in the future over a digital platform, should still be able to provide a broad consent.

Hybrids of broad and dynamic consent approaches are also being developed. For example, data subjects could be asked to provide a time-limited broad consent, renewed periodically, at pre-defined time intervals. An example of this model is a recently established German Medical Informatics Initiative, whose informed consent for the storage and re-use of patient data, including genomic data, is valid for five years (Bild et al., 2020). Alternatively, re-consent could be pursued only when there is a substantial change to the framework under which research is done, or when new forms of research with novel privacy risks and ethical issues become possible (Mikkelsen et al., 2019; Barazzetti et al., 2020). Indeed, more sophisticated

and modular informed consent solutions can be supported by emerging digital communication tools (Teare et al., 2021). Regardless, the following general considerations are likely to hold true for all consent models. Participants should have a meaningful option to withdraw their consent for ongoing study participation at any time, subject to narrow limitations. Consent must be complemented by ongoing communication of the relevant research activities with participants and the public, promoting transparency and accountability (Platt et al., 2014).

Conclusions

This chapter has provided an overview of the history and the current landscape of genomic data sharing, highlighting key ethical and legal issues and ongoing efforts to address them. These challenges are likely to grow in tandem with the increased scale, diversity and complexity of genomic data sharing. Genomic data sharing initiatives will continue to be faced with questions regarding how to appropriately safeguard against privacy risks, and what model of informed consent is best for long-term storage, sharing, and secondary reuse of genomic data. Carefully tailored balancing of openness and respect for persons in particular contexts must also be done with an eye to aligning with international approaches, or data risks repeatedly being trapped in silos of ethical and legal compliance. Undoubtedly, these discussions will be greatly influenced by scientific and technological developments in genomics; evolving standards for FAIRifying genomic data; innovative user-centric digital tools for informed consent management and continuous participant engagement; and the emergence of secured, federated data systems. The complexity and challenges of genomic data sharing should not shake our ultimate commitment to collaboration and advancing precision medicine for the benefit of all.

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Part IV
Biomedical Research: *Biomedical Challenges in Research*

Chapter 20
Human Challenge Trials in Pandemics: Risks and Benefits

Erick Valdés

Abstract Human challenge trials deliberately expose subjects to diseases upon consent to get more knowledge about the early stages of the disease and its transmission as well as to speed up testing of interventions. As human challenge studies are smaller, shorter and less expensive than other kinds of studies, by enabling a more efficient selection of vaccine candidates for further research and collection of significant data, they can imply relevant public health benefits. However, such studies are ethically sensitive because they are perceived encompassing high levels of risks both for participants and for third parties, which still encloses levels of uncertainty regarding these studies aftermaths. In this chapter, I will explore some HTCs' pros and cons by presenting the main arguments of both positions with emphasis in some aspects of scientific and social value of the studies, risks for participants, risk minimization strategies, review, oversight, safety monitoring, follow up, policy and regulatory framework for these sort of trials.

Keywords Human Challenge Trials · Pandemics · Vaccines · Informed consent · Public health

Introduction

Human challenge trials (hereinafter HCTs) consist of deliberately exposing subjects to diseases upon consent to get more knowledge about the early stages of the disease and its transmission as well as to speed up testing of interventions (Palacios & Shah, 2019: 1). In general, vaccines take several years to elaborate, and their development typically proceeds through three phases of clinical trials. In Phase 1, small groups of people receive the trial vaccine. During Phase 2, the clinical study is expanded

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and the vaccine is given to people who have characteristics similar to those the new vaccine is intended to. In Phase 3, the vaccine is given to several thousand people and tested for efficacy and safety. During this phase, participants either get the vaccine or a placebo. The efficacy of the vaccine is determined by comparing the prevalence of infection in the group that was administered the vaccine with the one which received a placebo. If everything goes well, the hypothesis that those in the vaccine group will be infected significantly less is thus tested.

As under human challenge trials, participants of both the vaccine group and placebo group are deliberately exposed to the infection, it is said that they are "challenged" by the disease organism. As researchers did not have to wait for participants to contract the infection such trials saved valuable time in developing a Covid-19 vaccine. However, as HCTs purposely infect participants instead of enrolling individuals naturally exposed to a virus, and even being a powerful tool to be better prepared for future pandemics outbreaks, such studies still are ethically controversial. As a matter of fact, whereas at the beginning of the current pandemic the world claimed for these kinds of studies, several voices still affirm that they can also lead to dangerous slopes, create imprecise atmospheres to research, and engender counterintuitive scenarios of diffuse certainty, specially related to informed consent process and the understanding and assessment of risks and benefits (Sekhar & Kang, 2020).

Also, as HCTs are smaller, shorter and less expensive than other kinds of studies, by enabling a more efficient selection of vaccine candidates for further research and collection of significant data, they can imply relevant public health benefits. However, human challenge studies are ethically sensitive because they are perceived encompassing high levels of risks both for participants and for third parties, which still encloses levels of uncertainty regarding these studies aftermaths (Jamrozik & Selgelid, 2020: e198).

In this chapter I will explore some HTCs' pros and cons by presenting the main arguments of both positions with emphasis in some aspects of scientific and social value of the studies, risks for participants, risk minimization strategies, review, oversight, safety monitoring, follow up, policy and regulatory framework for these sorts of trials. The delivery is updated, objective and impartial so that the public can get its own informed opinion on the matter. Yet, after a though revision of most updated bibliography I have to warn the readers that arguments for HTCs happen to be more profuse than those against.

Arguments For

These kinds of studies have shown an important ability to increase the understanding of response to viruses as well as of vaccines' performance (Sekhar & Kang, 2020). In this fashion, by implementing strong ethical protocols, oversight and new research tools, human challenge studies can uncover critical data to inform vaccine testing and development. Furthermore, being vaccines themselves one of the most successful public health interventions to control infectious diseases and knowing

that it takes so long to develop a new vaccine, applying HTCs in pandemics time seems like more than plausible.

Moreover, HTCs outcomes have been truly relevant. Well designed, careful and robust studies can offer a better comprehension of host-pathogen interactions, discover host factors that promote infection, recognize immune correlates of protection against viruses or disease, hasten the development and testing of vaccines and diagnostic for infectious diseases, (Sekhar & Kang, 2020: 2), validate tests of immunity and enhance knowledge about SARS-CopV-2 infection and transmission (Jamrozik et al., 2021: 634), among others.

It is also important to consider that the procedures to select and protect subjects are becoming more sophisticated. Indeed, they (i) identify the most promising vaccine candidates and (ii) validate them as effective subjects of large-scale Phase 3 trials, (iii) dwindle time and cost involved in research, (iv) reduce risks associated with vaccine development, (v) collect valuable information on vaccine efficacy, and (vi) boost success odds without asking for onerous actions from the subjects.

Another relevant point to take into consideration is that HCTs work where animals' models are not applicable or suitable to get knowledge on diseases in humans or when the disease is sporadic and the Phase 3 is not feasible. So, human challenge studies come into play a key role before the low prediction rates that animal models are able to provide for human host restricted diseases (Sekhar & Kang, 2020: 5).

In addition, according to the principle of risk parity (Chappell & Singer, 2020: 2), it would be permissible to expose certain individuals to some levels of *ex ante* risk to minimize overall danger in society. In this fashion, as Covid-19 pandemic has challenged traditional moral assumptions, it would also be permissible to expose fully informed volunteers to a comparable level of risk in ambits where there exist promising research into the virus. By doing this way, some collateral benefits arise, such as, skipping animal trials, speeding up vaccine development, and reducing doses to control infections.

On the other hand, from the start, HCTs showed that receiving a low dose of the virus led to mild cases of Covid-19, which allowed gaining sound evidence to develop a vaccine to bring protection to millions of people all over the world by saving a very relevant number of lives. Therefore, healthy young adults voluntarily exposed to the virus through receiving low doses of it became a risk worth taking by virtue of the benefits obtained from such exposure (Chappell & Singer, 2020: 6).

It has also been demonstrated that HCTs have more benefits than regular clinical trials (Su et al., 2021: 440). They are able to rapidly test whether or not new vaccines can prevent people from being infected by new variants of SARS-CoV-2. Moreover, they can speed up the development of new generations of more efficient and safer Covid-19 vaccines, even with the ability to protect people against asymptomatic infections.

Moreover, carrying out HCTs encompasses to gain knowledge on the duration of immune responses, by helping make decisions about the right time for vaccine boost, which is crucial to hold the herd immunity in the population (Su et al., 2021: 440).

Likewise, as time goes by, the World Health Organization Group has developed specific procedures and standards for biosecure facilities to prevent community from being inadvertently infected. At the same time, it has been demonstrated that an eventual boosted transmissibility does not increase risk to human challenge participants (Rohring & Eyal, 2022: 935).

It is also important to see, that as risks of severe adverse events in HCTs are very low (Manheim et al., 2021: 710–729), the specific risk of death for trial participants (young adults) is about 0,00025%, which can be considered as a reasonably safe risk rate (Rohring & Eyal, 2022: 936).

Furthermore, a compelling model of HCT can allow close monitoring of subjects during the study, by helping resolve some physiological basis for variation in disease's severity and progression from infection (Nguyen et al., 2021: 713). In this fashion, HCTs have provided good understandings on virus' development, which has implied to detect vaccine-enhanced disease. This finding is notable, especially considering that in humans, the clinical evidence for vaccine-enhanced disease in and for SARS-CoV-2 had been quite scarce thus far (Nguyen et al., 2021: 713).

Another argument for HCTs is that being these studies not risk-free they show a plausible balance between benefits and dangers, which finally favored allow their implementation. In fact, calculating the possible risk by using Bayesian models has been a good way to prove their plausibility as Manheim et al. have demonstrated (2021: 710–720).

In this way, Bayesian models can provide good insight into the overall risks of human challenge studies, which implies to inform participants with more precision about the eventual risks involved (Manheim et al., 2021: 717). Moreover, such models encompass the possibility of selecting multiple vaccines for global immunization and assisting therapeutic testing.

Another argument for HCTs is that there is no any other less risky study available to get the same amount of relevant knowledge gained through challenge trials in a similar timeframe (Schaefer et al., 2020: 5086). In this fashion, balancing necessity and value this kind of studies seems like very plausible and ethically acceptable. At the same time, at this point of pandemic it has been shown that HCTs are effective, at least for three important things: studying clinical progression, developing effective vaccines, and testing accurately candidate therapies.

Finally, it has been stated that coronavirus' risks for young healthy volunteers are similar to or lower than other socially accepted public services risks, such as, health care workers and liver donors, who are exposed to higher rates of risks than young adults participating in Covid-9 HCTs (O'Neill McPartlin et al., 2020: 1).

It is true that infecting deliberatively healthy humans with a dangerous virus may seem ethically counter-intuitive, nonetheless, there is consensus among most of scientific community that intentionally infecting HCTs' research participants can be ethically plausible under current conditions of modern challenge studies (Jamrozik et al., 2021: 634).

Arguments Against

At the beginning of pandemic several arguments against HCts were raised. Even though such concerns dwindled as studies went through, some of them still deserve attention. One of the most popular cases against human challenge studies is that these kinds of trials would be unethical (O'Neill McPartlin et al., 2020: 2) especially considering they show some fail on ethical requirements regarding both justice (fair selection of subjects) and beneficence (sound assessment of risks and benefits). Moreover, the social values of HCTs would be unlikely as we could have one or more vaccines without carrying out such studies (O'Neill McPartlin et al., 2020: 2).

At the same time, it has been argued that human challenge studies encompass too much uncertainty to participants, as risks related to these trials are too indeterminate and too abundant to be permitted. In this fashion there would be a substantial difference between clinical trials, providing direct and clear benefits to those involved, and HCTs where the risks have not been modelled and accurately recognized (O'Neill McPartlin et al., 2020: 2).

Another concern related HCTs points to their efficacy. In fact, formulations and dosing may differ between populations, for instance, based on age, by making their social value unlikely, in terms of reducing mortality (Kahn et al., 2020: 28539).

Also, the relationship between risk and benefits seems to be unreasonable as how much we know about infection with SARS-CoV-2 implies an evolving process far to be done. Some risks of the vaccine itself may only appear once a very large number of people have been vaccinated, namely, in a near future (Kahn et al., 2020: 28539). In the same order of ideas, enrolling only young adults for study can result in more limited benefits than scientists and population expect. This can boost the levels of public mistrust about the vaccine development (Kahn et al., 2020: 28541).

On the other hand, Santosh and Babik (2020: 514–516) argue that scientific knowledge of SARS-CoV-2 infection is insufficient to manage risks. Even though this concern was stated at the beginning of pandemic it still has some implications as infection's evolution while has permitted gaining important understanding about the infection it still seems to be insufficient at present. These authors also affirm that autonomous decisions of participants do not necessarily override potential risks so that involving into challenge studies and undertaking such kind of trials jeopardize confidence in the research.

Another interesting argument against HCTs can be found in Tambornino and Lanzerath (2020: 3-4). They state that COVID-19 infections can also emerge with very mild or even with no symptoms. In this way, what Chappell and Singer (2020):2) say regarding the permissibility of carrying out challenge studies by exposing some members of society to certain levels of risk under the assumption that such exposition has led to mild cases of Covid-19 is not compelling enough to allow those studies, especially considering that a low dose of virus might cause the risk of severe long-term illness or even death (Tambornino & Lanzerath, 2020: 4).

Overall, arguments against HCTs claim that extreme need of developing vaccines and fighting current pandemic is not a good advisor to make substantial self-determined decisions, and taking advantage of that perhaps is not ethical whatsoever.

Policy

While the year 2022 is almost over, with a large part of the world population vaccinated, when most of the countries have begun to make protection and care measures more flexible, and at a time when the panic of disease and imminent death has gradually moved away from our daily lives, the ethics and utility of HCTs is still a matter of debate.

Beyond the value that we give both to the arguments for and against this kind of studies, there is consensus that certain protocols and policies are necessary for their implementation. Perhaps, this is the most propitious moment to design such policies, since the experience of 2 years fighting SARS-CoV-2, can mean an important insight when determining and defining what key elements must be taken into account when carrying out HCTs.

According to most of experts, the main elements to be considered when implementing policy for carrying out HCTs are risks and benefits assessment, scientific justification, consultation and engagement, coordination of research, site selection, participant selection, expert review and informed consent.

Risks and Benefits Assessment

There must be a plausible balance between risks and benefits, meaning that it should be expected that potential benefits overweigh risks (Jamrozik et al., 2021: 636). This implies a systematic assessment of risks and benefits in research, by reasonably quantifying them and maximizing benefits and minimizing risks. At the same time, potential benefits and risks should be compared to other feasible studies available.

This is the ethical standard for this kind of studies, whose sensitive nature forces to consider their potential aftermaths very rigorously, especially concerning participants, society and third-party contacts of subjects (Jamrozik et al., 2021: 636).

Quantification of benefits must appraise: (i) when and how much faster vaccines might be available for use, (ii) how many lives might be saved, and (iii) how knowledge gained might contribute to benefit public health. On the other hand, quantification of risks should estimate: (i) number of subjects exposed to risk, (ii) total risk to participants (from latest data available), and (iii) marginal risk for participants (Jamrozik et al., 2021: 636).

Third-party risks should be minimized by using protective equipment for trial staff in facilities that allowed rigorous infection control. Experience has shown that participants in initial studies should be challenged one by one, with scrupulous

titration of viral dose. Likewise, those studies involving previously infected subjects should define correlates of protection and engender supplementary knowledge regarding immunity (Jamrozik et al., 2021: 637).

As the relationship risks vs. benefits happens to be one of the most important calculation elements to determine the utility of human challenge trials, the equation can be optimized by applying the principle of nonmaleficence (Beauchamp & Childress, 2019: 155–216). This principle reveals an implicit presence of utility as a criterion of moral correctness in bioethics. Despite establishing obligations of a categorical and unconditional nature, the principle of nonmaleficence is applied in deliberation following consequentialist balancing criteria. Utility is not explicit here, but it appears tacitly. Nonmaleficence's obligations differ from beneficence's ones. Whereas beneficence's obligations are laxer and more ductile, nonmaleficence's duties are much more binding because they ought to be followed impartially and, even, they provide reasons for punitive punishment when people do not respect them.

However, the greater binding weight of nonmaleficence does not imply, procedurally speaking, to be applied categorically in deliberation. In fact, in the context of current pandemic, it seems like any decision-making process should be utilitarian, as obtaining favorable consequences at the lowest cost possible becomes a strong criterion to evaluate human challenge trials' utility. Doing it otherwise can have pernicious effects, because it may encapsulate deliberation in dogmatism and even ideological fundamentalism. It's true that a researcher should always have in view the obligation to do no harm, and consider and understand it as a categorical and unconditional duty. Yet, the procedural scope of nonmaleficence is, in fact, related to consequentialist criteria, as in the boundaries of life and death is where the true deliberative value of this principle emerges. If nonmaleficence is exclusively understood as the highest standard or the overriding principle to decision-making, that might lead to a dogmatic closure of the possibility to tolerate minor risks and damages in order to obtain further benefits.

Scientific Justification

HCTs must have rigorous scientific justification as they point out very important consequences for public health (Jamrozik et al., 2021: 635). In fact, the more results of public importance the studies bring, the higher standards of scientific validation are needed. Scientific justification should consider elements such as feasibility of challenge studies, efficiency, coherency, and sound coordination of research leading to improve public health response to Cocid-19 (Jamrozik et al., 2021: 635).

It is especially important to expect results involving significant public health benefits, obtained sooner than would otherwise be possible. In this regard, Jamrozik et al. (2021: 635) indicate that human challenge studies should (i) inform the selection of the safest and most effective vaccines from among numerous candidates for further study, and (ii) inform complementary clinical measures and public health strategies to be implemented, by including correlates of immune protection, asymptomatic infection and transmission, for example.

On the other hand, researches should be aimed at obtaining a large amount of knowledge per participant without exposing them to severe or undue risk, by including, for instance, collecting additional samples while challenge trials are being carried out, specifying role of HCTs in vaccine development pathways, designing other research programmes, and planning of public health responses (Jamrozik et al., 2021: 635).

Consultation and Engagement

HCTs should be informed by consultation and engagement with the public as well as experts and policy-makers (Jamrozik et al., 2021: 637; London & Kimmelman, 2019: 38). Probably, it is not fair to introduce practices, techniques, and clinical essays by assuming a tacit public agreement. In this fashion, the British figure of social pact is not the best one. Because of the important impacts, effects and consequences that human challenge trials can provoke on people, a deliberative or public engagement model seems to be better.

Such consultations should consider public views on proposed research programmes and plans as well as techniques that enable fruitful dialogue about them. Therefore, public engagement goals should encompass assessing plausibility of HCTs, responding efficiently to public worries, maximizing transparency, and understanding potential impact to the whole society (Jamrozik et al., 2021: 637). At the same time, consultation and engagement should include minimizing risks to participants in coronavirus human challenge studies as subjects might face risks associated with the challenge infection and, in some cases, the experimental vaccine (Tambornino & Lanzerath, 2020: 5–7; Schaefer et al., 2020: 5086). Such risks should be minimized (Binik, 2020: 423–424), for instance, via the restriction of participation in initial studies to healthy young adults and the provision of high-quality medical care, including intensive care, if required (Jamrozik & Selgelid, 2020: 201). In this way, the Maximization-Minimization equation is optimized as human challenge trials should be aimed at enhancing such coefficient, both qualitatively and quantitatively. In fact, thus far it has been demonstrated that human challenge studies maximize benefits (speed, accelerated development) by reducing harms (less deaths, smaller number of subjects to experiment). At the same time, human challenge trials can improve the amount of cured people vs. victims both of trials and the virus.

Coordination of Research

SARS-CoV-2 challenge studies should include close coordination between investigators, funders, policy-makers, and regulators (Jamrozik et al., 2021: 637). Some coordination activities include public health agencies to prevent public health

response to Covid-19 from being unduly compromised, for example, while peak transmission periods are present.

Coordination measures should also involve efficient communication between researchers, policy-makers, and regulators, specifically regarding vaccine development. In this fashion, regulators should focus on how to use data for decision-making, and to determine what role those data should play in licensure or emergency administration of experimental vaccines (Jamrozik et al., 2021: 638).

In addition, coordination policies should focus on issues such as (i) Background risk faced by potential participants: individuals who are highly likely to be naturally infected with a pathogen during an epidemic (for instance, health care staff) might face a smaller increase in risk related to participation in human challenge trials than the general population (Jamrozik & Selgelid, 2020: 201); (ii) Uncertainty for participants: infection with unknown diseases might be associated with uncertainty (Jamrozik & Selgelid, 2020: 201). Thus, as unexpected aftermaths might occur and participants should be warned about it; and (iii) Risks to third parties: the potential for third-party risks must be always considered in any human challenge trials' calculation.

Informed Consent

Every SARS-CoV-2 challenge study must involve strong informed consent. Indeed, this procedure should be especially rigorous by considering the potential risks and uncertain aftermaths participants may be exposed to. Thus, HCTs have routinely incorporated tests of participants understanding while the process is applied (Jamrozik et al., 2021: 639). Such tests are based upon available data regarding risks and evidence on how relevant and critical information should be communicated to participants to maximize their understanding. Moreover, informed consent process should be revisited throughout the study as new relevant data may be obtained after the trial has begun.

The essential information to be delivered in the informed consent process for a SARS-CoV-2 challenge study should contain evidence on risks of contracting COVID-19 and mortality, nature of COVID-19 and treatment, prospects of success, study procedures, risks of experimental vaccines/treatments, potential for re-infection and negative consequences of getting antibodies, requirements for mandatory isolation, priority for treatment, compensation, post-trial entitlements, and alternatives to participation (Schaefer et al., 2020: 5087–5088).

It is important to notice that, as it has been pointed out, informed consent can be examined in two senses (Faden & Beauchamp, 1986: 276–277):

Sense one, a particular kind of action by individual patients and subjects, [and] sense two, the web of cultural and a policy rules and requirements of consent that collectively form the social practice of informed consent in in institutional contexts where groups of patients and subjects must be treated in accordance with rules, policies, and standard practices.

Informed consent in sense one can be defined as "an autonomous action by a subject or a patient that authorizes a professional either to involve the subject in research or to initiate a medical plan for the patient (or both) (Faden & Beauchamp, 1986. 278). So, informed consent is given if "a patient or subject with (1) substantial understanding and (2) in substantial absence of control by others (3) intentionally (4) authorizes a professional (to do I)." The fourth step is what characterizes informed consent as a particular kind of autonomous action, and, logically, if a person refuses to fulfill step (4) we are in presence of informed refusal. Central to this definition is the notion of authorization, which that "one both assumes responsibility for what one has authorized and transfers to another one's authority" (Faden & Beauchamp, 1986: 280).

In sense two, the authors do not refer anymore to autonomy, as sense two implies effective consent, consent obtained through procedures created to satisfy the requirements for an informed consent practice. As such, informed consent in sense two deals with regulations and rules of the behavior of the consent-seeker. This means we regulate the way of acquiring consent and our behavior must be in line with those regulations so as to obtain legitimate "informed consent", *effective* consent. It follows from this analysis that in some cases one can give informed consent in sense one but fail to give informed consent in sense two. When, for example, someone consents in sense one to donate a kidney but fails to fill the correct form, one successfully gave informed consent in sense one but not two. Conversely, one can actually consent in sense two to an intervention but fail to give informed consent in sense one, simply by filling forms required.

Therefore, in cases like HCTs, consent processes and participant selection criteria should be "such that there is virtually no doubt" that subjects clearly understand the potential risks involved and voluntarily accept to deal with them (Jamrozik et al., 2021: 639).

Final Remarks

It seems plausible to affirm that any ethical and legally binding juridical framework to justify the utility of human challenge trials should consider, at least, the following criteria:

Speed or Accelerated Development replacing the Phase 3 can considerably reduce the licensure process' time, making efficacious vaccines available more quickly. In this way, the risks involved would be justified by virtue of the benefits that can be obtained from accelerating the process.

Less Number of Subjects human challenge trials need a considerable smaller number of subject to succeed. This not only reduces the number of people at risk but also the potential number of infected subjects in the trial. The cost-benefit relationship is then optimized.

Residuality marginal risks vs. the potential and predicted benefits justify, rationally and reasonably, human challenges trials in pandemic times.

Tacit Social Pact this agreement figure is plausible, acceptable and juridically defensible here. It's true that this model seems to be quite unsuitable to introduce new technologies into the world. In this fashion, an argumentative model, at Frankfurt School style, seems to be more reasonable. Just assuming that all people agree with the surreptitious induction of new devices or techniques and taking that for granted is not enough. For example, the recently created algorithm to read human minds in order to allow people with brain palsy to express their will as their thought are translated, in real time, into words on a computer screen (Drew, 2022). However, at the same time, that algorithm can be used to literally read shopping tendencies, preferences and, even, wishes. In this case, it is possible that we need much more than a tacit agreement. Yet, in the case of pandemic where rapid and tragic decisions need to be made, a tacit social pact seems to be, at least, a good epistemological platform for decision-making processes.

In sum, it is true that human challenge trials involve risks, but adamantly rejecting them seems to obey, at best, an oblique hermeneutic. Therefore, as WHO has stated (Jamrozik et al., 2021), if human challenge studies are undertaken with prudence, caution, and oversight, the information obtained clearly justify the risks human subjects to face, insofar the risks and harms are residual in comparison to the expected benefits to be obtained.

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Chapter 21
Ethical Considerations for Vaccine Research

Ricardo Palacios

Abstract Vaccination, meaning induction of immunity through controlled exposure to antigens, has been mainly used as a prophylactic measure, but more recently as a therapeutic measure. As far as ethical dilemmas from therapeutic vaccines resemble those occurring for conventional treatment clinical trials, this chapter will focus only on prophylactic vaccines. Analogously, some of the ethical aspects of pre-exposure prophylaxis through medication or passive immunity are shared with prophylactic vaccines. This chapter will discuss the implications of having most vaccine trials not conducted in combination with health care, the compensation of vaccine study participants, the preventive misconception, the need to keep participant commitment in vaccine studies, post-trial access in vaccine trials, controlled human infection models, studies in special populations, and vaccine community-based studies.

Keywords Ethical dilemmas · Therapeutic vaccines · Prophylactic vaccines · Vaccine studies · Controlled human infection model (CHIM)

Vaccine Clinical Trials Are Not Usually Conducted in Combination with Healthcare

In general, vaccine trial participants are usually invited to join the study by investigators that are not taking care of participants' health as patients. Indeed, most of the vaccine trials exclude those with comorbidities requiring continuous healthcare (Zhang et al., 2022). This difference with therapeutic trials implies differences at several levels detailed below.

As the vaccine trial participant in most cases is not looking for healthcare, any procedure would be out of his/her usual routine. Therefore, the research staff would

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be required to obtain proper consent before any procedure, regardless of its complexity. Therefore, otherwise routine simple procedures like blood draws or medical interviews, would constitute study procedures and risks should be properly assessed.

Not being a "patient-volunteer" also changes the power relationship existing between the healthcare professional conducting the research and the potential participant. When the researcher is also taking care of a potential participant as a patient, the relationship is asymmetrical in terms of the need for care. But for most vaccine trial participants, no previous link exists between potential participant and the investigator. In this case it is the investigators who are the ones in need of participants, to succeed in the trial. Therefore, coercion or constraints derived from the patient condition are less likely for potential participants in vaccine trials in comparison to those in therapeutic trials.

One of the major challenges to conduct vaccine trials is to successfully attract potential participants to the clinical research facility. Several strategies according to the trial requirements are employed, but among them are usual advertisement as well as community outreach. Researchers should be careful in the design of those materials to avoid any misleading information. Common mistakes are avoiding stating clearly that the advertisement is for a research project or promising unproven benefits, like protection form a disease when this result is still not available. Motivation to participate in a vaccine trial varies a lot according to the awareness of the disease, perception of risk, and overall trust on science (Detoc et al., 2017). Of note, means to recruit and provide information to potential participants should be reviewed in terms of fairness and obtain approval from the corresponding Institutional Review Board/Independent Ethics Committee (IRB/IEC) before implementation.

Compensation and Payment to Vaccine Study Participants

Financial benefits are among the motivations used in several countries to participate in a vaccine trial. Nonetheless, that is a matter of discussion in the fields of clinical research and bioethics. Probably one of the starting points of the discussion is the polysemic nature of the word "volunteer". This word is rooted in the will, as expression of what a person wants to do, but also, to some extent, there is some expectation that such will is not attached to a link. Perhaps that is the reason a "paid volunteer" can be regarded as contradictory in essence (Wertheimer, 2012). Nonetheless, financial benefits are commonly used to attract potential volunteers in several countries.

There is an overall agreement that no participant should bear a financial burden to be part of the trial and a compensation of expenses, i.e. transportation, is reasonable. Any compensation should be given in a timely manner according to the expenses to avoid that a participant remains in the trial mainly to recover the expended money. IRB/IEC should review that the timing and amounts of compensation are appropriated to the local context and avoid the risk of having a compensation scheme that becomes a hidden payment. Moreover, compensations should not be a condition to the completion of the study or specific study procedures.

The controversy is whether additional payments beyond compensations might become an undue inducement. Some argue that this is a major concern for populations in unfavourable financial conditions, as certain amounts of money constitutes an offer unlikely to be refused and such situations could impair the capacity of a potential volunteer to properly assess the risks. Conversely, others consider that it is unfair to not provide proper benefits to someone who takes more risks, especially in earlier stages of the clinical development. In order to advance on this discussion, some other ethical principles should be considered. First, risk-benefit ratio assessment is mandatory for any clinical study. At the collective level, this assessment is conducted by the IRB/IEC considering foreseeable risks at the individual level and benefits at both individual and collective levels.

Usually, trials at earlier clinical development stages are more less likely to provide a direct benefit to the participant. In vaccine development however, the direct benefit can be also relatively low at later stages because it is correlated with the exposure and chance of getting a disease or an infection. However, when the researchers can demonstrate that expected collective benefits can largely overpass the level of socially acceptable risks that each participant is exposed to, the ethical approval is granted. Nonetheless, the decision of joining or not joining in a trial is taken at the individual level and additional benefits, i.e. payments, are used in some context to counterbalance the risk and the inconveniences of joining a study with low or no direct benefit. Independently of whether or not payments are allowed in the study, the duty lies with the investigator to minimize risks and IRB/IEC to assess the acceptability of those risks. In other words, regardless of the possibility of payment, other mechanisms should protect potential participants of disproportionate risks.

Then, if study risk is properly controlled by other mechanisms, unfair inclusion of people at higher vulnerability drives us to assess whether exploitation is occurring. There is consensus that clinical studies should not exploit participants, even with the highest potential social benefit. But the meaning of this principle varies according to cultural context. Scholars have advocated to consider the participation in clinical trials as any other temporary or sporadic employment for different reasons. One strong argument is that many human activities implying more risks are better paid, i.e. police officers. In that sense, the so called "clinical research exceptionalism" is unjustified and, somehow, not paying can be considered as unfair (Largent & Lynch, 2017). Furthermore, hiring participants as a regular worker has been proposed as a protective measure of a marginalized "professional guinea pig" career that is occurring "de facto" in some places (Abadie, 2015).

In contrast, there are moral views about what is acceptable to "sell" and this is reflected in analogous regulations like those for blood donation (Dufner, 2015). Thus, when a person allows the study procedures to occur that is not comparable to selling the workforce in the job market. It fits in a view that the human body cannot be a matter of commodification, so those procedures are only acceptable on a voluntary basis, meaning mainly on unpaid altruistic motivations (Walker & Fisher, 2019). Concerns on exploitation of volunteers as "commodities" are more evident when research is conducted in low- and middle-income countries. A large population of socially vulnerable people that can accept joining a trial for a limited amount

of money is at a higher risk of exploitation. At larger scale, and even with unpaid participants, this exploitation risk is extended to the whole society if the results are not intended to provide benefit to such country, i.e. the vaccine is not primarily intended for this market (Glickman et al., 2009).

The Preventive Misconception

At a later stage of clinical development, other aspects like awareness of the disease and societal benefits of the clinical research became more relevant as motivations for potential participants. At such stage, individuals at risk are usually invited to participate and their direct experience with the disease to be prevented and benefit derived from immunization can be strong incentives to encourage participation in clinical trials. It leads to another common risk for the participant called the preventive misconception.

The preventive misconception, derived from the therapeutic misconception, is an unappropriated expectation of direct benefit of the study product. Such expectation is considered as inadequate because a scientifically valid research question is founded on the uncertainty of the study results (Simon et al., 2007). The level of uncertainty is not a constant "flip of the coin" at each stage of the clinical development process. The likelihood of success is substantially higher in phase III clinical trials. But the results are not achieved until data can support them. Furthermore, use of scientifically sound controls is required in those study designs to build the efficacy and safety case of a new product. The potential participants should be carefully informed about the uncertainness implicit in the research process and the possibility to be allocated to a control arm to avoid a misleading decision to join a trial based on this unappropriated expectation of direct benefits of the study vaccine.

The preventive misconception, differently to the therapeutic misconception, can also impact the risk-benefit ratio. Several diseases may already have preventive measures available before the vaccine testing, i.e. use of preservatives in testing a sexually transmitted infection vaccine or avoiding crowds in closed spaces in airborne-transmitted virus vaccine. Then, expected risk of the trial considers that participants belonging to active and control groups might have some degree of adherence to those preventive measures. If, because of the preventive misconception, participants deliberately lower the adherence to other preventive measure, the exposure risk can be greater than initially planned leading to changes to the risk-benefit assessment conducted by the IEC/IRB and an unbalance in the exposure, jeopardizing the scientific endpoints. A proper informed consent process can mitigate the preventive misconception risk by adjusting participants' expectations and reducing deliberate risk-taking behaviours.

In an extreme case, a study vaccine produces an immune-mediated phenomenon called vaccine-enhanced disease that was evidenced in recent vaccine trials. That is a paradox response leading to higher incidence of disease or more severe clinical presentation among vaccine recipients as compared to those in the control arm

(Sridhar et al., 2018; Duerr et al., 2012). This phenomenon is unusual but should be disclosed in the consent process if scientific evidence indicated such risk. As well, standard preventive measures should be encouraged to all participants, and preventive misconception need to be explained during the consent process and follow-up.

One variation of the preventive misconception that can interfere also with the scientific objectives of the trial is when participants can differentiate active and control groups for any reason, most commonly due to differences in safety profile, i.e. commonly reactogenic vaccine compared with a placebo. In this case, the preventive misconception can lead to a lowering in preventive measure adherence only in those believing they belong to the active arm and increasing adherence to other preventive measures in those who believe they are in the placebo arm. This further unbalances the risk among groups and affect future comparisons. In this case, choosing a proper control according to the expected safety profile of the study vaccine will mitigate this risk.

Participant Commitment and Continuous Consent Process in Vaccine Trials

In a vaccine trial, participants usually receive the study intervention in the clinical research centre, so adherence to intervention is easier to control than in the therapeutic area. Adherence to the remaining study procedures, like sample collection and detection of incident cases, is more complex because participants are not patients enrolled in a routine medical care, but rather individuals that are not usually seeking for care at the clinical research centre, or even that can obtain care, if necessary, with other healthcare providers.

In this sense, the clear separation between research objectives and medical care should be crystal clear for the study participant during the consent process because the actual commitment to adhere to the study procedures is easier when the participant concurs in search of the answer to the research question and understand why those procedures are relevant to that purpose. The implementation of decentralized trials created new responsibilities for participants that should be in charge to complete forms, collect tests, and other activities in the trial. Therefore, adherence to trial procedures is more relevant to ensure the success of such studies (de Jong et al., 2022).

In vaccine trials, the study procedures can last for several months and even years. Therefore, renewing this commitment beyond the initially documented consent process is important to accomplish the scientific aims of the study. This continuous consent process is usually established on the open conversations between the study team and the participant. In that sense, there is also a duty to share relevant information on the product and early results of the study to keep participants up to date on the advances on the research question. Summaries in plain language can be shared with the volunteers after previous approval of the corresponding IRB/IEC.

Eventually, relevant study results can be divulgated in press releases or in the news. It is advisable that information that becomes public on the trial or on the product is also forwarded to study participants. That way, participants primarily learn about the result from the study team, and not from the news. That is a way to demonstrate respect and appreciation to the participants and keep the mutual commitment to conclude the study.

Post-Trial Access in Vaccine Trials

Since the 2000 amendment of the Declaration of Helsinki, post-trial access was a matter of several discussions. Such questioning led the World Medical Association to include in the declaration a clarification note to reinforce post-trial access as a research ethical duty. Nonetheless, most of the discussion was centred around the risk for patient participants to be deprived from a medication that might be effective for the study medical condition or denied in the case of participants in control arms.

The text on post-trial access changed in 2008 and 2013, but all of them have in common that the condition to proceed the access is an "intervention identified as beneficial in the trial". In other words, the research question was resolved by concluding that intervention has a favourable risk-benefit ratio. In therapeutic trials, this assessment seems clearer because the benefit is easier to be assessed. In contrast, benefit of a vaccine is proportional to the risk and that is relative to specific circumstances.

There are three levels to assess benefit of vaccine study results. The first is at the level of sponsor analysing and summarizing data collected in the study. The next level is that of the regulatory authority that would determine whether the data is suitable to support the vaccine market authorization. Finally the public health authorities, usually with the advice of a National/Local Immunization Technical Advisory Group, can issue a recommendation for use of the vaccine in a specific population of a territory (Steffen et al., 2021).

In that sense, following the recommendation of providing a study vaccine after the trial participation is beyond the result of the trial itself. Results of the study can be favourable, but the immunization is recommended only to some specific population groups with higher risk, and it is deferred to other groups. Then, understanding the study participant risk is also part of the required assessment (Wendler et al., 2020). For example, offering immunization to low-risk participants that received placebo in the framework of a lot-to-lot consistency vaccine trial would bring negligible benefit, regardless if the vaccine succeeds in obtaining the approval from regulatory authorities. On the other hand, if the health authorities make the study vaccine available for a population that includes the study participants, researchers should take provisions to allow those in the control group to get access to the vaccine without further delays. Providing the vaccine can occur in blind manner, i.e. calling participants and switching interventions between active and control arms (placebo-crossover), or be preceded by unblinding and offering immunization only to those in the control group. In both cases, valuable information can be analysed

beyond if the vaccine is offered to the control group (Fintzi & Follmann, 2021; Follmann et al., 2022). In any case, it is advisable that research protocols include and justify plans in this regard to be considered in advance by ethical and regulatory authorities.

Post-trial access in vaccine trials can show how different the routine practice is from the scientific aims of the study, because, in several cases, vaccines are subject to the health authority policies rather than individual physician decisions. Indeed, in many countries or during outbreaks, some vaccines are only available to specific groups determined by health authorities. In other words, there is no need to appeal to the classical idea of trial equipoise to reconciliate scientific research and medical practice because the decision of vaccination uptake is often beyond the scope of the physicians that conduct the trial. Therefore, as occurred during the study, risk-benefit ratio is also the major driver for the post-trial access (Wendler et al., 2020).

Controlled Human Infection Models

Among the different types of trials for vaccine clinical development, the controlled human infection model (CHIM) is probably among the most interesting. In this type of trial, as indicated, by the name, the purpose is to induce an infection in the study participant. Data from immunology and natural history of disease, as well as challenge of the immune response elicited by a study vaccine, are the most common reasons to propose a CHIM. In the latest objective, a CHIM trial after immunization might support a decision to move forward with vaccine clinical development to a larger clinical study and down-select among different vaccine candidates.

In this kind of study, equipoise has no room because no medical practitioner would intend to infect an otherwise healthy person (Miller & Brody, 2007). Likewise, no direct benefit is expected for study participants. Therefore, justification to run a CHIM is founded on the risk-benefit assessment, considering risks related to study procedures and social benefit.

Of note, not all infections are suitable to setup a CHIM, mainly due to individual risks. Usually, only self-limited infections or those with available effective treatments are considered as having a manageable level of risk for a CHIM. Most of these studies occurred in developed countries and in young healthy volunteers. Nonetheless, conducting CHIM in low-and-middle income countries can also be considered whenever scientific reasons are compelling and ethical provisions are taken, especially the consent process (Vaswani et al., 2020).

In addition to usual individual risks, the ethical assessment should also include provisions regarding bystander risks (Shah et al., 2018). Those are the risk of individuals outside of the study setting occurring as an unintended consequence of the study procedures. For example, an unintentional transmission to another person of the study infection. Those transmissions can be either by direct contact or by contamination, i.e. inappropriate sewage discard in faecal-oral transmission or

unexpected insect bite in vector-borne diseases. Researchers should assess bystander risks and submit mitigation or elimination plans to ethical review and, eventually, to the health authorities.

Special Populations in Vaccine Studies

In several cases, disease attack rates affect also special populations, like children, pregnant women, immunosuppressed patients, among others. Then, studies to determine effective vaccine dose might be required to determine how to protect those groups and to ascertain the safety of the product for them.

For some populations, the reason for inclusion is different according to the pathogen. For example, pregnant women can be included to protect them directly or to protect their children in the neonatal period. In any case, bystander risk should be considered also for their offspring, therefore included as part of the risk-benefit assessment in the context where the research is proposed (White & Madhi, 2015).

Children are a frequent target population for immunization. Therefore, trials should ascertain vaccine safety and efficacy at paediatric ages. As minors are not legally capable in civil law, they cannot consent and regulation on legally authorised person to consent according to local law should be respected. Nonetheless, children can provide assent when information is properly presented (Alderson, 2007). That is a common requirement from several IRC/IEC and local regulations. When the child is under a joint legal custody, consent of both parents is usually required. Likewise, if the minor reaches legal civil age during the trial follow-up, reconsent of the participant is required as parental consent is no longer valid.

Individuals with underlying medical conditions that can affect vaccine immunogenicity and/or safety, i.e. immunosuppressed patients, are usually excluded from the initial vaccine development. Nonetheless, studies on such individuals might be required to determine whether the vaccination is valuable for them and if changes in the immunization scheme are required. There are several types of immunosuppression with diverse impact on elicited immune response, so study design should account for such differences. Vaccine safety in this special population for some kind of products, i.e. live vaccines (Croce et al., 2017), requires precautions to minimize risks to participants.

Vaccine Community-Based Studies

After a vaccine is approved for use by regulators, additional trials can support the incorporation of the vaccine into routine immunization programs and determine effectiveness and long-term effects of vaccination. The most common studies in this regard are cluster-randomized trials and pilot implementation studies.

Community outreach is critical for planning those studies. Support from local authorities and in-depth knowledge of social dynamics are the basis for the planning. Specific strategies to introduce the study and the vaccine to the community will increase community acceptance (Palacios, 2018). In such regards, meetings with community leaders; including religious ministries, educators, healthcare professionals, and other civil relevant figures; are critical.

The study protocol should detail exactly what is and is not considered a study procedure. In some cases, the study procedures are limited to enhanced surveillance in an area where the vaccine was implemented, but no specific study procedures are proposed for individual participants. In others, the vaccine is approved and recommended for an individual in the study and they can take it outside of the study framework, sample collections or interviews might be requested, and such procedures differs from the routine. In those cases, individual consent is required for collecting and analysing such samples and answers. Cases where the study immunization is approved, but clusters are allocated to active or control arm (i.e. placebo), the vaccine administration becomes a study procedure despite it is licensed for the study population and requires individual consent. Of note, community leaders' acceptance never substitutes the individual consent from each participant. In all cases, the review of the corresponding IRB/IEC should be obtained in advance. This review should include whether a consent is required or not and for which procedures.

Final Considerations

Prophylactic vaccines are an outstanding tool to control several infectious diseases with implications at individual and community levels. In this regard, reassuring a comprehensive ethical conduction of vaccine studies will support the future immunization programs. Furthermore, implementation of large-scale vaccinations is possible only if based on results obtained out of an ethical trustworthy clinical research framework. The overall number of study participants in vaccine studies to reach licensure is usually several times higher than in other products and is a duty of all other stakeholder in the process to honour such effort with an ethically and scientifically sound clinical development.

Disclaimer *The views opinions expressed in the text are those from the author and do not necessarily reflect the positions or policies of GSK or GSK Vaccines s.r.l.*

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Chapter 22
Global Health Partnerships and Emerging Infectious Diseases

Nancy S. Jecker

Abstract Drawing on recent bioethics literature on emerging infectious diseases, as well as the authors' own previous analyses, this chapter addresses the ethical underpinnings of global health partnerships to combat emerging infectious disease. After an introduction to the topic, section "Introduction" proposes the twin ends of establishing structural justice and ensuring threshold human capabilities as key justice standards. It shows how these standards play a critical role in determining justice in global health partnerships. Section "Next Steps: Global Health Partnerships" illustrates these justice standards by applying them to the coronavirus 2019 (COVID-19) pandemic. Section "Conclusion" models multi-level global health partnerships that build-in justice considerations and proposes next steps for pandemic preparedness.

Keywords Global health · Emerging infectious diseases · Bioethics · Ethics pandemic preparedness

Introduction

Emerging infectious diseases are "diseases that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range" (National Institutes of Allergy and Infectious Diseases, 2020). Over the past fifty years, they have been on the rise worldwide and represent a growing threat to global health and security (Daszak et al., 2021). This is due to a range of factors, such as greater global interconnectivity; urbanization; growing interdependence with animals and their products; and lack of access to basic goods and services, such as soap and water, basic healthcare services, and essential medicines. Added to the mix are demographic factors, such as population aging and the associated rise in chronic

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diseases that can render people more susceptible to infectious agents; structural racism and poverty, which heightens risk of disease and early death; and deforestation and degradation of natural habitats, which brings wild animals into closer contact with human beings, raising the risk of cross-species spill-over of infectious agents from animals to humans. *Syndemic* is an emergent conception of infectious disease that reveals how an infectious disease agent clusters with pre-existing conditions, interacts with them, and can be reinforced and made worse by the social, economic and political contexts in which it arises. It shifts the focus from a purely biomedical model targeting an infectious pathogen in a decontextualized space to a model that highlights contextual elements and systems that create pathways for diseases to gain hold and spread (Jecker & Atuire, 2021a). The concept of syndemic reconfigures conventional historical understanding of diseases as distinct entities in nature, separate from other diseases and independent of the social contexts in which they are found. Rather, all these factors tend to interact synergistically in various and consequential ways, having a substantial impact on the health of individuals and whole populations (Singer, et al. 2017, p .941).

Syndemic features were on full display during the coronavirus 2019 (COVID-19) pandemic, creating a "perfect storm" (IHME, 2020). The first identified cases of the SARS-CoV-2 virus were reported in December 2019. They were apparently connected to a wet market in Hunan, China, where a tiny microbe made a zoonotic leap, perhaps from a bat infecting an intermediary animal, which in turn infected a human (WHO 2021a). By May 6, 2021, the SARS-CoV-2 virus had led to the deaths of up to 6.9 million people worldwide and sickened millions more (IHME, 2021). The COVID-19 pandemic rekindled debates about how to prepare the world for the growing threat of emerging infectious diseases.

This chapter uses a wide angle lens to view the conditions, systems, and structures required to address the threat of emerging infectious pathogens. Drawing on recent bioethics literature, as well as the authors' own previous analyses (Jecker, 2023; Jecker et al., 2022a, b; Jecker & Atuire, 2022; Jecker & Lederman, 2022; Jecker, 2022; Jecker and Atuire, 2021a, b; Jecker et al., 2020), justice is featured as a requirement for global health partnerships and structures. In the next section ("What Is Structural Justice?") the chapter sets forth the intuitive idea of structural justice and introduces the metric of threshold capabilities as a justice standard. Section "Next Steps: Global Health Partnerships" illustrates this justice standard using the example of the coronavirus COVID-19 pandemic. Section "Conclusion" models multi-level global health partnerships that inform global health governance and proposes next steps including systems for preventing, early warning, rapidly response, and sharing essential public health goods.

What Is Structural Justice?

Emerging infectious diseases create *systemic* risk for people everywhere due to globally interconnected systems. Increasingly, humans everywhere share a microbial world and all are threatened by the emergence of infectious diseases anywhere. However, the risks associated with emerging infectious disease are not shared equally; instead, risk tends to cluster disproportionately among certain groups, including people in low- and middle-income countries (LMICs) who may lack access to hygiene and basic healthcare services; people residing in congregate populations, such as prisoners, migrant workers, and older adults in long-term care facilities; racial and ethnic minorities and other health disparity populations that face higher risk of infection and of severe disease and death compared to the general population.

Structural Justice and Injustice

Structural justice interrogates the structures, systems, and conditions that systematically shape people's prospects for advantages and disadvantages in multiple areas, including health. Applied to the problem at hand, it focuses attention on how various factors put some populations at relatively greater risk of disease and early death and other populations at relatively less risk. The starting point for such an analysis is often the effects systems have on those who are placed at disadvantage. According to Powers and Faden, a *systemic disadvantage* occurs "whenever any social structural impediment profoundly, pervasively, asymmetrically, and near-inescapably diminishes an individual's most important well-being prospects, or in other words her prospects for a decent human life" (Powers & Faden, 2019, p. 16). Such impediments are often complex and intersect in ways that are mutually reinforcing. Their effects tend to be long lasting over the course of a lifetime and, frequently, over the course of generations. In this sense, disadvantage signals that a person or group with disadvantage (or advantage) holds a certain position relative to others in the pursuit of various goods or ends. Those with advantage have a 'leg up' and those without it have reduced chances for a decent life. In the context of a theory of justice, the relevant advantages and disadvantages are those that impact a person's ability to lead a minimally decent life.

When we apply a structural justice framework to emerging infectious diseases, the relevant structures tend to be expansive in three notable respects (Bell, 2018). First, their scope extends beyond individual states and affects human beings everywhere. Just as the structures, systems and conditions that one nation develops to address climate change affect people everywhere, so too, the structures, systems and conditions a single nation establishes to address emerging infectious diseases carries implications for all states and for human beings everywhere. Second, systems for addressing emerging infectious diseases are not confined to human beings, but

implicate non-human species and the environment. One of the root causes of pandemics is the loss of habitat which brings wild animals into closer contact with human beings and wildlife markets and farms that contribute to zoonotic spillover. Hence, structures and systems to address emerging infectious diseases will also carry important implications for how we interact with other species and the environment. Finally, the systems and structures that concern us are expansive in the sense that they tend to be passed from one generation to the next in an ongoing way, rather than being made anew by each generation. Expressed differently, systems have an inertial force and tend to perpetuate themselves, creating norms and expectations that shape patterns of behavior across time.

Central Human Capabilities

Given its far-reaching scope, how can a structural justice approach applied to emerging infectious diseases home in on just systems and partnerships for promoting global health security? One way of further specifying just systems draws on a conception of the diverse elements required to lead a minimally decent life. The intuitive idea is systems and structures should reasonably support people's capacity to lead a minimally decent life and this ethical requirement sets a minimal bar that must be met.

While different metrics can be used to characterize a minimally decent life, this chapter uses the approach of central human capabilities. A capabilities approach is distinct because it takes as its focus the central things that human beings can do and be. It was originally used to measure a nation's development by assessing the extent to which its citizens experienced capability gains or shortfalls (Sen, 1985). Working in a capability tradition, Nussbaum offers a normative interpretation of capabilities, which is multidimensional and includes such things as the ability to have a normal lifespan; be healthy and well-nourished; have bodily integrity and move freely from place to place; affiliate with others and with the world of nature; experience a range of human emotions; exercise the senses, imagination and thought; recreate and play; and regulate one's immediate environment (Nussbaum, 2011). Alternative capabilities lists are possible, although it has been argued that they should be life stage sensitive; reasonably balanced in ways that bridge cultural differences and challenge one-sided claims; and provisional or open to revision as new information or arguments come to light or major changes occur to human environments (Jecker, 2020).

According to a capability analysis, what it means for a person to be able to lead a minimally decent life is for them to have each of the central human capabilities at a threshold level.

Minimally Decent Lives

Since people have different abilities to convert resources into capabilities, supporting minimally decent lives requires different kinds and amounts of resources for different individuals and groups. A just system will make reasonable, rather than unlimited, efforts to support threshold capabilities. Some individuals have lifelong impairments that prevent them from ever realizing particular threshold capabilities; a just system supports people with permanent capability shortfalls by supporting other capabilities they have or can develop.

Drawing on this analysis, the justice or injustice of structures and systems to protect against emerging infectious diseases can be judged by assessing their impact on people's threshold capabilities. According to one interpretation, injustice occurs in structures "when social processes put large groups of persons under systematic threat of domination or deprivation of the means to develop and exercise their capacities" and, at the same time, these processes "enable others to dominate or to have a wide range of opportunities for developing and exercising capacities available to them" (Young, 2011, p. 52). Applying this framework to emerging infectious diseases, our focus should be on a narrower subset of central human capabilities related to health. According to Venkatapuram, we can think of health as a kind of meta-capability, that is, an "overarching capability to achieve a cluster of basic capabilities to be and do things that make up a minimally good human life in the contemporary world" (Venkatapuram, 2011, location 630). So understood, the capability to be healthy is "a kind of freedom, which is intrinsically and instrumentally valuable, and which almost every human being and society is likely to value, albeit for a wide variety of reasons" (Venkatapuram, 2011, location 689).

Structures for Global Health Security

Using the lens of structural justice and threshold human capabilities focuses our attention on the impact of frameworks and systems used to address emerging infectious diseases on human lives. Given the thinness of governance at the international level, it is helpful to model the kinds of global structures and systems that might be developed in the future and then ask how the justice standards set forth here can be used to shape and develop model systems. In tandem, we might ask whether the absence or continued absence of systems to address emerging infectious diseases should itself be understood as a form of passive injustice (Shklar, 1992).

Duff et al. characterize systems designed to protect against emerging infectious diseases as a kind of a collective defense system and specify an *effective* defense as encompassing structures with certain basic capacities, including capacities for: (1) *responsiveness* or the ability to flexibly and quickly identify and address threats on the ground anywhere in the world; (2) *expertise* or the ability to serve as an authoritative source for data and technical aid, including setting evidence-based global

standards; (3) *evaluation* or the capacity to evaluate countries' progress toward compliance with global standards and coordinate ways to remedy deficiencies; (4) *enforcement*, which includes incentives, sanctions or both; (5) *autonomy* or the ability to make decisions free of undue influence; (6) *financing* which is sustainable and protects governing bodies from undue influences; (7) *representation* from all countries and relevant stakeholders; (8) *multi-sectoral* engagement with groups inside and outside of government, including philanthropic groups, non-governmental organizations, universities, communities and field-level organizations; and (9) *commitment* to continue these efforts over the long-haul (Duff et al., 2021).

To ensure that structures satisfying these conditions are not only effective, but *just*, requires exploring how they impact people's chances to lead a minimally decent life. Rather than viewing the background conditions as given, the approach we are developing sees structures and systems as matters of justice that are ultimately shaped and created by human beings.

Structural Justice and Injustice During the COVID-19 Pandemic

To illustrate, consider the structures and systems in place when the first cases of human infection with the SARS-CoV-2 virus were reported and how this subsequently impacted people's ability to lead minimally decent lives. Beginning with pandemic preparedness, the world lacked a variety of systems that might have provided early detection and response to a novel coronavirus. Examples include a global surveillance system to spot infectious disease outbreaks anywhere in the world quickly and warn people everywhere (Huhn, 2020; Carroll et al., 2021); a rapid response team to address threats on the ground anywhere in the world and contain them; and a global surveillance network that could test a percentage of the global population at regular intervals after a dangerous infectious agent is identified (Gates & Gates, 2021). Was the absence of these systems an injustice?

To address this question, it is helpful to distinguish between harms and wrongs. Kamm draws this distinction in the following way:

> When the cause of one's death is a disease due to nature one is not wronged by nature or the disease. We have no rights against nature or diseases per se; they do not have duties to us not to harm us that they violate. However, if diseases are due to some people's negligent or unreasonably risky behaviour (let alone intentional wrongdoing), then those who died of the disease may be wronged by those people. This includes those in national and international organisations that are responsible for early warnings and containment of spreading disease. Wronging can also come about by a reasonably avoidable failure to provide assistance or resources to which people have a right (Kamm, 2021, no page number).

For Kamm, a *harm* refers to being made worse off relative to a prior state, while a *wrong* refers to harms that were reasonably avoidable and should have been avoided. Here, the "should" signals a relatively strong moral claim, expressed as a right or entitlement of justice.

The structural justice framework allows us to say that death and illness can be avoidable not only when an individual can be held directly liable, but also when death results from human systems and structures that people create and sustain or might have created and sustained but did not (Jecker, 2023). COVID-19-related deaths and illnesses count as wrongs on this analysis if they are both avoidable and if they reflect a failure to take reasonable measures to protect people's threshold capabilities for health. Based on Kamm's analysis, a crucial question becomes whether the COVID-19-related disease and deaths that ensued when the SARS-COV-2 virus spread rapidly undetected should be thought of as merely a harm, i.e., an act of nature, or as a wrong, i.e., largely preventable by a global pandemic preparedness systems of the kind Huff et al. model.

Pandemic Preparedness

One way to address this is to consider the expert knowledge and assessment available prior to the pandemic. The World Health Organization's (WHO's) September 2019 report, *A World at Risk,* gives strong support for the view that the disease and deaths were not just harmful acts of nature but a global moral failure. In it, the WHO presaged the COVID-19 pandemic, warning of "a rapidly spreading pandemic due to a lethal respiratory pathogen," and advised the world to join together by strengthening systems such as detecting and warning, sharing genome sequences, strengthening medical countermeasures and mitigating economic risk by obtaining preparedness commitments in advance of a health emergency (WHO Global Preparedness and Monitoring Board, 2019). Based on the 2019 WHO assessment, the failure to prevent disease and deaths that resulted from the COVID-19 pandemic was foreseen and specific systems that could have prevented or minimized this were not developed and deployed.

Vaccine Allocation

Consider next, the availability of safe and effective COVID-19 vaccines globally after the pandemic had taken hold. Safe and effective vaccines first became available in December 2020. In its 2020 report, *A World in Disorder*, the WHO called for "urgent action" to ensure that COVID-19 vaccines and other countermeasures would be allocated in a way that would have the most impact in stopping the pandemic, establish fair and equitable access, not be based on people's ability to pay, and ensure priority to health care workers and groups most vulnerable to severe disease and death. In addition, each country should receive an initial allocation of vaccine sufficient to cover at least 2% of its population and to cover frontline health care workers (WHO Global Preparedness and Monitoring Board, 2020, p. 7).

The resulting distribution fell far short of these aims. By May 2021, nearly 6 months into the initial vaccine rollout, multiple innovative vaccine designs had been developed by multinational pharmaceutical companies, including mRNA, adenovirus-vectored, and protein nanoparticle vaccines, which were proving to be safe and highly effective; yet, many African and Latin American countries remained almost totally devoid of vaccines (Hotez & Narayan, 2021).

While supply limits meant that some COVID-19-related disease and deaths were unavoidable, much of the severe disease and death that took place could have been prevented if vaccines were distributed more equitably. One way to gauge this is to consider what was possible using existing manufacturing capacities. In March 2021, drug companies were, in principle, in a position to produce sufficient doses of vaccines to immunize most of the world's population by the end of 2021 (Irwin, 2021). Assuming the market continued to be dominated by 2-dose vaccines, the world needed about 11 billion doses to protect roughly 70% of the global population and approach herd immunity. According to projections from Duke University's Launch and Scale Speedometer, more than 12 billion doses of COVID 19 vaccine could be produced in 2021; thus, "If manufacturers are able to reach their goal of more than 12 billion doses this year and if those doses were purchased and distributed equitably across the world's population, we could meet much of the world's needs in 2021" (Taylor et al., 2021, p. 2). Yet, as noted, the reality strayed far from that ideal. As of June 8, 2021, the Duke researchers forecast that at the current pace, it would be 2023 or 2024 before there were enough vaccine's to cover the world's population (McDonnell et al., 2020).

One way to further assess the mismatch between what might have occurred and what in fact did occur during the COVID-19 pandemic is to dig still deeper into the origins or the existing global vaccine allocation and examine the systems and structures that led to it. The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement is a legal framework established in 1995 by members of the World Trade Organization (WTO, 1995). Prior to TRIPS, intellectual property rights were protected internationally by flexible rules, tailored to a country's socioeconomic conditions. TRIPS dictated stricter protocols, mandating compulsory protection of intellectual property and requiring all WTO members to ensure minimal protection and enforcement of intellectual property rights within their territories. The central justification for this was that stronger intellectual property protections were essential to stimulate innovation, which benefits everyone (WTO, 1995, Article 7). As a result of TRIPS, when COVID-19 vaccines were developed, they were owned by a handful of pharmaceutical companies that developed them and held the patents. As of June 2021, 80% of global COVID-19 vaccine sales come from five large multi-national corporations (WHO, 2021b).

Applying a structural justice critique to this legal framework, prompts us to ask: who is advantaged and who is disadvantaged by TRIPS? What impact do patent protections have on the ability of disadvantaged groups to lead minimally decent lives (Jecker & Atuire, 2021b; Jecker, 2023)? The most obvious and direct beneficiaries of the TRIPS agreement were pharmaceutical companies, which profited from controlling the sale of COVID-19 vaccines. According to Wall Street analysts,

in 2021, Pfizer/BioNTech are expected to earn between $15 and $30 billion USD for COVID-19 vaccine sales, while Moderna could make between $18–20 billion USD and Johnson & Johnson $10 billion USD (Kollewe, 2021). While there were expenses that offset these earnings, net profits for pharmaceutical companies were expected to be high, because the research and development of COVID-19 vaccines was heavily subsidized by taxpayers. A 2021 review of published research on the technologies used in candidate COVID-19 vaccines, which spanned a range of diverse methodologies, found that these technologies were funded primarily by the public sector, principally governments (Kiszewski et al., 2021).

The other direct beneficiaries of the TRIPS agreement have been people in wealthier nations, which paid to secure a spot at the head of the vaccine cue by means of advance purchase agreements, which involve purchasing vaccine candidates still under development in exchange for a promise to be first in line to receive the vaccine if it is approved for sale. In October 2020, prior to the development of effective vaccines, more than half of global vaccine doses had been purchased in advance (McDonnell et al., 2020). Advance purchase agreements made it possible for people in wealthier nations to receive booster doses of vaccine before people in poorer nations (including frontline workers and people at heightened risk) had received initial doses, raising justice concerns (Jecker & Lederman, 2022).

The groups that stand to lose most directly from TRIPS are people living in poorer nations, whose governments could not afford to purchase COVID-19 vaccines. While some people in poorer nations obtained vaccines through COVAX, the international partnership that aims to accelerate the development of COVID-19 vaccines and distribute them equitably, COVAX was designed to assist with the cost of vaccinating just 20% of the population of eligible nations, with the remainder of vaccinations left for poorer nations to pay for by themselves, which many nations lacked the means to do. Moreover, supply delays, such as the March 2021 suspension of exports from India, a major global vaccine manufacturer, have slowed the supply of COVAX vaccines, as did the failure of global coordination that led to countries bidding against one another and driving up the prices of vaccines COVAX (and others) were required to pay (Bollyky & Bown 2020). Additional barriers to equitable vaccines distribution included the failure to share technical understanding and expertise (Hotez & Narayan, 2021).

An example of an alternative approach is Hassoun's proposal for a "Global Health Impact Index," which incentivizes pharmaceutical companies and other organizations by rewarding those that extend access to essential benefits, including vaccines, around the world, with the highest-rated companies receiving a "Global Health Impact label" to use on their products; for example, "If people prefer to purchase goods from, and invest in, Global Health Impact–certified companies, companies have an incentive to use the label to garner a larger market share (Hassoun, 2020, p. 74). Such scoring renders accessible key information about a company's social responsibility efforts as a way to encourage ethical consumption patterns by companies and consumers alike.

Needless to say, in the final analysis, everyone stands to lose from global health structures, such as TRIPS, which restrict access to vaccines against emerging

infectious diseases. Likewise, everyone stands to gain by vaccinating the world. As Faden et al. note, national self-interest and justice collide in the context of emerging infectious diseases, because these threats do not respect borders (Faden et al., 2019).

Next Steps: Global Health Partnerships

How can we design more effective and ethical systems to address the threat of emerging infectious diseases? What should global health partnerships in the twenty-first century look like? To address these questions, it will be helpful to briefly take further stock of existing structures designed to do this and their origins. Historically, protecting against infectious disease threats dates at least to the fourteenth century, when quarantine was first imposed to prevent the spread of bubonic plague across borders. Today, we have more highly developed transnational partnerships that have extended and formalized with the 1951 International Sanitary Regulations (WHO, 1951) and the 1969 International Health Regulations (IHR) (WHO, 1969). The IHR was originally designed to protect against cross-border spread of six specific infectious diseases (WHO, 2005, p. 8). Following the 2003 outbreak of severe acute respiratory syndrome (SARS), the limitations of border controls to stop disease spread became apparent. In 2005, revisions to the IHR were enacted to extend protection to "all events potentially constituting a public health emergency of international concern...." and to require states to develop and maintain a range of core capacities in addition to border control, including the ability to detect, assess, notify and report events, health risks, and emergencies of international concern" (WHO, 2005, p. 43). The regulations set 2012 as the deadline for compliance; however, by that date, just 20% of member states had complied and by 2014, only a third had done so (CDC, 2021). These shortfalls underscore limits of the IHR.

The COVID-19 pandemic exposed further shortcomings of IHR and of extant global health system more broadly. The WHO, originally established in the aftermath of the Second World War, lacks an independent funding source and lacks authority to enforce agreements, making compliance with its standards wholly voluntary. The WHO also lacks the ability to command resources required to respond to infectious disease threats; therefore, it cannot offer assistance to countries who need help during a health emergency. Since it serves at the behest of members states, the WHO's ability to render independent decisions free of undue political influence is also constrained. Thus, although 196 countries are signatories of the IHR, enforcement remains weak, a recurring challenge faced by many existing global governance structures, including much international law and regulations.

Addressing these concerns presents not just technical challenges related to establishing more effective global health governance structures, but ethical challenges. While national governments will continue to play an indispensable role, national governments will increasingly need to rely on international and regional partnerships, for-profit pharmaceutical companies, and multinational philanthropic organizations, with the mandate and authority to coordinate and carry out measures like

prevention, rapid response, financing, and enforcement (Jecker et al., 2022a). National governments will also need to depend on multisectoral engagement with civil society organizations, such as philanthropic foundations and advocacy groups, and on ordinary citizens (Jecker et al., 2022a). In addition to exploiting legal tools for implementing cross-border responsibilities (Jecker, 2022), solidarity with global health actors at multiple levels will be integral to realizing and sustaining just health care systems (Jecker & Atuire, 2022; Jecker et al., 2022b).

The Scope of Global Health Partnerships

One way to think of global health partnerships for the future is to consider them as an intersecting territory where multiple players meet. Following Blake, we might divide global actors into three broad and overlapping stakeholder's types: primary political agents, civil society organizations, and ordinary citizens (Blake, 2006). Each type represents a kind of "global citizen" in the sense that each has civic responsibilities and rights attached to their social roles.

First, primary political agents include the governments of nations that are the standard focus of scholarly discussions about political governance both within and between states. It also includes governance beyond the state. Thus primary political agents include global health governance, like the United Nations (UN) and the international organizations under its auspices (e.g., the WHO, WTO, International Monetary Fund, UN Children's Fund (UNICEF) and World Bank), as well as international laws, such as the Geneva Convention. However, under the current configuration, the power to enforce international standards and agreements rests with individual member states, rather than international bodies; the UN has no independent powers of enforcement or sources of funding.

A second level of global health governance includes civil society organizations, which include a diverse group, such as faith-based groups, unions, ethnic associations, non-governmental organizations, advocacy groups, large philanthropic foundations and political parties. Civil society organizations are "secondary political agents," in the sense that they occupy roles that require "deciding what to do in the face of state policy, rather than in the direct formulation of social policy" (Blake, 2006, p. 218). Distinct from ordinary citizens or a collection of them, civil society organizations are organized in ways that allow them to function as representatives or advocates for particular causes and points of view. Their role is undertheorized, as are the normative principles that apply to them. The justice principles germane to secondary political agents are not reducible to those that apply to primary political agents, since they do not directly govern. However, these groups often have more influence on government than ordinary citizens, because they are recognized as occupying roles of authority that enable them to enter public debates with political and social clout. Thus, they tend to wield more power because they can exert more normative pressure on primary political agents in response to policies and laws.

As a consequence of their power and privilege, second order political agents have heightened responsibilities which are role-related and include using their power and privilege in ways that meet the justice standards set forth previously (Sect. 22.2): taking reasonable steps to support minimally decent lives and capability thresholds. This approach aligns with Blake's analysis that infringement of dignity, often expressed as violations of rights, is a concern of global citizens, owed to people everywhere by virtue of a shared humanity (Blake, 2002). While Blake arrives at this conclusion by appealing to the harm of absolute deprivation, rather than threshold human capabilities, his conclusion matches the conclusion arrived in this chapter by appeal to threshold human capabilities.

Lastly, global actors increasingly include ordinary citizens, because individuals are increasingly interconnected in ways that cause individual actions to have widespread effects on people everywhere. This is occurring not just in the area of emerging infectious diseases, but through many other spheres where globalization has taken hold, such as transportation, mass communication, linked financial markets, global trade and supply chains, the internet and social media, and global challenges related to climate change, cyber security, nuclear and biologic weaponry, artificial intelligence and other areas.

One particularly striking way in which individuals come to function like global actors involves using technology to give voice to their views and those of their community. Ordinary citizens who function as global citizens in this manner are sometimes referred to as 'netizens,' a portmanteau of the English words 'internet' and 'citizen.' Falk characterizes "netizenship" as arising from bonds created primarily through association by internet, which establishes identities on the basis of affinities among individuals and groups that may be geographically isolated and disparate, marking a "shift from hierarchy to network" (Falk, 2016, p. 16). This form of global citizenship is vulnerable to capture, manipulation and abuse however, because people's digital lives can be influenced by "politicians serving powerful constituencies and companies seeking to maximize profit" (MacKinnon, 2012, location 242).

The line between ordinary citizens functioning in a networked space and civil society organizations is sometimes fuzzy, and some extant civil society organizations began on the internet, then grew into something more than a networked community. For example, the civil rights dimension of the Black Lives Matter movement began in this way (Chase, 2018), as did the environmental justice movement (Shrader-Frechette, 2002). Both expanded from networked communities to become global movements, but it is hard to say exactly when this took place. The environmental justice movement continues to grow, joining forces with advocates for global health, who see an alignment of (Dobson et al., 2020). As with primary political groups and civil society organizations, ordinary citizens or 'netizens' have responsibilities to function as global good actors, using their power and influence in ways that reasonably protect people's floor level human capabilities (Jecker et al., 2022a).

Next Steps

Returning to the topic of global health governance to address emerging infectious diseases, what role-related obligations can these diverse global actors play in preparing for and responding to emerging infectious diseases? Although a full answer to this question is beyond this chapter's scope, we can paint in broad strokes picture of what just global health partnerships and systems might look like at multiple levels.

Following the general suggestions of Duff et al. (from Sect. 22.1); the Independent Panel for Pandemic Preparedness and Response (Independent Panel for Pandemic Preparedness and Response, 2021), and the approach of One Health (AMVA, 2008), one way to define next steps is to convene a global health council to determine specific forms for leadership and coordination, financing and enforcement, and management of global public health goods. These could include both strengthening existing global health governance and creating new structures and systems where none exist.

Security against emerging infectious diseases requires an all-hands-on-deck approach to global health governance to make it more likely that people will have reasonable chances of leading minimally decent lives during future global health emergencies. It calls for more efforts to ensure the availability of *global public health goods*, which must include defense against the threat of infectious diseases by means of systems for prevention, early warning, rapid response, and essential supplies (Table 22.1).

In the strict sense, a *public good* refers to goods that are in a group's collective interest; yet they tend to be underprovided by the market because they are non-rival, meaning that their consumption does not exhaust them or prevent others from consuming them, and non-excludable, meaning that once they exist, it is difficult to prevent people from accessing them. For example, at a domestic level, roads and armies count as public goods. At a global level, public goods to protect against the threat of infectious diseases, like early warning, tend to be non-rival and non-excludable in these ways.

Table 22.1 Global public health goods

Type	Goal	Example
Prevention	Prevent infectious diseases from being transmitted from animals to humans	Surveillance, recognition, and response to zoonoses
Early warning	Contain infectious disease outbreaks with pandemic potential	Surveillance, tracking, and warning of emergent and reemergent infectious diseases
Rapid response	Quickly address threats detected on the ground	Rapid response teams that can be deployed anywhere in the world
Essential supplies	Ensure global access to supplies to save lives and prevent disease spread	Access to hygiene, personal protective equipment, oxygen, diagnostics, and vaccines

Securing global public health goods will require the kinds of multi-level global partnerships and governance this chapter has described. These forms of partnership and governance should instantiate justice and related values, providing reasonable support for minimally decent human lives and threshold human capabilities. A global health council should represent all countries and relevant stakeholders and have the ability to render decisions within its scope free of undue influence. It should designate an expert group led by scientists and public health experts to set authoritative, evidence-based standards for prevention, preparation and response. It should be empowered in ways necessary to protect basic human capabilities for health and health security for all nations, which requires facilitating engagement at multiple levels inside and outside of government across different scales and sectors in ways integral to global health security. A global health council should also determine means of enforcement and means to independently evaluate each nation's progress toward reaching standards. Since these efforts require investment, the council should have a stable source of funding adequate to address its tasks. For example, funding could include an international pooled fund presided over by existing institutions, such as the World Bank and WHO. It should avoid reliance on voluntary contributions to pay for most activities, which can result in secondary political agents (such as civil society organization and wealthy individuals) wielding undue influence, while undercutting the authority of primary political agents.

Conclusion

Recognizing the prospect of global health partnerships to affect change and enhance global health security is a first step to realizing healthy lives and communities everywhere. There is much we can and should do at multiple levels to prepare for and respond to the growing threat of emerging infectious diseases and to ensure global health justice and security. According to Young, it would be a form of "bad faith" not to take the steps required to improve existing systems; if we passively regard the complex workings of our society as like natural forces whose effects are fortunate for some, unfortunate for others, but not a matter of justice [this] inappropriately reifies them. By treating them under the black box of luck rather than seeing them as the outcome of practices and policies that could be altered, moreover, we adopt a stance of bad faith in respect to our own responsibility for them (Young, 2011, p. 40).

In the case of global health challenges like emerging infectious diseases, one way to avoid bad faith is to appreciate the broad-based capacity of different actors to function as global citizens and their normative power and responsibility to do so.

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Chapter 23
Precision Medicine

Fruzsina Molnár-Gábor

Abstract Precision medicine combines genetic, environmental and lifestyle variability to inform disease diagnosis, treatment and prevention, allowing exact medical interventions both on individual and population levels. Data-driven precision medicine measures constitute an informational intervention that is dynamic in time, space and in terms of actors and groups involved, as well as regarding the relevance of results and the causality of decisions. Correspondingly, normative guidance for decision making is characterised by strong proceduralisation. When justifying data processing, the changing role of patients in relation to data processing needs to be respected. It not only influences the design of informed consent, but significantly impacts data security in response to identified risks. Further issues in precision medicine include dealing with anonymisation as well as the return of research results. New tools such as machine learning and its application through neurotechnologies pose challenges to patients' autonomy, benefit production, sharing, justice and equity. In response to the need for dynamic guidance to engage with these particular challenges, procedural measures and tools framing conduct of precision medicine have emerged, including codes of conduct, closer ethics committee scrutiny and data stewardship models. These tools enable ethics-by-design and contribute to coordination between ethical and legal rules.

Keywords Precision medicine · Data-driven · Machine learning · Neurotechnologies · ML-based devices

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Precision Medicine

Definition, Delimitation and the Translational Turn

Precision medicine grounds the diagnosis, treatment and prevention of diseases on the variability in genes, environment and lifestyle (Jonsson & Stefansdottir, 2019). In order to achieve this grounding, it aims to obtain and integrate genotypic and phenotypic information from molecular, physiological and environmental exposure as well as the behavioural level (Goetz & Schork, 2018).

The term *personalised medicine* is often used as having the same meaning, although there is an important difference. The latter term implies inter-individual variation in disease processes and tailoring medical interventions to unique characteristics revealed by genomic investigations, clinical information and real-world data at the individual level (Joyner & Paneth, 2019). In contrast to such a granular understanding, the term precision medicine focuses on stratification into subgroups or subpopulations for the purpose of targeted, i.e. precise, interventions (Kao, 2018). While stratification is not a new method of diagnosis, treatment, and prediction, the scale and speed of *stratified medicine* have increased dramatically in recent times (Batten, 2018) due to the amount of available high-resolution and longitudinal data and transformative technologies for its analysis and interpretation. Stratification through precision relies on an all-inclusive, complex and systemic assessment of health and disease (Auffray et al., 2009), lately further developed into a network-based systems paradigm (Tan et al., 2019). An *evidence-based* practice of *systems medicine* has been called for in order to promote the transfer of precision medicine results into healthcare (Beckmann & Lew, 2016). Paired with a stronger focus on information influencing health interrelated with genomic data, such as lifestyle, environments and communities, precision public health expands from individualised treatment to the broadest stratification, supporting health inferences and intervention on population level (Juengst & Van Rie, 2020; Khoury et al., 2016; Meagher et al., 2017).

Related to precision medicine, the term *translation* is used to describe the transfer of knowledge (Mandal et al., 2017) about disease mechanisms gained in the laboratory to clinical practice and health-related decision-making, public health and corresponding policies, and vice versa, thereby improving methods of diagnostics, therapeutics and prevention (Seyhan, 2019; Hunt, 2018; Petrini, 2011; Webb & Pass, 2004). The boundary between research on the one hand and clinical treatment and care on the other thus becomes blurred. As a consequence, precision medicine is not only systemic in that it connects individual and public health levels through stratification, but also in that it encompasses ethical constraints and moral issues within both research and healthcare contexts, until now separated in their significance as targets of policy application and in the ways they are handled within corresponding fields of governance and regulation. Ultimately, this leads to the need to respect a *translational turn* within the focus of corresponding normative and social sciences. Respecting the *translational turn* pushes concerned sciences towards an

alignment of their subject matter, a partial approximation of their methods as well as of the aims of their anticipatory guidance beyond their disciplinary particularities, which has been reflected in the development of *ELSI* ('ethical, legal, social issues') as an interdisciplinary research and policy movement (Kaye et al., 2012; Hilgartner et al., 2017).

Setting the Stage for Bioethical Analysis

Characteristics of Data-Driven Precision Medicine

The decisive trigger for the development of precision medicine has been the technology of human genome sequencing (Collins, 1999). Thanks to increasing patient participation and a number of successful application examples in which examined genomic data have demonstrably contributed to improving patient management (Claussnitzer et al., 2020), genomics has been at the forefront of cancer medicine (cf. only Berger & Mardis, 2018; Huntsman & Ladanyi, 2018), followed by the fields psychiatry (e.g. Carter et al., 2017; Chang et al., 2018), cardiology (cf. Tada et al., 2020), drug (cf. Haley & Roudnicky, 2020) and diabetes research (e.g. Kwak & Park, 2016), as well as public health (Lacaze & Baynam, 2019; Ray & Srivastava, 2020), to name but a few, with an increasing broadening towards omics (cf. Pirih & Kunej, 2018 for its taxonomy).

Unlike with conventional medical interventions, most investigations ahead of precision medicine interventions do not require any substantial intrusion into the physical integrity of the person. On the contrary, the main focus of this investigation is data acquisition: it is the informational intervention that stands in the foreground (cf. Heyen, 2012 for an analogy with genomics; Molnár-Gábor & Weiland, 2014). Subsequently, the initial claim to focus on the individual's health based on a specific medical indication morphs into an individual treatment aim that is preventive in nature, as well as into an interest in using health information gained to benefit stratified and public health investigations and treatments. With genomic data being extended by further health-related and real-world data, there is an ever-growing data pool at hand, whereby research aims related to this are changeable over time (Jonsson & Stefansdottir, 2019). Limitations to the analytical approach are undesirable or not possible. Using a broad bioinformatics filter, additional findings can be generated that provide information about a wide variety of genetic predispositions and possible future health developments (cf. Tabor et al., 2011 for genomics only; Fischer et al., 2016). The interpretation of data further requires molecular biology, bioinformatics and increasingly public health expertise, whereby the interpretation can also differ depending on the state of the art in science and technology, or might need clarification in the future.

The amount and diversity of data to be studied, their pooling and the methodology for their analysis, which is based on high statistical validity (in genomics: Molnár-Gábor & Korbel, 2017; in public health: Benke & Benke, 2018; Prosperi

et al., 2018), are decisive for precision medicine. Certain patterns in large data sets are identified and hypotheses are formed from them in order to predict developments, decisions or behaviours and to assign these predictions to specific stratified groups. Further clarification is regularly required to ascertain whether and what correlation and what risk statement can later be used to substantiate actual causalities in disease identification, development and treatment. Until then, correlation assumes a similarly important role as causality within the translational process.

The distinctiveness and diversity of many diseases and disease types, including cancer, combined with the small number of patients for many disorders, not only effectively precludes conventional research discovery based on local sample cohorts, but also mandates cross-matching and sharing data between centres to increase cohort size and enable discoveries, replication and the translation of findings into therapies (Molnár-Gábor & Korbel, 2020). Lately, emerging projects have relied on patients' genomic data, together with other sensitive information, being shared on a large scale across numerous countries (cf. ICGC/TCGA, 2020).

Ultimately, knowledge transfer in precision medicine relies not only on data sharing as such, but also on data transfer in the sense of the transfer of scientific content during the transition between the different phases of the intervention (Hulsen et al., 2019). Data sciences and the development of tools and devices to collect, analyse, interpret and share data hence become the pivotal point in precision medicine.

The Changing Circumstances of Bioethical Issues

Data-driven precision medicine on individual, stratified and public health levels fundamentally changes the situation of patients, affected persons, groups and communities, as well as the related ethical challenges.

The predictive content of health-related results contributes to extending their meaning for the affected persons in time, as analysis, interpretation and extension of data can be continued *in silico* after initial collection (Rehmann-Sutter, 2012). The changes in the concrete object of analysis and interpretation as well as in their methods contribute to research and care increasingly being designed and conducted independently of the patients as physical (animate) beings (Molnár-Gábor, 2017). Parallel to this, diseases and disorders can be modelled and examined in the laboratory in such a way that emerging results can readily be integrated into treatment and further research without additional interaction with the patients. Furthermore, patients can also be examined outside of the clinic and in their own individual private context with the help of various technologies and devices, as is the case with telematics and through self-directed health apps. Altogether, they threaten to turn patients into a "wandering", mobile database. Integrating real-world data relies on both publicly available data sources that can be consulted (Rosen et al., 2020) and patients contributing their own input through appropriate devices. The latter option can lead to more involvement related to data provision, but also, possibly, to the increased medicalisation of various life issues of those affected. Parallel to this

development in healthcare, commercialised direct-to-consumer offers in precision medicine increasingly come to the fore (Moore, 2020).

Changes in the roles of major actors and the involvement of new affected persons and stratified groups in precision medicine lead to a blurring of the traditional focusing on the individual in bilateral, personal relationships of care (cf. Konstantinidou et al., 2017 for the contrary). Besides the relevance of genomics within families and for patients' relatives (Wolf et al., 2015), stratified and public health outcomes of translational medicine will generally take on community meaning (Juengst & McGowan, 2018), which can be further enhanced through data integration and federation. This contributes to a dissolution of conventional attributions of interests to those involved in precision medicine. Moreover, interests (Schaefer et al., 2019) can increasingly no longer be seen as condensed positions to which regulations governing data processing and bioethical guidance have until now responded. Conflict lines and overlaps between interests become changeable and blurred related to the same individual actors, or to affected actors belonging to the same or to a different group, and increasingly between individual and public interests.

Precision medicine thus not only requires new negotiations between individual rights, target group interests, and overall public welfare (Juengst & van Rie, 2020). In essence, it turns data collection, analysis and the application of interpretation results from a traditionally specific intervention into a dynamic process through which new health information gathered from single patients concerned can be generated and used successively and continuously on stratified levels and for public health measures as well as for the development of corresponding health policies. Accordingly, the need to coordinate and balance various interests involved in precision medicine also becomes a dynamic demand, contributing to a strong procedur-alisation of decision-making exercises.

Overall, from a bioethical perspective, the model of shared decision-making in medicine (MacLean, 2009) encounters an unexperienced expansion in terms of time and space, actors, groups and populations involved and affected, in relation to the relevance of results and the causality of decisions as well as with regard to normative guidance needed. Commitments of traditional medical ethics to patient autonomy are extended to include concerns for group health interests (Meagher et al., 2017); traditional research ethics principles aimed at protecting individual participants have become supplemented with social obligations (Vos et al., 2017). Questions about individual and community perspectives of control over the generation of as well as access to and usage of identifiable health-related information (Juengst & Van Rie, 2020) lend a strong privacy and data protection perspective to challenges for autonomy. At the same time, individual disposition over health information diminishes as genomic risk stratification occurs – disparities raised have effects going beyond individual levels (Meagher et al., 2017). The exact benchmark of the obligation to avoid harm by protecting the privacy of identifiable information and by demonstrating professional transparency about information is revealed by health-related data changes (Brothers & Rothstein, 2015). The risks of stigmatisation and discrimination (Ferryman & Pitcan, 2018), distraction and disempowerment increasingly need to be addressed by measures of oversight and mechanisms

of control (Haga, 2017). The creation of corresponding norms, their design, and structure with regard to the relation between bioethical guidance and binding legal regulation demand conceptual engagement with the governance of precision medicine. Last but not least, while engaging with these challenges, inherent and created (Minari et al., 2018) tensions among the values that drive and justify precision medicine on individual and public health levels (Rosen et al., 2020) need to be consciously encountered: control, transparency, accountability, justice, social value, harm minimisation, public health benefit and trustworthiness.

Ethical Concerns and Moral Quandaries

Justifying Data Processing

The Changing Role of Patients in Precision Medicine

Patients have different roles in precision medicine in relation to data processing: justification of data processing, and overview and control over data processing. The legitimising role of patients is reflected in consent. Their overview over data processing, which leads to its monitoring and evaluation, is enabled by transparency and information obligations as preconditions for their empowerment in conjunction with their right to access data about themselves. Patients exercise control over data processing through their individual rights, enabling them to actively intervene in processing operations. In this sense, individual rights help to operationalise patients' self-determination in relation to their data. They are also suitable for bundling different, often contradictory, positions of patients' interest related to the processing of their data in precision medicine contexts, thereby providing them with the basis to assert their interests according to their individual preferences in complex weighing situations, the outcome of which is delimited by respecting the most important values and corresponding ethical obligations intimately linked to autonomy and human dignity as well as integrity.

Increasing data usage for population health and in the public interest pushes back the role of patients in the process of justifying, assessing and controlling health data processing. Data research empowering communities but also putting burdens on them have lately given rise to the call for a focused discussion on ethical principles guiding data research and sharing in the public interest, such as proportionality, equity, accountability and trust, as well as their application in practice (Ballantyne, 2019). Public interest in data usage has recently been framed as societal permission and social licence (Muller et al., 2021; Ballantyne & Stewart, 2019), which enables the recognition of broader stakeholder interests in data processing, but can only be legitimised by increased patient engagement. While data processing in the public interest must accordingly rely on a strong legitimacy related to input, procedure and organisation, it can enforce ethical principles such as inclusivity and accountability that are also leading principles in the focus on precision medicine at the individual

level. Operationalisation of trustworthiness when building such data processing systems, and before that, the identification of the relevant public interest as well as the means of a dynamic maintenance and reinforcement of the societal permission need to be further defined. Particular attention should be paid to common ethical and legal terms such as public interest that have divergent meanings dependent on the exact normative framework, resulting in the fact that a "licence" for a certain data processing conduct opposes individual interest in protection in the ethical sense and might go beyond the understanding embodied in legal frameworks (e.g. Ford et al., 2019).

Informed Consent

The restriction of the concept of informed and voluntary consent has been discussed for a long time in bioethics. It has since been impressively proven that the classical model of informed consent as a one-time act of approval is based on a truncated understanding of autonomy (cf. only Donchin, 2000; Brownsword, 2004; Manson & O'Neill, 2012; Christman, 2011). Concerns around the voluntary nature of consent have emerged primarily when participants belong to a socio-economically disadvantaged group or are in a situation of institutional or hierarchical dependency (O'Neill, 2003). Such dependencies may already arise among patients without a good health situation, resulting in concerns around power imbalance becoming inherent in the medical context.

Increasing medical data processing typical in the context of precision medicine has only further aggravated concerns about the justification of informational intrusion (McGuire & Beskow, 2010). Informational self-endangerment through consent is even being mooted in an increasing number of data processing situations. In addition to the reasons of uncertain information content and communication deficits, there are other closely related uncertainties concerning the secrecy, permanence, impact and value of information (Hermstrüwer, 2016). The consequences of these uncertainties related to data processing appear to have serious effects on decision making in often highly sensitive life situations in medicine.

In order to address the restrictions on consent to data processing, various concepts for its further development have been elaborated. In view of constraints on specific consent, broad consent (Fisher & Layman, 2018) can be used if the concrete design of data processing does not allow a comprehensive purpose to be defined at the time of data collection. In order to avoid blanket or vaguely formulated, and hence invalid, consent and to compensate for the abstract wording of broad consent, corrective measures that enhance transparency and confidence as well as measures implementing data security must be taken (DSK, 2019). Common measures to promote transparency are, for example, the publication of a research plan and the establishment of a website to inform study participants and patients. Additional measures for data security include technical-organisational instruments to minimise risks to privacy such as special provisions to restrict access to the collected data. Trust can be established, for example, by increasing the involvement of patients in data

processing, granting, for example, the possibility to object before the data are used for new questions of investigation (DSK, 2019).

It is explicitly the increased involvement of patients that prominently distinguishes dynamic consent from other consent models. With dynamic consent, parallel to the flexible design of the research project, the basis of justification in the form of approval by the patient or participant is broken down in terms of time and content (cf. only Kaye et al. 2015). Based on this concept, general consent is obtained at the beginning of the research, and this can be progressively updated through smaller-scale extensions to additional data processing steps, often combined with tiered (Forgó et al., 2010) or layered (Bunnik et al., 2021; Bunnik et al., 2013) consent. Proponents of dynamic consent emphasise its advantages in fulfilling bioethical requirements, also in relation to data processing. Accordingly, it allows the conditions regarding expressiveness, specificity, informedness and unambiguousness of consent, revocability and clear recording of the will to be satisfied particularly well (Prictor et al., 2019). Critical voices nevertheless emphasise that dynamic consent offers no advantage in the informational dimension of approval, because it cannot simplify the complexity of the information provided, with detailed and continuous information leading to "information overload" and deterring patients (Sheehan et al., 2019; Steinsbekk et al., 2013).

Dynamic consent reflects a phase-oriented justification of data processing; the proceduralisation in the design of the justification accompanies the progress of the research project. It further emphasises the systematic proximity of the justification and the control of the data processing by the patient by closely coupling the principle of transparency by linking information obligations with the justification for data processing. Dynamic consent puts patients increasingly in a position of being able to assert their control with regard to the information provided throughout the consent process and thus to also position themselves in relation to their previous decision-making with regard to the approval of single data processing steps. Through this set-up, dynamic consent contributes to the operationalisation of patient autonomy and leads to a merging of the various roles of patients in relation to the data processing. In the precision medicine context, dynamic consent has the advantage that it best reflects the structure of a traditional communicative interaction between the actors involved. By giving greater weight to decision-making processes, it not only corresponds conceptually to the shared decision-making model of medical ethics, but also strengthens the understanding of privacy, which is captured as the result of formal and active freedom exercised by patients. With this, it can contribute to gradually smoothing out the imbalance of informational power between data processors and patients that stems from the different nature and level of their health-related knowledge and from natural constraints on the ability to judge each other's knowledge (for more details, cf. Molnár-Gábor, 2021).

Furthermore, dynamic consent lends itself to a comparison of the information content conveyed in different processing contexts and also the flow of communication, especially due to the structuring of communication on the digital level. At a later point, it is also culturally conditioned, so that dynamic consent can be used as an important basis for the emergence of a standardised practice of cross-border

consent that seeks common patterns of participation in cross-border translational data sharing programmes that are recognisable for the individual (Molnár-Gábor, 2021).

In practice, consent to data processing is often obtained at the same time as consent to the medical intervention in the course of a study or, more generally, to a treatment that is subject to the medical law standards of the relevant regulatory regime as well as medical ethics requirements. Increasingly, consent to a treatment that ultimately relies on data processing and is in compliance with ethical principles is considered to be an appropriate protective measure for the benefit of patients under data protection law, releasing consent having to justify data processing in a legal sense, but upholding its function to empower patients while complying with obligations stemming from medical ethics.

With precision medicine increasingly occupying the domain of public health, issues of consent in terms of groups and communities come to the fore. First, justification for data processing related to stratified groups relying on consent is a complicated issue in the absence of a recognised legal standing of affected groups (Weijer et al., 1999). Second, a new kind of trade-off emerges between the imperatives to protect patients and to integrate research and practice for the collective good, which must be guided by the principle of relational autonomy (Lee, 2021). In the course of its implementation, bolstering individual choices underlies the precondition of enhanced transparency, with transparency in turn preconditioning public deliberation about fairness and equity in data usage for public health (Lee, 2021).

Particular Issues Related to Privacy, Confidentiality and Disclosure

Data Security as a Reaction to Risks and Balancing Interests

Precision medicine situations are complex due to multipolar interests spread between actors, conflicting interests associated with the same actors, increased vulnerabilities related to data sharing as well as precision medicine's public health perspectives. This gives rise to complex circumstances that require the concurrent application of relevant ethical principles and values, which often leads to the emergence of competing obligations that need to be carefully weighed and balanced when making research-, health- and care-related decisions.

When framing a major balancing need between the public and private interests in a simplified way and weighing these obligations, consideration must be given to the fact that intervening in the privacy interests and protection needs of patients is increasingly justified by the stratified benefits of the intrusion. The advantages of the intrusion at community and population levels can then be seen as benefits; the intrusion itself and its possible consequences, are mainly focused at the individual level as risks, whereby individual benefits for patients can additionally contribute to individual- and, in particular, privacy-related risks that have to be minimised.

Risks to data protection and privacy can be reduced by data security measures. By reducing the risk, the privacy interests concerned are less at risk, which in turn influences the weighing of corresponding obligations to protect against those risks and obligations to promote the ethical mandate of data sharing and usage in the interest of individuals and stratified groups as well as the public. With these divergent weighing exercises in mind, the primary role of data security can be seen in mirroring the outcome of the trade-off between the different facets of competing interests in weighing processes, to which the balancing of obligations will respond (Molnár-Gábor, 2023). In this way, trustworthy, coherent and secure data processing systems emerge to become a decisive principle of precision medicine.

Anonymisation

Within precision medicine, genetic data pose particular challenges for data protection, as they contain a large number of genetic tags that enable re-identification and are also regularly processed in a highly contextualised manner and combined with other data relevant in the particular context. Accordingly, risks for privacy through the reidentification of patients and participants are generally high. Based on the understanding of identifiability according to a contingent (or relative) notion of autonomy (Purtova, 2018), the decision on the ethically justified level of data protection and corresponding protection obligations can only be made depending on the actual data processing operation including the actors accessing data and information. The contingent understanding of autonomy also means that, from an ethical perspective, contextually anonymised data cannot be treated arbitrarily.

Altogether, the relative understanding of anonymity has three implications. First, anonymisation is not a technical but primarily an organisational measure to respond to the ethical challenges of data processing in precision medicine. While the boundary between technical and organisational measures is fluid, anonymisation is by no means a measure that takes place only on the technical, computerised level, but requires organisation and personnel. Second, contextual protective measures become ethically imperative, initiating sector-specific professional obligations. These are to be applied not only under the premise of integrating professional knowledge, but can also contribute to simplifying the assessment of privacy challenges through concretised ethical requirements in specific areas of processing. This can simplify proof of compliance with guiding values and ethical principles. Third, contextual processing rules can also help to define the transitions between privacy-relevant and -irrelevant processing operations in a given area by defining ethical privacy mandates in relation to the typified processing operation (in this sense, cf. Mourby, 2020). Besides data security and risk management measures, these may include purpose specifications, access rules, documentation requirements, but also procedural requirements in the case of unintentional identification (Mourby, 2020). Establishing these safeguards will help to further concretise medical privacy ethics obligations as part of broader informational governance within precision medicine.

Return of Results

Genomic analysis regularly yields information that can be used to make statements about disease patterns or health risks that are not primarily intended in the context of diagnosis and treatment (Molnár-Gábor et al., 2014). The combination of genomic data with other health-related data in precision medicine and appropriate bioinformatic filters lead to such findings that relate to present and predictive health status and can no longer be considered incidental, but must be expected (Lyon, 2012).

Additional findings from precision medicine contexts place new requirements on the physician's duties to provide information and on their responsibility for treatment. These requirements should still offer protection against unauthorised treatment and treatment that is not sufficiently justified by information, the validity, utility and actionability of findings, whereby the return of such results itself is subject to separate consideration and has been guided by more than a decade of scholarly discussions.[1] How to avoid additional findings leading to introducing insecurities to patients' perception of their own state of health? Do the principles of autonomy and integrity, which grant patients far-reaching decision-making options related to their health, justify a right to be informed about such findings, even if they are not actionable? Questions then arise as to the exact penetrance threshold at which a finding is actionable or needs to be communicated at all or how to deal with the problem of affected third parties. The prospect of additional findings has implications for the doctor's duty of care. Are they allowed to consider the communication of treatable or curable findings and thus give priority to duty of care of non-harm over the patient's right not to know? Are they allowed to comply with the right to information of family members at risk and place this above their duty of confidentiality and possibly above the patient's right not to know? Information about additional findings also imposes responsibilities on patients relating to the communication of such findings to those also affected, to reproductive decisions and also to responsibility for their own state of health (Kollek & Lemke, 2008). These questions only serve to outline types of leading ethical concerns related to the return of results.

On a practical level, it should be noted that if a list of diseases or gene mutations is drawn up for which a search is to be carried out in addition to the diagnostic question, the doctor's mandate changes: the doctor must not only pursue the initial diagnostic question, but also search for the findings on the list, often described as a "positive list". Such lists might initiate an extended treatment mandate, linked to the "minimum list" established by various professional societies (cf. Green et al., 2013). Alternatively, some emphasise that a combination of the physician's assessment prerogative as to whether various categories of findings can be reported back, and the experience about the patients' decision-making whether to use their right to

[1] An extensive reappraisal of the scholarly literature on dealing with additional findings and the return of results of (translational) research, including its semantic description, cannot possibly be reproduced here. For examples, cf. Wolf et al., 2008; Knoppers & Dam, 2011; Hayden, 2012; Green et al., 2013; Zawati et al., 2014; Pereira et al., 2016; Wolf & Evans, 2018; Dyke et al., 2019; Clayton et al., 2021.

know and not to know, should play a decisive role in establishing action corridors for the return of results. Such "experience registers" allow a list of significant findings or genes to be compiled, which can be expanded over time and with growing knowledge about their actionability. Expanded by the documentation of notification experiences, such registries can function as forerunners of codified professional standards and allow an early respect for patient engagement (Tanner et al., 2016). With the emerging public health relevance of results and findings, new types of ethical weighing lines have opened up that demand respect for additional guiding elements in the balancing of public and private interests, duties of care and practicability (cf. Forsberg et al., 2009).

New Tools in Precision Medicine: Emerging Ethical Challenges Through Artificial Intelligence and Neurotechnology

AI tools and neurotechnology can contribute to patient empowerment in health contexts and beyond, and make significant a contribution towards allowing patients to experience a degree of autonomy, freedom of action, integrity and dignity that would be inconceivable without these tools (Ienca & Ignatiadis, 2020).

However, the application of such tools in precision medicine can have restrictive effects on patient autonomy. If artificial intelligence (AI) and machine learning (ML) systems are used to make a diagnosis or a treatment plan, but the physician is unable to explain to the patient how these were arrived at, this could limit the patient's informational basis to make free, informed decisions about their health (Mittelstadt, 2017). The risk that ML-based systems in medicine might even directly restrict choices related to a patient's health, and in this way manipulate them (Nuffield Council on Bioethics, 2018), must be weighed against the patient's self-determination. Besides calculations about risks influenced by an AI system, such concerns may arise in cases where a (semi-)autonomous intelligent system is granted decision-making power based on an evolving and adaptive algorithm, such as when intelligent closed-loop devices actively interfere in the state of the brain (Kellmeyer et al., 2016).

The results of neurodata processing can greatly influence the future behaviour of the person concerned. In addition, it becomes more difficult to position the person affected by a neurotool, for instance a brain-computer interface (BCI), with regard to continuously running information processes and their results as a whole if it is unclear which parts of perception are due to their own brain activity and which parts are the result of brain-stimulating processing by an algorithm (Kellmeyer, 2021). The processing of neurodata could thus ultimately have an effect on the person's relationship to themselves (abolition of self-authority; Gertler, 2020). Dynamic interactions between a patient and an 'intelligent' neurotechnological device may thus have a transformative effect on the sense of agency and the active self, inducing ethical constraints around identity and its connection to decision-making (Sarajlic, 2015). Such constraints on self-determination can serve as an example to demonstrate competing rights and interests of the patient in relation to the same data

processing: negative liberty, i.e. the freedom from unwanted interference with one's mental states and/or cognitive capacities by others, and the positive freedom to fully realise one's cognitive capacities including through treatment and care (Kellmeyer, 2021, with further references).

Additionally, a third perspective of autonomy may be compromised by bringing diagnosis, treatment and care to the patient. Medical AI systems might limit a patient's social interactions, where autonomy manifests itself on an interpersonal level, and raise the risk of social isolation in situations of vulnerability (cf. Sharkey & Sharkey, 2012; cf. also the concept of relational autonomy).

ML and neurotechnology tools challenge privacy in a different way to more established instruments in precision medicine. First, the sensitivity of neurodata is currently disputed (Rainey et al., 2020). It is unclear to what extent data on people's cognitive system open up access to a person's mental blueprint. Neurodata also have predictive potential, because the activity pattern of neurons maps structures of thinking may have significance for the person's actions as a whole. In terms of predictive potential, however, neurodata differ substantially from genetic data in two respects (Molnár-Gábor & Merk, 2021). First, their predictive potential can be harnessed to a much greater degree. For example, when supplementing human cognitive abilities with BCI technologies, data can be analysed in a very close temporal sequence in a first step and brain-stimulated in a second step. Second, neurodata are more characterised by informational uncertainties than genetic data or other health data with predictive significance due to so-called cognitive biases, for example because of an uncertain information content or an uncertain information effect.

While genomic information and information derived from its combination with other health data are difficult to clarify and to explain, thus remaining as information that the patient cannot directly experience and reflect upon (Rehmann-Sutter, 2000), brain data increases difficulties around its perception by the patient as it is often produced on an unconscious level (Lavazza, 2018). This restriction is particularly evident in the application of the right to be forgotten, which is intended to prevent the permanent persistence of information about a person in order to ensure the possibility of the free development of personality (Mayer-Schönberger, 2009). The concept of forgetting does not necessarily include a third party, but means the disappearance of the information as such (Molnár-Gábor, 2019). In relation to neurodata, the right to one's own oblivion of data is becoming increasingly important. Due to the close proximity of these data to the patients and participants and their identity, it is increasingly difficult to distinguish which data served as the basis for decision-making and which data were nevertheless returned to the patient in some form and were thus included in the structure of their decision-making. The process of one's own forgetting is necessary when information processing detaches itself from the patient or participant and becomes independent, only to be fed back into their own decision-making processes (Molnár-Gábor & Merk, 2021).

Benefits for patients arise through respect for their well-being, whereby the patient's subjective knowledge and life experience should guide any decision-making process, particularly the evaluation of risk information, false positives and false negatives. This knowledge should also inform measures of explaining and communicating health-related decisions made by involving AI applications.

The safety and reliability of AI systems is crucial to avoid malfunctions and undetected errors that might induce knock-on effects, producing harmful implications for patients. In addition to technical errors in ML-based devices, informational uncertainties associated with neurotechnology could cause physical injuries, for example, if the wrong control commands arrive in the case of digitally controllable prostheses (or other aids), or if there is a time delay in correcting errors in the control system, resulting in harm to the patient's body or people in the vicinity (Yuste et al., 2017; Nuffield Council on Bioethics, 2018). AI might also be used for malicious purposes such as covert surveillance or the collection of revealing information about a person's health without their knowledge (Fenech et al., 2018), for example based on an analysis of movement and mobility patterns detected by tracking devices.

Transparency and accountability are cornerstones of the just application of AI in healthcare. Difficulties related to the explainability of AI results create problems for validating the output of AI systems. Although AI applications have the potential to reduce human bias and error, they can also reproduce and reinforce biases in the data used to train them (Courtland, 2018). Concerns have been raised about the potential of AI to lead to discrimination in ways that may be hidden, as, for example, datasets used to train AI systems are often poorly representative of the wider population and, as a result, could make unfair decisions that reflect wider prejudices in society and lead to an uneven distribution of benefits of AI in healthcare (DeCamp & Lindvall, 2020). AI-based systems might work less well where data are scarce or difficult to collect and render digitally, negatively impacting underrepresented communities and individuals, for instance with rare medical conditions (Fenech et al., 2018). Altogether, data quality and data diversity emerge as values associated with the development of tools for precision medicine. Biases may be embedded in the algorithms themselves, reflecting the biased assumptions of their developers (House of Lords, 2018; cf. Martinez-Martin et al., 2021 for further types of biases). In this regard, it is vital to guide the implementation of AI by defining clear norms of accountability, as they can contribute to fair compensation in the event of harm. Corresponding professional obligations must encompass training and qualification requirements for medical staff (Nuffield Council on Bioethics, 2018; Brouillette, 2019; cf. Safdar et al., 2020 for insecurities of own workforces) and the reservation that ML-based systems may only be used by medical professionals. Maintaining their skills to be able to take over if AI systems fail might prove crucial in order to ensure the well-being of the patients and avoid harm to them in a just manner.

The challenges of knowledge transfer must be considered on the way to establishing ML-based applications in public health. These can only be addressed in a limited way by establishing professional duties or obligations for manufacturers. For this reason, measures are also necessary at the governance level that lead to better handling of the risks and need to be located within the realm of the leading principles of transparency, explainability and plausibility. Their implementation and application can foster an increased understanding of how AI systems function, also on a societal level. Such measures can be realised in many ways, from research funding to training and education (Campbell et al., 2007), as well as in the form of

different tools to increase the competence of the actors, operators and manufacturers involved. From the perspective of accountability design, enhancing competent handling of AI systems, focus should be placed on ethical issues relating to interactions between humans and machines (cf. Reeves et al., 2021).

New precision medicine tools fuel discussion on equality and equity. Both principles strongly relate to the challenges raised by diverse types of biases through these tools, the connecting obligation of non-discrimination and just application, and the elimination of disparities in health research and care. The use of new tools in public precision medicine is explicitly framed by some as an instrument to combat inequality and the disregard of equity (Cooper et al., 2015). As new medical technologies are implemented in care, inequalities and equity challenges regarding benefit-sharing from the application of these technologies due to costs (Alami et al., 2020), access burdens and the disease- as well as individualised and stratified context-specificity of the technologies and software (WHO, 2019) will play a crucial role and need to be considered when defining obligations related to their development and application. On the other hand, measures of patient empowerment (Schulz & Nakamoto, 2013) and public engagement (Wiens et al., 2019) must increasingly focus on developing and reinforcing the competences of those affected by these technologies as well as preparing, designing and conducting public involvement and commitment on participatory levels of deliberation and decision-making.

Governance: Ethics and Law

The development, specification, and standardisation of obligations corresponding to values and guided by ethical principles can contribute to building a field of reference for conduct in precision medicine. Reference fields of conduct that are transparently guided by an ethical perspective help to increase individual, stratified and public empowerment in the respective field and can contribute to establishing and enhancing trust in compliant conduct.[2]

The substantive-material standardisation of rules of conduct is inherently limited in areas of high ethico-moral constraints such as precision medicine. This is particularly relevant against the backdrop of the empirical turn in bioethics (Borry et al., 2005; Hurst, 2010), an approach which advocates greater focus on social context and experience and less focus on basic principles. The incorporation of empirical research into bioethics enables moral guidance to be given for specific situations and helps bioethics to become ethics in action. Ethics-in-action will usually be framed by guidance relating to the question of how a certain field, i.e. precision medicine can be practiced and will focus on procedural measures informing translational medicine. Its emphasis on the social context of research and healthcare also makes it a fruitful approach in the context of public precision medicine.

[2] For a conceptual presentation of the relationship between bioethics and biolaw, cf. only Knowles, 2001; Ashcroft, 2008; Sperling, 2008; Lecaros, 2019; Valdés, 2019.

Procedural measures and tools framing the conduct of precision medicine have emerged in recent times, opening up to the integration of values and corresponding obligations in the decision-making processes. The most prominent examples are the establishment of codes of conduct, the broadened involvement of ethics committees, and data stewardship models.

Codes of conduct are collections of sectoral behavioural rules developed by the research community itself.[3] In this sense, such self-regulation is understood as the development of specific self-obligatory norms of behaviour through the setting of professional standards (Molnár-Gábor & Korbel, 2017). Codes of conduct point out routes of decision-making and corridors of action; their standards can be understood as interpretative aids for the implementation of general norms in a specific area.

Input legitimacy is crucial for the development of such codes in order to produce appropriate guidance for conduct. Accordingly, experts must be involved in the establishment of the standards to ensure disciplinary suitability of the regulations. Beyond the experts of the subject matter, the inclusion of ethical standards of conduct is a decisive element of input legitimacy of any rules of conduct and particularly for actors of such professions that cannot rely on an established canon such as bioinformatics, but are increasingly held accountable for respecting various facets of ethical standards in their conduct. Additionally, most legal systems define possibilities of giving binding legal force to self-regulatory measures by private actors, including codes of conduct, by referring to them in binding law or by particular legal measures giving them binding force through e.g. labour law measures. Ultimately, rules of codes of conduct representing state-of-the-art behaviour in sectoral areas can, over the long term, become the standard for reasonable care (for more detail on input legitimacy, cf. Famenka et al., 2016).

A greater involvement of ethics committees in decisions relating to data processing in precision medicine can now be observed in practice (cf. already re: MTAs, Chalmers et al., 2014; Ferretti et al., 2020). Ethics committees increasingly demand a description and justification of data processing in research study applications, which they tend to examine from a mixed perspective of privacy and data protection ethics combined with the main data protection principles. The ethical review of compliance with these principles is gaining particular relevance in the approval of research projects and precision medicine studies. The significance of such increasing ethical consideration of data processing is two-fold. First, many principles related to the ethics of privacy and data protection are also anchored in data protection law (Bygrave, 2014), revealing a concerted action in the normative governance of data protection. Second, some data protection laws explicitly address the binding nature of ethical reviews when regulating particular aspects of data protection, such as in scientific research, or in connection with broad consent.[4] While ethics

[3] Codes of Conduct are also anchored in EU data protection law, cf. Art. 40 of the EU General Data Protection Regulation (GDPR).

[4] Cf. Recital 33 of the GDPR. According to this (non-binding) provision, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognised ethical standards for scientific research. Hereby, compliance with recognized ethical standards can be fulfilled by adhering to ethics committees' authorisation of the research planned.

committees, with a few exceptions, are regularly not commissioned to monitor adherence to data protection law, they are instructed to examine compliance with ethical obligations, including those rooted in the principles of data protection. Accountability, data minimisation, purpose limitation, transparency, and lawfulness are also ethical principles of data processing adherence to which can be an indicator of compliance with the law, but are no proof for compliance with legal regulations per se.

Cooperative forms of health data processing must also be designed from the governance perspective. The uncertainty surrounding the disclosure of data to external research actors often significantly contributes to the overall lack of trust in the further use of health and genomic data, even in protected form. To remedy this, data trustees can act as independent entities between the data provider and the data user to mediate data in such a way that its confidentiality and integrity are adequately preserved (Delacroix & Montgomery, 2020). With the help of a trustee, doctors can thus offer their patients the opportunity to make their genetic and health data available to further research in a protected form and to benefit translationally from it without exposing themselves to the risk of a breach of data protection or without losing control over their data. Insights into the delineation of the various purposes of data trustees, their powers and responsibilities, their accountability, and their procedures and modes of operation, provide information about how data protection and ethics concerns can be taken into account in their modus operandi, especially when communicating with participants (Rinik, 2020). Data trustees are increasingly defined by law and anchored in the governance of health data sharing. UK Biobank Ltd. is a prominent example of a successful data trustee initiative, with other countries following suit in establishing such entities. UK Biobank Ltd. was established as a not-for-profit limited liability company and enables access, including commercial access, to health data for research purposes (Bell, 2020). Other than that, the draft Data Governance Act of the European legislator also focuses on specific forms of enhancing trust in data sharing.[5] Data sharing service providers (data intermediaries) are expected to play a key role in facilitating data aggregation and sharing, and thus have the potential to contribute to the efficient aggregation of data and facilitation of data sharing (Recital 22 of the raft Act).

The boundary between ethics and law cannot be blurred; ethical principles only become legal principles when they are cast into their concrete form in compliance with the formal and material requirements. This being said, all three measures – the drafting of codes of conduct, the emerging practice of ethics committees and the development of data trustees – contribute to increased coordination between ethical guidance and legal rules in the area of precision medicine. Codes of conduct are developed based on a bottom-up approach and by integrating ethical advice, with the possibility to gain factual and legal binding force. Data protection laws increasingly mandate ethics committees to provide for the justification of the planned research and for patients' integrity. Data trustees navigate patients' and participants'

[5] Proposal for a Regulation of the European Parliament and of the Council on European data governance (Data Governance Act). COM/2020/767 final. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52020PC0767&from=EN

control over their data in different contexts, regularly instructed to adhere to the will and expectation of the patients and participants. At the same time, they are called on to register stratified and public attitudes towards data sharing and different data usages. By establishing their practice of navigating in areas that are not precisely defined by the law with regard to specific data processing situations or their own procedures of conduct, they can contribute to capturing and implementing individual, stratified and long-term, population-level attitudes to precision medicine.

Taken together, these governance measures can contribute to a formalised ethics-by-design in the performance of precision medicine and can reinforce coordinated and referenced conduct between ethical rules and obligations, where applicable, also prescribed by the law.

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Chapter 24
The Development, Implementation, and Oversight of Artificial Intelligence in Health Care: Legal and Ethical Issues

Jenna Becker, Sara Gerke, and I. Glenn Cohen

Abstract Artificial Intelligence (AI), especially of the machine learning (ML) variety, is used by health care organizations to assist with a number of tasks, including diagnosing patients and optimizing operational workflows. AI products already proliferate the health care market, with usage increasing as the technology matures. Although AI may potentially revolutionize health care, the use of AI in health settings also leads to risks ranging from violating patient privacy to implementing a biased algorithm. This chapter begins with a broad overview of health care AI and how it is currently used. We then adopt a "lifecycle" approach to discussing issues with health care AI. We start by discussing the legal and ethical issues pertaining to how data to build AI are gathered in health care settings, focusing on privacy. Next, we turn to issues in algorithm development, especially algorithmic bias. We then discuss AI deployment to treat patients, focusing on informed consent. Finally, we will discuss existing oversight mechanisms for health AI in the United States: liability and regulation.

Keywords Artificial Intelligence · Health care · Machine learning · Data & health AI · Oversight

An Overview of Health Care AI

Although AI lacks a clear definition (Scherer, 2016), our discussion of AI centers around software that can reason on its own, process and identify images, or process and analyze text. A subset of AI, machine learning software, can learn and improve

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as it is used, recognizing patterns in data (Hao, 2018). AI/ML is increasingly used in health care, from clinical support to administrative optimization. The potential for health AI is certainly great. AI-based software can be used to improve diagnostic accuracy, identify complex clinical trends, and decrease costs for health systems. However, as a novel technology, questions abound surrounding AI development and its use in health care.

Clinical AI software may be used for a wide range of purposes. These products are used today to aid in the diagnosis or treatment of patients (FDA, 2018a), detect diseases like strokes from medical images (FDA, 2018b), or predict a patient's risk of deterioration from an illness like COVID-19 (Brodwin, 2020). The Food and Drug Administration (FDA) has already cleared or approved at least over 500 AI products as medical devices (FDA, 2022a). As we will discuss in Section V, FDA only regulates a subset of clinical AI products. Therefore, the number of FDA-authorized AI products does not demonstrate the full scope of AI usage in clinical settings.

Although much of this chapter focuses on the clinical applications of AI, AI is also used in health care administration, for example: to schedule patient appointments (Murray et al., 2020), assign hospital beds (Forneas, 2018), or allocate care management resources (Obermeyer et al., 2019). Although non-clinical in nature, these algorithms can certainly impact a patient's access to care.

The development and implementation of health care AI follow a few standard steps. The AI developer must acquire data to train, validate, and test the algorithm. The AI developer must develop the algorithm and train it on the data set, as well as validate and test the model. Then a health care organization implements the AI-based software in the real world. But these seemingly straightforward steps raise a number of questions. How do developers obtain health data? When is patient privacy violated by developer use of health data? Is the data set representative of the broader patient population? In what ways can development practices create bias in health AI? Must providers obtain informed consent from patients before each AI use? How do legal and regulatory systems oversee the effectiveness of these products and their safe use? We discuss these questions in the following sections.

Obtaining Data for Health AI

An initial step when developing an AI product is obtaining relevant data for algorithm training, validation, and testing. In the health care context, this can be particularly fraught due to patient privacy considerations.

(a) Training Data: Where It Comes from and Where It's Going

AI/ML is generally trained on large data sets to ensure model accuracy. Developers may obtain these data from a number of sources. Primary health data, like patient diagnoses, clinicians' notes, and laboratory results, are often found in electronic health records (EHRs), controlled by health care organizations. The rise of ambient data collection in hospitals via audio and video collection has led to another rich

source of hospital-controlled data (Gerke et al., 2020a). Primary health data can also be found in health insurance claims, as well as laboratory and pharmacy records.

Health care AI may also be trained on data from non-traditional sources. Patient health apps, like glucose monitoring or menstrual tracking apps, store troves of user-generated data. Life insurance companies also have access to large amounts of patient health data. Finally, organizations with access to large amounts of health data may have data that can be used to make inferences about a patient's health (Price & Cohen, 2019). An individual's search history or consumer data may reveal intimate health information, such as whether the person is pregnant or lives with chronic illness.

With the rise of AI usage in health care settings, the market for health data has flourished. While health care organizations can and do develop their own AI, software companies have increasingly entered the field. Over the last few years, Google has partnered with several large health systems (Japsen, 2019; Dave, 2019; Evans, 2021) to create health AI products. Several EHR vendors have released integrated AI products. Startups have been developing health AI in a range of areas, from precision medicine to patient engagement (Toews, 2020). Thus, in many cases, AI development requires health care organizations to share patient data with third parties.

(b) Data Sharing: Protecting Patient Privacy and Autonomy

The rapid growth of health care AI development has led to questions surrounding patient privacy. First, how does sharing health data outside a health care system impact patient privacy, and how do current privacy laws guard against potential privacy harms? Second, should sharing data to develop health care AI require patient approval?

(i) Health Data Privacy in the United States

Defining privacy is a surprisingly complex task, and scholars have debated the definition of privacy for decades. But one prominent theory of privacy, useful for our purposes, defines it as "contextual integrity," where norms of information sharing are governed by the context surrounding information flow (Nissenbaum, 2004). A privacy violation occurs when these contextual norms are violated, such as when an unintended party gains access to the information.

In the case of health data, the consequences of a privacy violation can be severe. Individuals may experience social stigma and embarrassment, employment discrimination, or even be denied life insurance due to contextual privacy violations involving health information. If health privacy is under-protected, individuals are more likely to find themselves subject to such privacy harms. But if health privacy is overprotected, technological innovation may be dampened, and the benefits of applying AI/ML to large health data sets may be lost.

Health data privacy in the United States is primarily governed by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. HIPAA's privacy protections, developed in 1996, fall short in today's technological context in two key ways.

First, HIPAA only applies to specific "covered entities" and their business associates (Gerke et al., 2020b). Under this framework, not all health data is protected by HIPAA – only individually identifiable health information controlled by specific types of organizations, like most health care providers, health plans, and healthcare clearinghouses (Price & Cohen, 2019; Gerke et al., 2020b; 45 C.F.R. §§ 160.102, 160.103). However, as described above, many more types of organizations have access to health data today, including life insurance companies and technology companies, such as Google, that are generally not considered to be "covered entities."

Second, HIPAA does not adequately protect against reidentification risk for data shared with third parties (Price & Cohen, 2019; Gerke et al., 2020b). Under the Privacy Rule, covered entities may share health data with third parties if that data is deidentified. Deidentification under HIPAA's Safe Harbor merely requires the removal of 18 discrete data elements like names, social security numbers, and telephone numbers (45 C.F.R. §§ 164.502, 164.514(a)–(b)). When health data sets deidentified under the Safe Harbor standard are combined with sufficiently large external data sets that also contain information about the patient, it may be possible in some cases to reidentify the patient – thus it is probably more accurate to say that we have made data harder to reidentify than to treat it as truly completely deidentified. This may be particularly true for some kinds of information that is relatively unique, like genetic information.

These shortcomings are meaningful in the AI context. HIPAA may not apply to a large number of AI developers with access to large health data sets, leaving individual's health data unprotected. Further, health data shared with AI vendors like Google, who have access to large amounts of consumer and in some instances location data, may be at a higher risk of being reidentifiable in some circumstances (Dinerstein v. Google, 2020). The expansion of AI development and data sharing has the potential to lead to real patient privacy harms, and federal law does not fully protect against these harms.

(ii) Patient Consent for Data Sharing

In general, under HIPAA, health systems are, for example, *not* required to obtain patient consent to share deidentified patient data with third parties. Requiring patient consent for all data use and sharing would, perhaps, increase patients' autonomy over their health information. But this requirement, if meaningful, would come at a significant cost.

Obtaining meaningful patient consent each time a patient's data are used and shared to create AI products keyed to specific uses would be monumental and could lead to statistically significant gaps in data sets.[1] If a large health system sees a million patients a year, reaching out to each patient in their EHR data set would be

[1] By "meaningful" we intend to distinguish at the extreme what we might think of as pro forma consent. For example, where the first time a patient enters a health care facility, they sign a form they likely never read that they consent to future use of their data with the identifiers stripped; if they have read the form, chances are they really do not understand the risks and benefits, because how could they without being given specifics about intended uses, what other data sets are present that may be triangulated with this data set, the cybersecurity practices of various data holders, etc.?

a time-consuming and expensive task. The health system would be less likely to want to use the health data for developing AI, which may impede innovation. There is also some concern that a regime that allowed use only with consent might generate important gaps between the data set that is generated and the true full population of patients (Cohen, 2018). Certain patient populations, like patients with stigmatized diagnoses, may be less likely to approve their health data being shared or used outside the context of their own care (Watts, 2019). This could lead to AI products being less accurate for these under-represented populations.

How to resolve the debate between patient autonomy and the benefit of access to these data is contested, but we are skeptical that paper pro forma informed consent does much to right the balance. One of us has argued that patients have a duty to share their health care data for AI and analytics purposes in some instances – where the "user" will be government or a hospital system that is directly aimed at the public good and can provide strong protection against hacking or malicious reidentification (Cohen, 2018). Assuming the risk of reidentification can be reduced, either by removing additional identifiers or through agreements with third parties, the risks to individual privacy may be low if non-zero. The potential gains from AI innovation in health care are significant, perhaps outweighing the risk of reidentification. Patient privacy and autonomy may be protected in other ways. For example, hospital-level data governance boards, made up of both patients and experts, could be utilized to protect patient interests while also not requiring individual patient input (Price & Cohen, 2019). In that model, a trained and informed group of stakeholders would weigh privacy risks against the potential technological benefits rather than relying on individual patient consent (Cohen & Mello, 2019).

But the debate is far from resolved, and indeed across the world we are seeing very different approaches.

AI Development: Data Representativeness and Algorithmic Bias

Although AI has the potential to improve health outcomes across patient populations, the risk of AI bias is also very real. This bias can develop in several ways. First, without data sets that are representative of the patient populations served by the AI, its predictions may be less accurate for those groups. Second, errors in algorithm development, such as using proxy variables, can lead to biased outcomes. Finally, AI can exacerbate existing inequities in health care, reflecting an already biased system.

(a) Data Representation

AI bias can be caused by a lack of representation in AI training data. If an algorithm is trained on data that is not reflective of the environments in which it is used, recommendations and output will be less accurate.

Patient populations vary by health system. Differences in race, ethnicity, socioeconomic status, or health conditions can lead an algorithm that performs well in one health system to perform poorly in another health care organization. For example, if an algorithm designed to detect skin cancer from photographs is trained on data from a health system with primarily White patients, the algorithm will likely degrade in performance when deployed at institutions with greater racial diversity. This would lead to bias, as the algorithm would detect cancer more accurately for White patients than for Black and Brown patients.

Patient populations, as well as treatment patterns and practices, can also vary by location. A recent study demonstrated that the majority of peer-reviewed deep learning image-based diagnostic software was trained on data from patients in California, New York, and Massachusetts (Kaushal et al., 2020). Algorithms trained only on data from certain locations may not be easily generalizable to other locations.

Professor Nicholson Price has argued that AI trained in "high resource" environments, like academic medical centers, are less effective when deployed to lower-resource settings (Price, 2019). First, patient populations differ between the institution supplying the training data and the organization deploying the algorithm. This is similar to the diversity issue discussed above, where demographic differences between patient populations may lead to bias. Second, the recommendations supplied by AI products from high resource contexts may be inappropriate in lower resource settings. An algorithm may recommend treatment that is not available in the health care organization, or it may recommend more expensive procedures over less costly but effective procedures.

The issue of data representation could be alleviated by training AI on data from a diverse group of health care organizations. But this is certainly easier said than done. Health systems developing their own AI products may struggle to find partner organizations willing to share their patient data. Smaller AI vendors may lack relationships with a large number of health systems. Or, developers may find that partnering with more famous health care organizations helps when advertising new AI products. Federal programs, like NIH's All of Us initiative, aim to help create and distribute inclusive, deidentified data sets that AI developers can use for algorithm training. But until such a program comes fully to fruition, training AI on broadly representative data may be out of reach for some developers.

(b) Algorithm Development: Labeling Bias

Issues of AI bias may also arise due to decisions made when developing an algorithm. A prime example of bias caused by algorithmic decision-making is "labeling bias." Labeling bias can occur when AI developers use proxy variables, factors used in place of the actual quantities attempting to be measured. The disconnect between what the algorithm is in fact measuring and what the algorithm is intended to measure can lead to bias (Obermeyer et al., 2021).

In a particularly notorious example, researchers found labeling bias in a widely-used algorithm used to refer patients for care management services that was developed to measure a patient's risk for requiring significant health care resources (Obermeyer et al., 2019). But rather than predicting patient health

outcomes, the algorithm instead used a patient's predicted cost as a proxy for health (Obermeyer et al., 2019). Under that framework, developers appeared to assume that lower predicted health care costs indicated better predicted health. However, health care costs for an individual patient do not only vary based on the patient's health. Cost of care also varies based on the patient's access to care. Because Black patients face unequal access to care, this use of a proxy variable led the algorithm to under-identify Black patients for increased care management resources.

Labeling bias can arise in a variety of health care settings. Although eliminating the use of proxy variables to address the potential for labeling bias is ideal, it can be challenging, if not impossible for algorithm developers to measure the "ideal target" in certain scenarios (Obermeyer et al., 2021). For example, if an emergency department triage algorithm is designed to predict the resources an incoming emergency patient will use, rather than whether the patient actually requires immediate care, the resulting algorithm may be biased based on a number of factors that impact resource consumption, including race and insurance status (Obermeyer et al., 2021). However, whether a patient needs immediate care may be difficult to measure, and these algorithms may require the use of proxy variables to approximate the "ideal target." Therefore, it is important for developers that use proxy variables to analyze their algorithms for potential bias (Obermeyer et al., 2021).

(c) Existing Bias and Disparities

Finally, health AI may be biased based on existing bias and disparities in the health care system. An algorithm's training data may be perfectly representative, but if some patient populations systemically receive poorer care than other patients, that bias will be learned and reflected in algorithmic output. Health care in the United States is racist, from medical school curricula to the historic segregation of hospitals and clinics (Benjamin, 2019). Professor Deborah Hellman has argued that using AI in such settings "compounds injustice" (Hellman, 2021). First, the data itself may reflect bias. For example, if physicians are less likely to accurately diagnose Black patients with skin cancer (McFarling, 2020), a skin cancer detection algorithm trained to learn based on prior physician diagnoses will be similarly biased. Second, the data may reflect the impact of systemic injustice on individual health. This could lead an algorithm to recommend certain treatments or resources at a higher rate for some subgroups over others, which may similarly lead an AI to be biased.

While all these sources of bias are important, an all-things-considered judgment about algorithms must also consider the extent of bias in the status quo non-AI-assisted forms of medicine that the AI seeks to improve. It may *both* be true that an AI is biased (in the sense that it performs less well for X group than Y group) and that it is *less* biased than the standard practice of medicine in a field, such that its use all-things-considered reduces bias. The Perfect should not be the enemy of the Good. But what if it both reduces bias for some groups (even the majority of groups) but exacerbates bias for some groups? How should we consider the trade-offs here? More general political theories about distribution can be helpful – one could imagine, for example, a Prioritarian theory of bias distribution where reductions in bias

to the least well-off group count "more." While most of the existing literature has focused on bias connected to what the law treats as suspect classes – race and gender – there is no reason to believe that these are the only biases rampant in AI adoption. Should, for example, a bias unrelated to a suspect classification (or only weakly associated with it), such as bias against rural patients or patients with pets, count as the worrying kind of bias in this analysis? Part of the question is how much we think the obligation to correct for bias is primarily about accuracy versus being about a way to compensate for prior forms of injustice. While the current interest in bias in health care AI is laudable, there is still plenty of first-order questions such as these for bioethicists to consider as they examine which biases to tolerate versus target.

Using AI: Is Informed Consent Required?

Once AI is developed and deployed within health care systems, we must ask whether patients should be informed on the use of AI in their care.

In the United States, the doctrine of informed consent determines what information must be disclosed to patients in the provision of their care. In standard contexts, such as surgery, this often entails a discussion of the risks and benefits of a procedure. If a patient is not sufficiently informed, a physician may be held liable for a breach of their duty to obtain informed consent.

What physicians must disclose to patients to meet informed consent requirements is primarily based on case law and varies by jurisdiction. In some jurisdictions, physicians must disclose information that a "reasonable physician" would disclose (Cohen, 2020). Other jurisdictions require physicians to disclose risks that would be "material" to the patient (Cohen, 2020). Finally, a few states limit informed consent requirements to surgical and other invasive procedures (Cohen, 2020).

Applying the doctrine of informed consent to health AI is not particularly straightforward. Let's say a physician uses an AI product as a guide in decision-making, such as in considering an AI-based recommendation as to whether to recommend a specific surgical procedure as opposed to watchful waiting. This AI-based recommendation may be one of many data points a physician reviews when making their decision for which surgical procedure to recommend to a patient. A "reasonable physician" would not generally disclose all of the factors they considered and their entire reasoning process to a patient. Is there something special about AI's contribution as opposed to, say, experience with prior patients or medical journal articles? Similarly, many of the things that go into the "old school black box" – the physician brain deciding what to recommend – are not things we typically think of as "material" for informed consent purposes. Should AI be treated differently because of particular patient sensitivity to AI involvement in care?

Legally speaking, the failure to disclose the part that AI played in a recommendation is unlikely to give rise to tort liability for failure to provide informed consent (Cohen, 2020). But ethical obligations often appropriately go beyond the legal

floor. Would it be more ethical to be very explicit about the role of AI in their decision-making? The answer is far from clear. Over-disclosure of AI usage, even when AI use is not material to a patient, may make it challenging for patients to meaningfully evaluate risks (Cohen, 2020). As AI becomes more prevalent in health care, patients may be so inundated by disclosures that they are unable to analyze the risks of each product.

But some scenarios may arise where patients may reasonably expect to be informed of AI usage along with its associated risks. For example, a patient may find a physician's AI use material if a health system maintains a policy requiring physicians to follow the recommendation of AI-based software. Rather than weighing the recommendation of the software along with the physicians' own knowledge and training, the AI product would become the sole determinant of a patient's care plan.

Disclosure might be more important when an AI product plays an outsized role in a patient's care. For example, assume a physician relies on an AI recommendation, as if the AI-based software is a specialist with relevant expertise. The patient should perhaps be informed that the physician lacks sufficient expertise and is relying on an AI product as a quasi-member of the patient's care team (Cohen, 2020). Some scholars have argued that physicians should be required to elucidate the role played by AI in a patient's care (Schiff & Borenstein, 2019).

There has been a particular concern in the law and ethics of AI with "black-box" systems, where AI is not interpretable nor explainable, such as many neural net systems (Babic et al., 2021). Should a physician disclose to the patient that an AI was involved in the care and the reason why the AI made the recommendation it did was *not* one the physician could explain even if she wanted to? Patients may not trust such an opaque recommendation. On the other hand, physicians regularly rely on products they do not understand, including aspirin. Explanation is just one epistemic warrant that something will be good for a patient. If a provider does not understand *how* a particular drug or device works, they may still be confident that the product *does* work, based on clinical trials or other evidence that underly regulatory approval (London, 2019). However, in the current regulatory world, much of the AI used in health care has *not* gone through rigorous clinical trials or a searching regulatory review. Should we "default" into disclosure for such AI systems? Is there a way to make that consent meaningful, especially given the opaque nature of these systems?

Finally, does the analysis of informed consent change when a system is used to help make decisions to allocate rivalrous goods such as an organ, an ICU bed, etc.? If a particular patient refuses to allow AI involvement in that decision-making, this affects not only what they will receive but also the distribution to other claimants. Is this an instance where "informed consent" should be bifurcated – patients should be informed about AI involvement in their care, but if they want to be considered for the allocation *not* be given an opportunity to opt-out of AI analysis?

These are heady questions bioethics has only begun to wrestle with.

Oversight of Health AI

At least two existing mechanisms can be used to oversee health AI development and use in the United States. Physicians, health care organizations, and AI developers may be held liable in tort when patients are harmed by health AI usage. Further, some health AI products are currently regulated by FDA.

(a) Liability for Health AI Use, Implementation, and Development

New health care technologies like AI often lead to complex questions surrounding liability. Physicians, health systems, and software developers (among other actors) may be held liable for patient injury caused by health AI (Maliha et al., 2021). Can the United States' liability system adapt to balance patient protection from dangerous products while also encouraging innovation and the adoption of innovative technologies?

(i) Physician Liability

Physicians may be held liable for medical malpractice if their use of an AI product leads to patient harm. For example, if a physician follows the recommendation of a patient deterioration algorithm that suggests a specific intervention and that intervention harms the patient, the physician may be held liable for the injury. However, under the current liability framework, a doctor would not *always* be liable in this scenario. Instead, liability often depends on whether a physician followed the standard of care expected from such a clinician.

Some scholars (including two of us) have suggested that the current rules of tort liability will prompt physicians afraid of malpractice to use AI merely for confirmatory purposes, to follow the current standard of care (Price et al., 2019). Of course, this narrow use would significantly limit the potential benefits of AI usage whose main goal is to improve overall outcomes in medical care and/or to tailor care to the needs of specific patient populations. For example, if an algorithm used to predict patient deterioration suggests an intervention that deviates from standard practice but leads to a higher survival rate for critically ill patients, we *want* the physician to depart from the standard of care in that case. More generally, it is important that the liability framework for physicians should not deter physicians from using AI when it improves patient care.

Of course, determinations about departures of the standard of care are often in the hands of juries. A recent study found, using individuals playing the role of jurors, that physician liability for AI usage is influenced by whether the AI output deviates from the standard of care, but that the standard of care is not the only factor considered by juries (Tobia et al., 2021). Physicians are less likely to be held liable for harm caused by following the recommendation of an AI product that aligns with the standard of care. But physicians are not necessarily shielded from liability by rejecting all AI recommendations that deviate from the standard of care. Instead, the study indicated that jurors would also give significant weight to whether the

physician followed the AI recommendation, displaying a greater trust in AI among lay individuals than anticipated (Tobia et al., 2021; Price et al., 2021).

Because of the centrality of the standard of care for physician liability for AI usage, it is important to acknowledge how the standard of care can change over time. Physicians should encourage their professional organizations to take active steps to evaluate practice-specific algorithms, and in so doing, may shape the law's understanding of when following and disregarding an AI are appropriate or not.

(ii) Health System Liability

Hospitals and health systems may also be held liable for AI usage and implementation. Health systems may be the better actor to accrue liability for harms caused by the use and implementation of products like medical AI. First, hospitals and health care organizations are likely more financially equipped than individual physicians to pay for damages and increasing insurance rates. Second, removing the burden from individual physicians may help encourage physicians to use new AI products. Finally, health systems are already responsible for the safety of their medical equipment and clinician training.

Hospitals can use their resources to ensure that AI products are implemented safely and that clinicians are properly trained on their use. For example, a hospital system may be held liable if they fail to train physicians on the use of AI, leading to patient harm. Or, a health care organization that does not ensure that an AI system is safe for its intended use, such as a children's hospital implementing an AI tool designed for adult patients without retraining or testing, would likely be liable for any resulting injury (Maliha et al., 2021). The potential for liability may discourage some hospital systems from implementing AI-based products. But hospitals are no more likely to accrue liability for AI usage than for implementing any other novel medical device.

(iii) AI Developer Liability

AI developers may be held liable for product defects, although the barriers to establishing liability over AI vendors are relatively high. A key barrier to liability may be that the bulk of medical AI in use today is used to *aid* physician practice and decisions rather than being used on its own to directly treat patients (Price, 2017). Further, unlike tangible products, software products do not easily fit into the existing products liability framework (Brown & Miller, 2014). Finally, as the regulation of these products ramps up, AI developers are less likely to be held liable for product failures that harm patients (Maliha et al., 2021). Instead, that liability is more likely to fall back on physicians using the software and health systems implementing the product. Perhaps, especially in the case of black-box algorithms where physicians and hospital systems may be unable to sufficiently audit the effectiveness of AI-based recommendations, liability will shift to hold developers accountable for errors (Maliha et al., 2021). However, as our system of liability currently stands, liability concerns should not deter AI developers from continuing to create innovative health care algorithms. But concerns about liability may be so low that

developers are not sufficiently incentivized to develop safe products without an effective regulatory regime.

(b) FDA Authorization of AI-Based Medical Devices

Regulation is another oversight mechanism that can help ensure health AI products are safe and effective. FDA regulates medical devices, including health care AI that qualifies as Software as a Medical Device (SaMD) under the Federal Food, Drug, and Cosmetic Act (FDCA). Although FDA has the authority to regulate AI products, the agency's authority over health AI is somewhat limited, and the agency's regulatory plans remain unclear.

(i) Health AI Constituting a Medical Device

FDA's authority over health care AI is relatively narrow under the FDCA. FDA regulates devices designed for "use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease" (FDCA § 201(h)(1)). Although this authority certainly covers a broad array of AI-based software, software that impacts patient care through use in administrative or operational contexts fall well outside FDA's authority. The Twenty-First Century Cures Act narrowed the medical device definition in 2016. For example, in general, software that supports or provides recommendations to clinicians is not considered to be a medical device and thus not regulable by FDA if the product also provides an explanation of its recommendation that is understandable by the intended user (FDCA § 520(o)(1)(E)).

Of the AI-based software that may be regulated by FDA, the agency maintains discretion over which algorithms it will actually regulate. FDA released guidance in September 2022, which expanded the scope of clinical decision support software the agency intends to regulate (FDA, 2022b).

(ii) FDA Regulatory Structure and Challenges

The regulation of AI-based software leads to a number of unique challenges not faced by FDA in its regulation of tangible medical devices. FDA's regulatory plans for software devices, and AI-based software more specifically, remain in flux.

FDA's traditional device review mechanisms, as FDA has noted (Gottlieb, 2017), do not translate well to the oversight of AI-based medical devices, especially "adaptive" AI algorithms that learn and update with use. FDA piloted a certification program specifically for software devices called the Software Pre-Certification Program (Pre-Cert) (FDA, 2019a). The Pre-Cert program would have allowed algorithm developers that demonstrate excellence in key areas like product quality and patient safety to be eligible for a more streamlined premarket review of their software devices or no premarket review at all. However, after the completion of the pilot, FDA sunseted the Pre-Cert program (FDA, 2022c), leaving open questions surrounding how FDA will regulate software devices.

A couple of key issues remain unaddressed by FDA's current plans. First, how FDA will ensure the safety of algorithm updates, especially for adaptive AI, is unclear. Although FDA has released a discussion paper surrounding updates for AI/

ML-based SaMD (FDA, 2019b) and a recent Action Plan (FDA, 2021), much still needs to be figured out, such as how to continuously ensure the safety and effectiveness of these devices (Babic et al., 2019; Gerke, 2021).

Second, truly understanding the impact of health AI in practice not only requires an understanding of whether the medical device itself is accurate, but also on a wide range of external factors, like the accuracy of medical record input data, how clinicians will react to device recommendations, and the longer-term impact on patient outcomes. Addressing these contextual variables requires a "system view" approach (Gerke et al., 2020c) whereby regulators would, for example, require more frequent human factors testing.

Conclusion

AI has the potential to transform health care, improving patient outcomes and reducing administrative inefficiencies. But a number of issues remain unsettled, such as protecting patient privacy, preventing algorithmic bias, whether to obtain informed consent, and establishing effective oversight structures. These issues must be addressed to ensure the safe, effective, and ethical deployment of health care AI.

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Part V
Animals, Food and Environment: *Using Animals in Scientific Research*

Chapter 25
The Use of Animals in Basic Biological Research

Monica Levy Andersen and Daniela Santoro Rosa

Abstract The use of animals in experimental research dates back to ancient Greece, and there has been debate over the ethics of using animals in this way for hundreds of years; however, this debate has intensified over recent decades. The scientific and technological advances brought about by experimental research using animals are undeniable, and have substantially contributed to the progress of medicine and the increased life expectancy of humans. These advances have had a profound impact on our society and lifestyle. However, the growing use of laboratory animals in modern Science has raised a number of questions, including whether or not it is ethical to use animals in biomedical research, and whether the research findings are translatable to humans. It is the purpose of this chapter to review some of the scientific advances brought about through experimental research with animals, together with some of the moral dilemmas that scientists must face when seeking to test their hypotheses using live animals.

Keywords Animals · Experimental research · Legislation · Biological research · Speciesism

Brief History and Importance of Animal Testing in Biomedical Research

Humans have long used animals for food, transport, and companionship. The use of animals for research dates back to the dawn of medicine in ancient Greece. Aristotle and Hippocrates first described the structure and function of the human body based on animal vivisection (with exploratory surgery of live animals). Galen, the Greek physician of the Roman emperor Marcus Aurelius, advanced the study of physiology to unprecedented levels based on the vivisection of pigs, monkeys, and dogs.

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This knowledge provided the basis of medical practices for the following centuries and was largely undisputed until the renaissance (Franco, 2013; Andersen & Tufik, 2016).

During the renaissance, Vesalius, a Flemish anatomist, realized that there were anatomical differences between humans and animals (Fig. 25.1), and started performing dissections of human cadavers, challenging the established religious conventions at the time. Although Vesalius was more interested in human anatomy, he acknowledged the value of physiological experiments in animals as an educational and training resource. During the period that is now referred to the age of enlightenment, Rene Descartes stated that unlike humankind, animals are "machine-like" beings, incapable of feelings and pain. Although sometimes misinterpreted, this Cartesian philosophy would allow questionable animal experiments in a time where anesthesia was not available. Jeremy Bentham later opposed this view in 1789, stating that: "The question is not, can they reason? Nor, can they talk? But can they suffer?"

The physician–physiologist Claude Bernard introduced principles and methods for experimental research, arguing that only properly controlled and rigorously conducted animal experiments would provide consistent information on physiology and pathology. Despite the alleged cruelty in his experiments, in which the paralyzing agent curare was used to experiment on awake animals, Bernard's publication of *Introduction à l'étude de la médecine expérimentale* was an important milestone for a new generation of physiologists by laying the foundation of experimental medicine (Franco, 2013). The advent of anesthetics and the similarities between man and

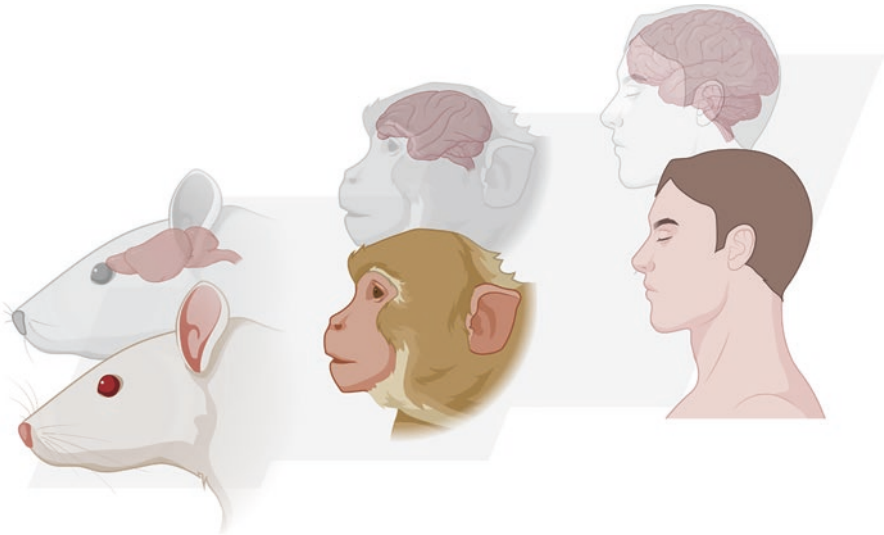

Fig. 25.1 Illustration of the anatomic differences observed in the mouse, monkey and human brain. Image created with BioRender (biorender.com)

animals proposed by Charles Darwin in The Origin of Species helped to increase the popularity of animal experimentation in the nineteenth century. It is important to mention that not only humans benefited from the medical innovations derived from animal testing; Veterinary Science and animal husbandry have also made significant progress by using the results from animal experiments to develop novel therapies and technologies to help save animal lives.

Animal research and testing have produced great advances in Medicine and Biology, contributing to the understanding of human and animal physiology parallel with the development of Medicine. Over recent centuries, animal research has pushed the boundaries of science and created modern medicine as we have come to know it, having a pivotal role in the development of countless novel medical therapies and devices. Most, if not all, of the modern scientific breakthroughs which had the greatest impact on modern medicine were either discovered through animal experiments or first tested on animals.

An immense contribution was made to the field of heart surgery from testing the procedures in animals when, at the turn of the twentieth century, pioneering physicians started testing the surgical procedures to repair heart valves in dogs and pigs. Insulin was discovered in the 1920s by injecting aqueous extract of the pancreas in diabetic, pancreatectomized dogs, revolutionizing the treatment of diabetes (Vecchio et al., 2018). The efficacy of penicillin as an antibiotic was first tested in a live organism using mice in 1940. The development of hip prosthetics was first tested in sheep in the 1950s.

Another area that has seen great progress with the help of animal testing is behavioral psychology. Ivan Pavlov first described classic conditioning measuring salivation in dogs. Operant conditioning was first studied by B.F. Skinner by testing the behavior of pigeons, and later rats, contributing immensely to experimental psychology (Skinner, 1976). Antidepressant drugs were developed using rats by testing molecules that act on the brain.

Most of the knowledge we have today in the field of sleep physiology and the different stages of sleep come from experiments with cats (Jouvet et al., 1959). The applicability of asthma inhalers as a treatment was first tested in guinea pigs and the employment of magnetic resonance imaging (MRI) as a diagnostic tool was first tested in pigs. This is to mention just a few cases where animal experimentation and testing have brought medical breakthroughs that improved people's lives.

Following the atrocities committed by the Nazis during World War II, who performed experiments on Jews and other minorities, the Nuremberg code determined that every experiment with humans "should be planned and based on results obtained from animal experimentation". Nowadays, nearly all of the novel drugs released into the market go through preclinical development using laboratory animals at some point. The exception for this trend is the cosmetic industry, which decided to ban animal testing altogether in favor of alternative methods, such as artificial skin.

Despite the undeniable progress that animal experimentation has brought to modern medicine, there are two main concerns among the scientific community that may jeopardize the applicability of animal findings in clinical practice: their

translational potential and reproducibility. The former refers to the growing concern that biological phenomena, as well as potential therapies, discovered in laboratory animals may not be applicable to humans. This puts every new scientific finding at risk of not being relevant to the pharmaceutical industry and medical practice. For this reason, research institutions and funding agencies encourage and value a translational approach to research.

The latter is a methodological crisis in which many scientific studies cannot be replicated or reproduced, particularly in Medicine and Social Sciences. It is often referred to as a reproducibility crisis and poses a grave threat to all fields of science, since the replicability of research findings is one of the most important aspects of the scientific method. In a survey by the journal *Nature* of 1576 researchers, 70% of the interviewees reported that they could not reproduce the findings of other research groups, and more than half claimed they could not replicate their own findings (Baker, 2016). Among the suspected reasons for this, besides scientific fraud, are the lack of appropriate blind investigators, the absence of proper positive and negative controls, inappropriate statistical tests, and failure to show all the data.

Taken together, the scientific breakthroughs of the last two centuries, from great discoveries in physiology to novel therapies to treat human diseases, highlight the importance of animal testing for the progress of medicine and animal sciences. However, the more advanced a field of life science gets, the more challenging it becomes to translate the findings to humans and to replicate these findings. For this reason, it imperative to establish validation criteria for the animal models that replicate human physiology and diseases.

Validation of Animal Models

Modern science has experienced a shift from studying animal physiology in an intact organism to the development of models that replicate human diseases in laboratory animals. Animal models are representations of human disease and physiology that can be manipulated and are used to test hypotheses on disease mechanisms and novel therapies. Some human diseases are easier to model in experimental conditions than others. For instance, zoonotic infections are caused by pathogens that can infect both humans and animals alike, and although they might cause a distinct disease in different species, animal models can be easily applicable. Other infections that are not zoonotic can also be reproduced in animals, although humans are the main host for the pathogen. Other human diseases with more complex etiologies might pose a greater challenge to model in laboratory animals, especially those that do not develop spontaneously and may, therefore, have to be induced experimentally. Neuropsychiatric and immunological disorders are good examples of diseases that have to be experimentally induced in laboratory animals.

These animal models are essential to connect scientific laboratory research to clinical practice. They are very useful to develop a better mechanistic understanding of the disease itself, to develop potential therapies, or to validate the applicability of a given procedure. Nevertheless, no animal model is universal and completely replicates human disease. For this reason, McKinney and Bunney first introduced validation criteria for animal models of depression (McKinney Jr. & Bunney Jr., 1969; McKinney, 1989). Although their research was focused on psychiatric disorders, their criteria apply to any experimental disease where animal models are used. Their initial validation criteria were later simplified by Willner (1984) into three: predictive, face, and construct.

Predictive Validity

This criterion is based on the idea that an animal model should share a similar drug effect with the human treatment, and how well it can be used to predict the effect of currently unknown therapies. It is extremely useful in the drug discovery process (Sams-Dodd, 2006) and ideally, it is combined with face and construct validity, but that is not always the case. For example, the tail suspension and forced swimming tests are behavioral tasks that have been used by the pharmaceutical industry in the drug discovery process for many decades to test the anti-depressive potential of a compound based on the fact that classical anti-depressive drugs decrease the immobility time in these tests. However, this behavioral model is not so useful to test whether or not an animal is technically depressed, since it does not have good face and construct validity.

Face Validity

This is achieved when an animal model replicates partially or completely the biology and symptomatology of the human disease. For example, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of Parkinson disease and the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis. Both cases have an excellent parallel with the human disease in terms of biology (degeneration of substantia nigra dopaminergic neurons and autoimmune response to myelin, respectively) and symptoms (motor disability), being used for many decades to model these diseases (Potashkin et al., 2010). They are often used to test potential new therapies, and also have good predictive validity. However, they do not replicate the true pathophysiology of the disease since they are not spontaneously developed by laboratory animals and have to be experimentally induced.

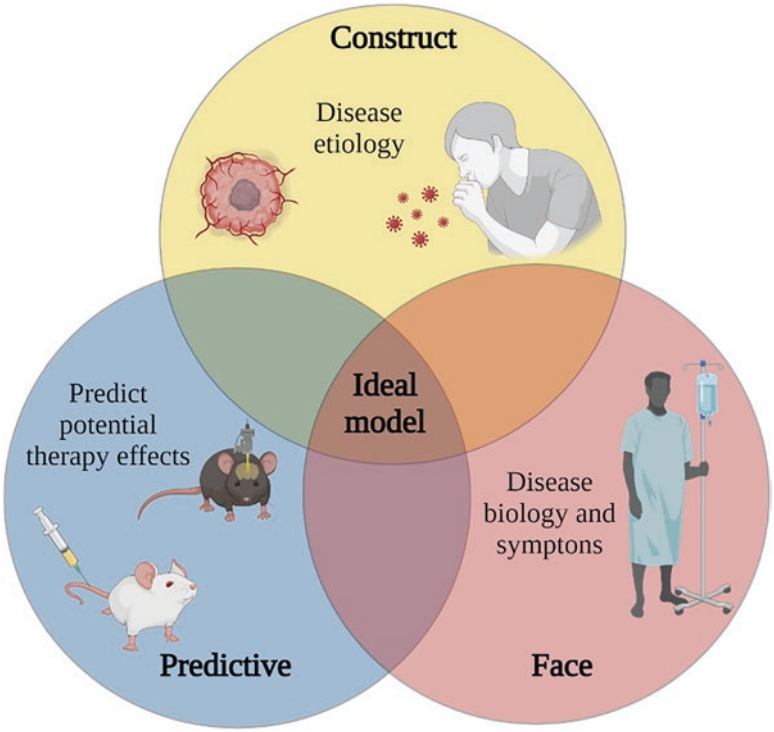

Fig. 25.2 Illustration of the three validation criteria of an animal model and how well it replicates specific aspects of the human disease. Image created with BioRender (biorender.com)

Construct Validity

This refers to an animal model that shares a similar etiology with the human disease and how well it can be used to replicate the disease phenotype. This validity often comes together with predictive and face validity. For example, the models of depression induced by chronic stress in rodents, such as chronic unpredictable stress and repeated social defeat, share a common etiological agent with human depression (chronic stress, construct validity), induce a similar disease phenotype (anhedonia, face validity), and can be used to test novel compounds in drug discovery (predictive validity).

These criteria are illustrated in Fig. 25.2 and have been extremely useful in guiding researchers in the selection of an appropriate model according to the research objectives, as well as to determine the potential limitations of a preclinical finding. At least one of these criteria has to be fulfilled for the research with that given preclinical model to be translatable to humans. The more criteria that are met, the better the model is at replicating the human disease, and the greater is its applicability. However, if none of these criteria are met by a given animal model, it is advisable to search for alternatives.

Ethical Concerns and Animal Protection Movements

Despite the medical advances that animal experimentation has brought, the growing use of laboratory animals in research has resulted in an increased focus in society on the ethical and moral dilemmas related to this type of research. We address some of these concerns in this section.

The first concern arises from the question of whether or not it is justifiable to use other species for our benefit. One can claim that humanity is not morally superior to any other species and, therefore, must not exploit these species for food, transport, and research. These practices are considered cruel by many, and disregard the fact that these animals, from farm to laboratory, are sentient beings capable of feeling pain and suffering. From the philosophical point of view, this is referred to as speciesism – the idea that the human species is morally superior to all others, therefore having greater rights over them, and being free to treat them how they like, whether that be as a food source or as the subject of laboratory experimentation. Some consider speciesism as a form of discrimination that compels differential treatment according to one's species.

This debate about the treatment of animals encouraged the creation of animal rights and protection movements all over the world, such as People for the Ethical Treatment of Animals (PETA), the European Coalition to End Animal Experiments (ECEAE), the Center for Alternatives to Animal Testing (CAAT), and the 1R Institute of Promotion and Research for the Replacement of Animal Experimentation. These organizations call for an end to the exploitation of animals, including in scientific testing and experimentation, arguing that it causes unnecessary pain and suffering to animals, that the applicability to humans is often difficult to prove, and that the benefits that animal testing provide, if any, do not outweigh the suffering imposed on the animals and could be obtained in alternative ways. Their concerns led many cosmetic companies to cease animal testing and invest in the development of alternative methods, such as artificial skin.

As for biomedical research, it is more difficult to replace animal testing with alternative methods that completely replace the intact organism in all its complexity. The thalidomide tragedy is a good example of the importance of proper animal testing. After being proven safe for the treatment of morning sickness in pregnant women based on preclinical testing in rodents, it was later discovered that thalidomide is teratogenic and causes birth defects in humans, including malformation of limbs (Vargesson, 2015). Following new preclinical tests, this time in non-human primates, the emergence of teratogenic effects revealed that this effect is restricted to primates, and rodents are largely unaffected. This event taught the scientific community important lessons about why they should not skip steps in preclinical research, particularly when it comes to drug safety.

Notwithstanding, researchers agree that ethical animal experimentation has to be conducted under certain conditions. Consequently, guidelines were developed by the American Psychological Association to safeguard animal welfare and the proper use of animals in research. According to the *Guidelines for Ethical Conduct in the*

Care and Use of Animals (2012), in respect of the justification of the research, there should be a reasonable expectation that it will:

(a) Broaden the knowledge of the processes involved in the investigation, as well as to pursue better comprehension of the workings of each species;
(b) Determine the reproducibility of previous research;
(c) Supply results that benefit the health of humans or other animals.

In addition to these criteria, the research has to be conducted employing every possible method to prevent or minimize animal pain and suffering, by respecting and understanding their physiology and behavior. The humane endpoint, in which the animal experiment must be interrupted and the animal euthanized to prevent further suffering, was created as a requirement for every research project. Every researcher must acknowledge that the use of animals in research is a privilege that has to be protected to mitigate the illnesses of humans and animals. This can be achieved by the employment of responsible and ethical practices in their research.

This trend culminated with the creation of Laboratory Animal Science (LAS) as a field of knowledge in the 1950s. This field is comprised by the understanding of an animal's complex biological and environmental requirements, microbiome, genetics, nutrition, and social organization, and led to considerable advances in the field of animal experimentation. Together with LAS, new laws were implemented in many countries, and animal welfare organizations that promoted the responsible use of laboratory animals and ethical practices in biomedical research were created.

Legislation for the Use of Animals in Research and the Creation of Animal Welfare Oganizations

With the growing concern of society and animal protection organizations about animal experiments, several laws to regulate the use of laboratory animals were created. The rise of the use of legislation to protect animal welfare in experimental research has promoted the development of minimal standards for the use of laboratory animals and encouraged the creation of national and international organizations with the purpose of safeguarding the advance of ethical biomedical research by establishing guidelines and providing training for researchers and staff.

Although growing public concern over the last few decades has promoted an increase in animal welfare legislation, it has a relatively long history. The first animal welfare law was introduced in the UK in 1876 and was named the "Cruelty to Animals Act" and established that researchers can be held accountable and prosecuted for cruelty if an experiment causes pain without any proper justification relating to prolonging or saving human life. Since then, other countries have introduced legislation to safeguard the welfare of animals.

Two important directives were issued in Europe to regulate the use of animals in experiments. The first, the *Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS 123)* was drafted in 1985.

This first document laid the foundation for the creation of the *Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (86/609/EEC)*. This comprehensive and strict piece of legislation applies to any animal pain, suffering, or lasting harm during experiments and covers the use of proper housing, the care of laboratory animals, as well as anesthesia and euthanasia methods.

In 1978, the Federation of European Laboratory Animal Science Associations (FELASA) was created to bring closer the different European animal science associations and develop common resolutions and reinforce the 3 R's principles (the guiding principles in respect of animal welfare, described in detail in Sect. (The 3 R's) across its 28 country members. It also accredited European research institutions to provide training and certification in LAS. The LAS course prepares the personnel for the use of laboratory animals in research, covering theoretical and practical training in animal physiology and common procedures and handling, as well as in each country's existing legislation. The LAS course certifies researchers and animal technicians in respect of conducting experiments, killing animals, animal husbandry, and/or submitting ethical applications, and is required to gain access to animal facilities and conduct animal experimentation.

In the US, the *Animal Welfare Act of 1966* created minimal accepted standards of animal treatment and care. However, it excluded rats of the genus *Rattus* (laboratory rats) and mice of the genus *Mus* (laboratory mice), as well as birds and cold-blooded animals. The National Research Council later included laboratory animals in the *Guide for the Care and Use of Laboratory Animals* (1996), which established guidelines for the housing and care of laboratory rats and mice. The accreditation of research institutions by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC) was introduced in 1971, with the revision of the *Animal Welfare Act*. It was later determined that each research institution establish an Institutional Animal Care and Use Committees (IACUCs) to apply and reinforce existing laws about research with animals in the US.

In Brazil, there was a marked breakthrough in 2008 with the approval by the Congress of law 11.794, more commonly known as the Arouca Law, which was the first piece of legislation to regulate animal use for teaching and experimentation at the national level and was much welcomed by the scientific community. This law laid the foundation for the creation of the National Council for Control of Animal Experimentation (Conselho Nacional de Controle de Experimentação Animal – CONCEA), an organ affiliated with the Ministry of Science and Technology, which is responsible for accrediting research institutions and establishing rules for the humanitarian use of animals in biological research. The Arouca law also required that any institution that uses animals for research establish an Animal Ethics Commissions – Comissão de Ética no Uso de Animais (CEUA), and established penalties in case of non-compliance with the law (Andersen & Helfenstein, 2015; Maria Garcia et al., 2018; Andersen & Winter, 2019; Dittrich et al., 2019).

Regardless of the country of origin, the main objectives of these organizations are to reinforce the existing legislation, impose penalties for non-compliance and promote the 3 R's, the main guiding principles for the use of animals in ethical

biological research. In addition to the legislative provisions, research institutions all over the world have established animal ethics committees, which review submitted research proposals on an individual basis. People with and without biomedical backgrounds, as well as members of animal welfare organizations form these committees. The task of the committees is to make a careful ethical evaluation of the research objectives and experimental procedures of each proposal, and determine whether the benefits of the proposed experiment outweigh the potential animal suffering. They often suggest changes in the experimental practices and humane endpoints, as well as defining the animal discomfort as minor, moderate, or severe, to ensure that researchers establish adequate protocols throughout the experiment. Any deviation from the previously agreed research plan has to be approved by the same committee. The work of the animal ethics committees is reinforced by animal care personnel, who help to mitigate the suffering of laboratory animals during experiments and improve their welfare.

The 3 R's

The creation of LAS as a field of knowledge in the 1950s led to substantial improvements in animal welfare and *in vivo* experiments. Its guiding principles are the 3 R's, which stand for replacement, reduction, and refinement and was first introduced by Russell and Burch (Fig. 25.3) in their 1959 book "The Principles of

Fig. 25.3 Russell and Burch, the creators of the 3 R's principles for ethical animal experimentation. (image published courtesy of Fund for the Replacement of Animals in Medical Experiments. www.frame.org.uk)

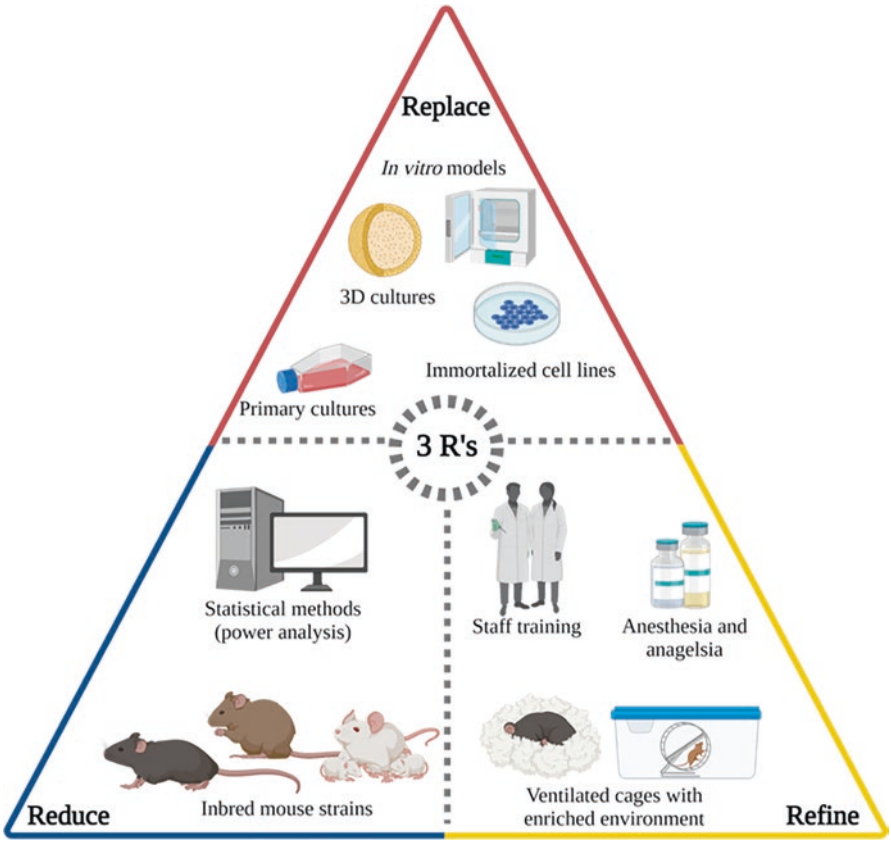

Fig. 25.4 The 3 R's principles for ethical animal experimentation. Image created with BioRender (biorender.com)

Humane Experimental Technique" (Russell & Burch, 1959). These principles helped scientists to introduce new alternative methods into their research to improve animal welfare, reduce unnecessary suffering and substitute live animals in their experiments whenever possible. In this section, we will briefly describe these experimental strategies, which are illustrated in Fig. 25.4.

Replacement

Replacement refers to the use of alternative methods in biomedical research that would completely abolish, whenever possible, the use of laboratory animals in the experimental practice without weakening the ability to obtain quality research data and the advancement of the field. Several tools have been developed over the last decades to substitute the use of live organisms in scientific experiments.

The first and best-known developed method for replacement is the *in vitro* system, either using immortalized cell lines or primary cell cultures. The use of immortalized cell lines is one of the most common approaches and has several advantages. These immortalized cell lineages come from multicellular organisms that, due to mutation, escape the normal cellular senescence and death and can be sustained for prolonged periods. Common origins for cell lines are isolated tumors and embryonic cells, cells that have undergone a viral-induced mutation that disrupts the cell cycle, artificial expression of proteins that are essential for immortality, etc. They can be easily stored by freezing for long-term use, which makes their purchase from online depositories and delivery relatively simple. Once the culture is established in laboratory, it can be maintained for long-term application and can be used for several different research purposes, including, but not limited to, target identification and validation, and testing the efficacy of new compounds in the biopharma industry.

The second *in vitro* strategy is the use of primary cells for research experimentation. Although the use of live animals is still required to obtain these tissue cells to be tested *in vitro*, the experiment is often terminal to the animal and poses no suffering from the animal welfare perspective. The use of tissue slices has also been introduced, particularly for electrophysiological experiments, with good results. Additionally, the number of animals required to obtain tissue cells for a primary cell experiment is a fraction of that which would have been necessary for an *in vivo* experiment. For this reason, primary cell cultures also qualify for the reduction aspect of the 3 R's.

One modern *in vitro* approach is the 3D culture, also known as organoids or mini-organs. This type of *in vitro* system replicates the cell-to-cell interactions in a three-dimensional microenvironment that happens in live organisms, as opposed to the two-dimensional environment in commonly used *in vitro* systems (Petri dishes and culture plates), and it has been extensively used to model diseases and to test new compounds.

Reduction

Reduction methods are experimental alternatives that would reduce the number of animals required for *in vivo* studies, whenever replacement methods are not viable substitutes. Reduction strategies come in a variety of alternatives, ranging from statistical tools to mouse strains.

In this respect, statistical methods, such as power analysis, can be extremely useful to decrease the number of animals used in a certain experiment. Power analysis can determine the number of animals per group required to reach statistically significant results. It does not necessarily reduce the number of animals used per se, but helps to avoid using more animals than necessary by establishing the appropriate sample size in advance based on preliminary experiments.

Another common way to reduce the number of animals used in a preclinical setting is the use of inbred strains. These mouse strains are obtained through a rigorous

inbred mating system between siblings across more than 20 generations, which removes genetic heterogeneity and generates a population of animals that are almost identical to each other. This low genetic variability increases the consistency of the biological responses and the research data, improving the reproducibility of results and allowing the use of a lower number of animals per group. Among these mouse strains, the C57BL/6, BALB/c, DBA, and A/J are the most commonly used in biomedical research.

Methods for the standardization of the animal environment and housing can also be considered reduction tools since they create conditions of equal health standards and controlled microbiological populations. The use of individually ventilated cage systems, environmental enrichment, socially stable groups, and balanced nutrition, among others, are strategies that can be employed to standardize the health condition of the laboratory animals, hence promoting greater consistency in research data and reducing the number of animals used.

Refinement

Refinement methods are approaches that aim to reduce the discomfort and suffering of laboratory animals during scientific experiments by carefully observing and respecting the animal behavior and physiology. Equal conditions and the standardized housing of animals, according to the animals' specific needs, as mentioned in the reduction section, are also appropriate methods of refinement. In addition, environmental enrichment in the cage that encourages the innate behavior of the animals in respect of behaviors such as nest building, burrowing, foraging, exploring, and gnawing is an important refinement method to reduce stress levels and increase well-being. For example, bedding and nesting material, hiding structures, toys, running wheels, and chewing materials are items that can help to create a healthier and more interactive environment for the laboratory animals.

In addition, providing adequate anesthesia and analgesia to the animals, as well as determining the humane endpoint and providing individual care in experiments deemed to be severe are mandatory practices in respect of good animal welfare. It is also vital that the staff and researchers who work with live animals have received the proper education and training to improve experimental procedures in respect of animal care (Fig. 25.4).

Final Considerations

There has been a great deal of recent discussion on how to conduct animal experiments and advance the field of biomedicine in respect of the development of new knowledge and therapies and, at the same time, address the growing concern of the general population and the animal rights movements about animal welfare. Over the

last decades, the importance of the role of laboratory animals in pushing forward the boundaries of biomedical science is undeniable. Medical advances in cardiology, metabolism, psychiatry, genetics, and pharmacology would not have been possible without animal testing. These scientific breakthroughs helped to increase the life expectancy of the population and improve animal welfare. However, it is important to find the right balance between animal welfare and biomedical research when it comes to the use of laboratory animals in scientific experiments.

On one hand, it is not uncommon to find a growing feeling among researchers that the progressively stricter rules for the use of laboratory animals in experiments will eventually make biomedical research unviable beyond *in vitro* experiments. Unreasonable demands from ethics committees, and persecution and even threats from some sections of the animal rights movement, add to these concerns. On the other hand, it is the responsibility of the researcher to consider the eventual benefits that their research will bring to the field and make a careful evaluation on whether or not this new knowledge/therapy/technology outweighs the potential animal suffering that the experiments might cause. If it does not, one should be aware of this and seek alternative methods, whenever possible.

In addition, the members of ethics committees should bear in mind the potential progress of the biomedical field and refrain from making irrational requirements that can potentially harm the researcher's capacity to perform *in vivo* experiments. Institutions, such as CONCEA in Brazil, FELASA in Europe, and AAALAC in the US can provide educational training to ethics committee members in that regard.

Collectively, the challenge for the next generation of scientists is to find the right balance between the continuation of biomedical advances and the growing concerns about animal welfare. Keeping strategies, such as the 3 R's, in the forefront of the minds of researchers, as well as raising awareness of the general population about the importance and potential benefits of biomedical research are very helpful to bridge the gap between the scientific community and society, who must work together to fight misinformation and promote the progress of biomedical research.

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Chapter 26
The Use of Animals in the Study of Human Disease: Key Roles of General Ethical Principles

Jerrold Tannenbaum

Abstract This chapter presents and defends key ethical principles for the use of animals in the scientific study of human disease. The discussion focuses on the roles that general ethical principles, and sets or collections of such principles, play in this research. Because of the importance and wide applicability of general principles in ethical assessment of human health-related animal research, the chapter is able to provide a useful overview of ethical issues raised by this research. The chapter discusses the roles that sets of general principles play in providing ethical guidance to those involved in this research, and in expressing their central obligations and ideals. The chapter identifies the ethical core of human health-related animal research: the basic general ethical principles that govern its use and care of animals.

Keywords Human disease · Animals · Welfare · Ethical principles · Health

Introduction

Aims of the Chapter

This chapter presents and defends key ethical principles for scientific research that employs animals to understand, and ultimately to prevent, alleviate, and cure diseases that afflict humankind. The discussion also identifies a number of ethical and empirical issues that these principles involve or imply and that need further consideration. The chapter aims to provide readers who may not be closely familiar with human health-related animal research, as well as those who are involved in this research, a useful account of the importance of general ethical principles in this crucial part of the battle against human disease.

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Preliminary Definitions and Considerations

In discussing *ethical* issues and principles relating to the use of animals in the study of human disease, the chapter considers issues and principles that pertain to whether animals so employed are treated in ways that accord with human ethical obligations *to these animals*. Some ethical questions raised by the use of animals in health-related research do not pertain directly to whether animals are used or treated properly. Among such issues presented, for example, by the genetic engineering of animals with organs that can be transplanted to humans (xenotransplantation) are whether these organs would create unacceptable risks of infectious disease for transplant recipients, close contacts of recipients, or the general public; and how, if there is a limited supply of such organs, they should be allocated. Issues raised by xenotransplantation that are relevant to the ethics of the use of animals as understood here include whether it is ethically appropriate to use animals to provide organs for humans; whether animals employed in research to understand how to provide these organs are properly treated; and whether animals bred and raised for these organs will be properly treated.

The term "disease" in humans as used in the chapter includes any condition that would be characterized as health-related and can threaten or shorten life, or cause pain, distress, significant discomfort, or disability. Disease as understood here is the central focus of biomedical scientific research generally, which as expressed in the Mission Statement of the US National Institutes of Health (NIH) is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." (NIH, 2017).

As is reflected in the NIH Mission Statement, by the "study" of human disease, the chapter means the pursuit and advancement of knowledge through scientific research that has as its *ultimate* aim the prevention, alleviation, or cure of human disease. It is appropriate and important to characterize the part of the battle against disease conducted by scientists as the *study* of disease. For it is the advancement of *knowledge*, gained by observation or experimentation, that scientists contribute to this endeavor. The chapter does not consider the pursuit and attainment of knowledge for its own sake as a justification for animal research. This justification is accepted by many animal researchers, including many who seek knowledge that will also prevent, alleviate, or cure disease. Moreover, animal research motivated by intellectual curiosity sometimes contributes to advances in battling human disease (Tannenbaum, 2019).

The terms animal "use" and "research" are employed in the chapter interchangeably. The term animal "testing" is often employed as synonymous with "research." This is not in my view helpful, because testing as usually understood involves the use of numbers, often large numbers, of subjects to assess the soundness of a previous hypothesis, or to determine the efficacy or safety of a given substance or

medical procedure or treatment. Much animal research is conducted on relatively few animals and is intended to explore various kinds of hypotheses before anything resembling a "test" can be performed. However, some animal research projects that are properly characterized as tests can be part, and sometimes an important part, of understanding the nature of a disease and how to combat it. Such testing is included in the use of animals or animal research as understood here.

The chapter refers to research described above as "human health-related animal research" or "HHAR." The chapter discusses HHAR conducted in laboratories on animals that are owned or possessed by these facilities for the purpose of research. Such research represents the overwhelming majority of HHAR projects. A relatively small but increasing proportion of health-related animal research is conducted by veterinary clinicians on privately owned animals (usually pet dogs or cats) that is intended to assist these animals or kinds of animals, and is also intended to contribute to understanding the same or similar diseases in humans (Kol et al., 2015; Lairmore & Khanna, 2014).[1] Because of human diseases that originate in or are transmitted to humans by wild animals, an increasing amount of field research is being done on wild animals that aims to understand how such diseases affect humans as well as these animals (Buttke et al., 2015; Kaur et al., 2008). Many of the ethical principles relating to laboratory HHAR apply to HHAR in pets and wildlife (e.g., that any procedure conducted on a research animal should minimize, and wherever possible prevent, experiences of pain or distress). However, these latter kinds of research raise distinctive ethical issues (Baneux et al., 2014; Paul et al., 2015) that cannot be discussed here.

Finally, the chapter includes within the meaning of the term "principles" not only certain very general philosophical or ethical truths, but also practical guidelines and directives that are of immediate use in the design, conduct, and ethical assessment of HHAR. (For a defense of proposed animal research "principles" in a sense that does not include such directives, see Beauchamp & DeGrazia, 2020, pp. 1–41.) Many of the principles examined here require additional principles to clarify their application in the wide range of kinds of experimentation that HHAR encompasses. However, the ethical principles—and more importantly the sets of principles—presented in the chapter are intended to function primarily as practical guides for action.

[1] It is also noteworthy that many vaccines, medicines, and diagnostic and surgical techniques employed by veterinarians to benefit pets and other animals including antibiotics, cancer chemotherapeutic drugs, anti-inflammatory steroids, diagnostic ultrasound, spinal anesthesia, hip replacement surgery, compression plating of complicated fractures, and surgical stapling, were first discovered or developed using animals in research intended to benefit humans (IOM, 1991; Loew, 1988; Quimby, 1998). Continuing contributions to *animal* health provide a derivative and secondary, but by no means unimportant, justification of HHAR.

Importance of Ethical Issues in HHAR

Some might think that ethical issues in HHAR receive a disproportionate amount of attention. It is fair to say that more has been published on ethical issues relating to the use of animals in scientific research than on any other subject in animal ethics. However, far fewer animals are used in HHAR, and in the totality of all animal research, than for other purposes.[2] Moreover, extensive legal regulation and oversight of HHAR in many countries impose significant *ethical* requirements, including minimization of animal pain or distress, meticulous veterinary supervision and care, and enriched environmental conditions (e.g., AniWA, 2008 [Switzerland]; ASPA, 2016 [UK]; AWA, 2015 [US]; AWAR, 2020 [US]; EAA, 2021 [Netherlands]; EU, 2010 [EU]; GAWAR, 2013 [Germany]; NHMRC, 2013 [Australia]; PCAL, 1994 [Israel]; PHS, 2015 [US]; SABA, 2007 [Singapore]; SAWA, 2018 [Sweden]) that are not generally afforded to the vastly larger number of animals used in meat production, for example.

These facts notwithstanding, there are good reasons for those who participate in HHAR and those who benefit from it—which is virtually everyone—to give serious attention to ethical issues in HHAR. Because most HHAR is funded by government (FASEB, 2017), approval by the public that ultimately pays the freight is essential. Yet public support does not appear to be commensurate with the significant health benefits HHAR has produced for so many people.[3] It is therefore important that

[2] Mice and rats represent the vast majority of animals used in HHAR worldwide, at least 90 to 95 and perhaps as much as 99 percent (Carbone, 2004). The US Animal Welfare Act (AWA) covers research on dogs, cats, nonhuman primates, guinea pigs, hamsters, rabbits, and other warm-blooded animals that the US Department of Agriculture (USDA) Secretary may determine (which includes pigs, ferrets, and sheep, for example), but specifically excludes rats, mice, or birds bred for research (AWA, 2015 § 2132(g)). Accordingly, the AWA does not call for the counting of these latter species. Nor does the US statute that covers mice and rats used in NIH or NIH-funded research, the Health Research Extension Act (HREA, 1985). Because the US, the largest user of research animals, does not tally numbers of these species, and the second largest user, the UK, counts the number of research procedures and not animals, it is difficult to estimate with confidence how many animals are used in research generally or in HHAR in these countries or worldwide. Annual estimates for the US range from 25 to over 100 million (Grimm, 2021; Tannenbaum, 2019, pp. 10–11). One study concluded that in 2015, 192.1 million animals were used worldwide for all research purposes (Taylor & Alvarez, 2019). In contrast, the United States Department of Agriculture reports that in 2020 there were slaughtered in US commercial facilities for human consumption 9.346 billion chickens, 227.6 million turkeys (USDA, 2021g), 32.8 million beef cattle, 132.8 million hogs, and 2.23 million sheep and lambs (USDA, 2021e). In 2020 there were also in the US approximately 9.4 million dairy cows (USDA, 2021f) and in April of that year, 392.77 million laying hens (USDA, 2021d).

[3] For example, a 2018 poll of the Swedish public found that 55% supported experiments on animals "for medical purposes," with an additional 24% stating that their support "depends on" (unspecified) circumstances (SRC, 2019, p. 11). A UK poll in the same year found that 65% of the public supported "use of animals in scientific research as long as it is for medical research purposes and there is no alternative." However, support fell from 75% in 2002 (Ipsos MORI, 2018, p. 18). One US poll found that in 2018 47% of the public favored, and 52% opposed, "use of animals in scientific research," (Pew, 2018) A 2021 poll found that in 2021 52% of Americans believed that "medical testing on animals" is "morally acceptable" and 44% that it is "morally wrong." (Gallup, 2021)

animal researchers and those who oversee or regulate their work be able to convince the public that their research is justified. Moreover, although legal regulation of HHAR seeks to ensure minimization of pain and distress and promotion of research animal welfare, virtually all research animals used in laboratories are kept in cages or enclosures and cannot engage in all behaviors typical for their species. Some experience pain or distress. It is surely an ethical truism that any being that can experience pain, distress, or other unpleasant sensations or feelings should not be caused such experiences by those who use them for their own benefit, without an articulatable and sufficient reason. Furthermore, because HHAR is conducted for one of the most admirable and important goals we humans can have—saving human life and preventing and alleviating suffering—anyone associated with HHAR should welcome the task of ensuring that methods employed to attain this highest of goals reflect the highest ethical standards.

Stages of Laboratory HHAR

The central ethical question relating to a laboratory HHAR experiment is whether it is ethically appropriate to conduct the experiment. If an experiment ought not to be done, *whatever* happens to the animals would be unjustifiable. Among questions relevant to the appropriateness of an experiment that can have ethical components are whether what the experiment seeks to learn should be studied by using animals; if so, what species of animals should be used; how many should be used; what kinds of experimental techniques are acceptable; whether animals should be allowed to experience unrelieved pain or distress; and if, when, and how animals should be killed.

These are the kinds of questions that many seem to identify with asking about the appropriateness of an HHAR project. However, there is much more, regarding what happens to animals, to a laboratory experiment than the experiment itself. The typical HHAR project also includes the breeding of animals by a commercial supplier, or in the case of some facilities and species breeding within the facility; transportation of animals to the facility or laboratory; housing of animals when experimental procedures are not being conducted; supervision of animals by veterinary and animal care staff when they are in facility housing; and disposition of animals at the end of the experiment. Ethical issues can arise during any of these stages of a project. Serious consideration of the ethics of an HHAR project, or kind of HHAR, must include attention to all these stages. An ethical failure in one stage could be sufficient to invalidate a project or to require changes. It sometimes may be possible to make a project that is justified even better from an ethical standpoint by making improvements in one or more of the stages other than the experiment itself. The animal research community worldwide pays considerable attention to conditions in which animals are housed and how they are cared for when not under experimentation, because most research animals spend far more time in, and can be affected at least as much by, housing conditions as by what is done in the laboratory.

General Ethical Principles and the Diversity and Complexity of HHAR

This chapter focuses on the articulation and defense of *general* ethical principles for the conduct of HHAR for several reasons.

First, HHAR is an enormously diverse and complex enterprise. There is a wide range of human diseases that animal research has addressed, a wide range of kinds of animals used in this research, and an even wider range of experimental techniques employed in studying these diseases. Some of these diseases and techniques raise distinctive ethical issues regarding their use of animals. And although certain ethical issues relating to HHAR have been and will continue to be raised, new issues continually arise—as animals are used to address new or newly significant diseases, as new research techniques are developed, and as more is learned about how various kinds of experiments affect, and are affected by, the welfare of the animals.

In light of the diversity, complexity, and developing body of ethical issues in HHAR, a relatively brief discussion of these issues must perforce focus on very broad principles that apply to HHAR generally. However, as is demonstrated below, a discussion of such principles is far from a substitute for serious consideration of the ethics of HHAR. Only by identifying broad ethical principles is it possible to organize, and approach in a systematic and useful way, the variety of ethical questions that HHAR can raise. Moreover, for those who are not intimately familiar with HHAR, as well as for those who are, a survey of general ethical principles that govern this research can provide an informative overview of ethical issues in HHAR.

General Principles as Justifications

Another, and related, reason to focus on general ethical principles in HHAR is that, as is the case in all areas of ethics, assessment of particular conduct or kinds of behavior almost always relies on appeal to general principles. For example, after it was learned that paralyzing curariform drugs used to anesthetize human surgical patients did not eliminate their pain but only made it impossible for them to express it, the use of such drugs to restrain research animals during painful procedures was universally condemned and prohibited by law (e.g., AWA, 2015, §2143(a)(3)(C)(iv)); US Principles, 1985, Principle V). Although preventing pain behavior instead of pain is obviously unacceptable, the prohibition of using paralyzing drugs instead of effective anesthesia in HHAR rests on a general ethical principle, which can be called the *pain and distress minimization principle* (and is discussed further below): *When an HHAR project is justified in using animals in any way that has the potential of causing them pain, distress, or other significantly unpleasant sensations or feelings, the project should prevent the occurrence of such sensations or feelings if possible, eliminate them if and when they occur, or minimize them if and when in light of justified experimental aims they must occur.* Moreover, as is discussed below,

this general ethical principle rests for *its* justification on a number of other even more general ethical principles relating to animals in general and research animals in particular. Virtually everything that can be done with animals in HHAR—ranging from when it is appropriate to use animals in the first place and what species to use, to acceptable procedures in experimentation, to proper housing and veterinary care, to what should be done with animals after an experiment is completed—relies for its justification on some, and often more than one, general ethical principle.

General Principles in Sets of Ethical Standards

There are available to investigators a number of *sets* of general ethical principles for HHAR. These collections tend to be brief, consisting typically of no more than a dozen broad principles. They are regarded by many involved in HHAR as useful tools in designing, conducting and assessing the ethical appropriateness of experiments. Having a relatively brief and easily accessible set of principles in one place provides a location as it were in which to find ethical guidance relevant to one's research.

It is the importance of general principles in the justification of practices in HHAR, and the relevance of these principles to wide ranges of typical or recurring practices, that make such sets of principles useful. For example, the pain and distress minimization principle—which appears prominently in some form in all current sets of ethical principles for HHAR—provides justification for more than prohibiting the use of paralyzing drugs. This principle requires various courses of action, depending on the particular facts at hand, whenever *anything* done to or with a research animal in *any* stage of a project can be accomplished by causing no or less pain or distress. The principle requires—among a multitude of things—that animals: are handled by experimenters and research staff as gently as possible; not be physically restrained during an experiment unless necessary and that any restraint is as brief as possible and causes the least amount of pain or distress possible; are given pre- and post-surgical anesthesia or analgesia when consistent with experimental aims; and are killed when necessary for experimental purposes without pain or distress.

Such sets of general ethical principles have been adopted, as official policy, by major professional organizations whose members conduct, or are involved in the care of animals used in, HHAR (e.g., AALAS, 2021; AES, 2020; AHA, 1985; APA, 2012; APS, 2014; ASIH, 2004; ASLAP, 2008; ASP, 2001; CCAC, 1989; FASEB, 2021; ICLAS, 2013; LAVA, 2016; SfN, 2016; SOT, 2008). Investigators need not be a member of a particular group to find its ethical statements applicable to their research. Some of these professional, and other, collections of general principles are intended to apply to animal studies of particular diseases or kinds of diseases (ACS, 2019 [cancer]; AES, 2020 [epilepsy and seizure disorders]; AHA, 1985 [cardiovascular disease]; APA, 2012 [mental illness and behavioral disorders]; SfN, 2016 [neurological disorders]; Tannenbaum, 2017b [epilepsy and seizure disorders]); to

research on general medical conditions that range across diseases (Tannenbaum, 1999 [pain]); to research on certain species (ASIH, 2004 [amphibians and reptiles]; ASP, 2001 [nonhuman primates]); and to investigators (Tannenbaum, 2017a). Some sets of general ethical principles for HHAR or animal research generally have been adopted by government authorities that have the power to compel compliance with these principles by law (e.g., EU, 2010; US Principles, 1985).

General Principles in Statements of Central Obligations and Ideals

The relevance of general ethical principles to wide ranges of practices in HHAR facilitates another very important use of sets or collections of such principles. The sets of ethical principles of the professional organizations cited in the previous section have been adopted in part to serve as expressions of the central ethical obligations and ideals of these groups. These principles assist in educating members about their ethical responsibilities to research animals, and serve as standards that can be used if questions arise about research practices or the behavior of particular members. These sets of principles are also presented as a testament to the seriousness of the commitment of these groups to the ethical conduct of HHAR—and an invitation to the general public and government to expect compliance with these principles. Professional associations spend a great deal of time and effort writing, re-affirming, citing, and when necessary amending, these ethical standards and discuss them regularly at meetings and research seminars. Their role in promoting ethical animal research cannot be overestimated.

An Instructive Example: The US Principles

An instructive example of a set of general principles that is intended to serve as a convenient source of basic ethical standards, and to articulate central ethical obligations and ideals of HHAR, are the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (Principles* or *US Principles).* The *Principles* are set forth in Table 26.1. They are required by law to be applied in all HHAR conducted or funded by the NIH (HREA, 1985; PHS, 2015, para. I) and other US government agencies (e.g., DoD, 2019; NSF, 2019). The *Principles* have been incorporated into the statements of ethical standards of a number of professional organizations (e.g., AALAS, 2012; ASLAP, 2008; SfN, 2016). The *Principles* are the best known, and most often cited, set of ethical principles for HHAR in the US, and perhaps worldwide.

The flexibility and broad applicability of the *Principles* are apparent. The *Principles* are intended to apply to all kinds of animal research, including HHAR, and identify relevance to human health as one of several considerations that can

Table 26.1 U.S. government principles for the utilization and care of vertebrate animals used in testing, research, and training

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species.
I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et seq.) and other applicable Federal laws, guidelines, and policies.
II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.
III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.
IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.
V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.
VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.
VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.
IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group, such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration. (US Principles, 1985)

justify animal experimentation. The *Principles* provide virtually no specific directions. They do not specify, for example, precisely what species or how many animals investigators should employ in various kinds of experiments; when and what sedative, analgesic or anesthetic agents should be used; when and how animals should be killed; what housing conditions are appropriate for the animals in any given project; when and what kinds of veterinary care must be provided to animals in a project; and what kinds of training in the proper use and care of animals must be provided to scientists and staff involved in a project or kind of project. What the general ethical rules in the *Principles* require depends on the particular facts of a project or a kind of HHAR including its aims, methods of research, and species employed.

The *Principles* reflect their intended role of focusing the attention of those who conduct or are directly involved in HHAR on rules that are essential for the ethical conduct of this research. However, significant gaps in the *Principles* detract from their usefulness in addressing a number of important ethical issues. For example, Principles IV through VIII, which constitute the bulk of the document, apply to the *performance* of research projects or to the housing and care of animals in *ongoing* projects and do not relate to how one is to determine whether a given animal experiment, or kind of experiment, is ethically appropriate in the first place. The only principle that addresses this issue directly, Principle II, merely identifies advancing human health (among other aims) as a legitimate goal of animal research and calls upon researchers to give "due consideration" to how a given experiment is relevant to human health. Neither this nor any of the other principles identify factors that should be included in such consideration, or how much weight these factors should be accorded in determining whether an experiment is justified. Although Principles IV through VI identify minimization of animal pain or distress in experiments as obligatory, neither these principles, Principle II or any of the other principles indicate whether and when pain or distress that an experiment might cause could be sufficient to render it ethically unacceptable.

Core General Principles and the Central Ethical Structure of HHAR

Addressing these omissions might well make the *Principles* a more complete and useful set of basic ethical standards or expression of central obligations and ideals of HHAR. Nevertheless, it is important to appreciate that the *Principles*, like the sets of general ethical principles of professional groups referenced above, have limited albeit important roles. These sets of principles can be used as convenient sources of ethical standards, or as statements of central obligations and ideals that can be presented forcefully to researchers and the public, precisely because they are brief. Other than typically beginning, as in the *Principles*, with a statement of the importance of animal research in understanding disease, these sets of principles do not contain even cursory *arguments* for their principles. Nor do they indicate how their various principles follow from or imply other of their principles. Nor do these sets of principles contain supporting commentary that explains why their principles are correct and how they are interrelated. These sets of principles do not do these things because researchers who use them *assume* the correctness of their principles and thus view these principles as reliable *starting points* in designing and conducting experiments or in dealing with colleagues or the public. Those who use these sets of principles also *assume*, and do not look to these principles for a demonstration of, the overall ethical appropriateness of HHAR.

Because of the importance of general principles in the ethical assessment of research practices, and the relevance of some of these principles to wide ranges of typical or recurring practices, it is possible to identify a set of general ethical

principles for HHAR that *does* provide support for statements in current collections of principles. Moreover, such a set of general principles can serve two additional important functions. Such a set of principles can assist in *making the case* for HHAR and various ways it uses animals by indicating more fully how, and why, ethically conducted HHAR includes attention to the interests of animals as well as of humans who benefit from it. Second, such a set of principles can identify what is properly characterized as the *central ethical structure* of HHAR: general principles on which all assessments of the ethical appropriateness of research and animal care practices in HHAR ultimately rest.

The Ethical Core of HHAR

There is I want to suggest a set of sound general principles that is already present in the ethical attitudes of those who are involved in HHAR and that can be regarded as its *ethical core*. This core as I conceive of it does not consist of all general ethical principles, or even all significant general ethical principles, in HHAR. The principles in the core are the most important ethical principles in HHAR. These principles serve as final touchstones for all ethical decision-making in HHAR, because as particular issues are considered, ultimately one and sometimes more than one of the principles in the core will be cited as determinative. Despite their generality, core principles often provide substantial guidance regarding the appropriateness or inappropriateness of research practices and treatment of animals. Core principles sometimes do this directly, and sometimes imply other core or non-core principles that apply to an ethical issue or factual circumstances at hand.

The logical structure of the ethical core enables it to be used to make the case for HHAR and to describe its central ethical structure. At the base of the core are what I shall call *foundational* ethical principles and supporting factual truths on which rest all the other principles in the core. Some of these foundational principles and truths do not refer explicitly to animals or the use of animals in research. From these foundational ethical principles and factual truths, there follow, in light of additional relevant facts, what I shall call (non-foundational) *basic* principles in the ethical core: successively more concrete general principles that explain further the meaning or appropriate applications of the principles from which they follow. Put another way (and as is illustrated below), we begin by stating and defending foundational ethical principles and relevant facts. These principles do—and should—strike the vast majority of people as sound. From these principles, employing important facts relating to humans, animals, and HHAR, we can deduce somewhat more concrete sound general principles. And from these latter sound general principles and additional relevant facts we can deduce additional sound general principles that are still more concrete. This process can be repeated as general principles require clarification or are applied to additional issues. However, at some point in this process, one reaches principles that should not be regarded as part of the ethical core of HHAR. These principles are not sufficiently general, and do not apply to a sufficiently wide range of ethical issues, to be core principles.

Where one draws the line between principles in the core that are so clearly foundational that they should be regarded as the basis of the core, and core principles that are not foundational, may sometimes be open to disagreement. The principles and supporting facts I classify as foundational are the most general, and the least objectionable (at least to the vast majority of people), and from which the process of deducing successively more concrete core principles *begins*. For example, I include in foundational core principles the principle that harming animals in HHAR must be justified, but I do not include principles that indicate what *constitutes* harm and *when* and *why* causing such harm is or is not justified. Drawing the line in this way facilitates identification of core principles that clarify more general principles, and allows the presentation of these clarifying principles to be organized around issues they address.

The ethical core of HHAR is not static, and the substance and precise wording of its principles are open to discussion and debate. As is noted below, it may be possible for a principle (e.g., that research animals should be provided pleasurable experiences) that does not follow from or is not suggested by an existing core principle, to make its way into the core. Such a new principle might reinforce, although for a different reason, some of the existing core and non-core principles; it may also imply new core or non-core principles. As more is learned about techniques of animal research and about research animal welfare, and the concerns and emphases of the research community and the public develop, a principle that already is implied by a current principle in the core but previously might not have been included in the core itself can be added. For example, a principle that has long been in the core is that as expressed in the *US Principles*, "(t)he living conditions of animals should be appropriate for their species and contribute to their health and comfort." (Principle VII) In light of what has been learned about research animal behavior and welfare since the *Principles* were written in 1985, some implications of Principle VII have gained significant prominence in their own right. Thus, the US National Research Council (NRC) *Guide for the Use and Care of Research Animals* (*Guide*), which must like the *US Principles* be applied in animal research funded by the NIH, states that "(a)n appropriate housing space or enclosure should also account for the animals' social needs. Social animals should be housed in stable pairs or groups of compatible individuals unless they must be housed alone for experimental reasons or because of social incompatibility." (NRC, 2011b, p. 51) This statement is universally endorsed in the animal research community, and applies to so many species used in HHAR, that a general requirement of social housing when appropriate clearly belongs in the ethical core. As does, for the same reasons, the obligation to provide, when consistent with justified experimental goals, environmental enrichment, which can be defined as "a combination of complex inanimate and social stimulation and generally consists of housing conditions that facilitate enhanced sensory, cognitive, motor and social stimulation … [and] provides the animals with opportunities to perform some of their species-specific behavioral repertoire." (Sztainberg & Chen, 2010, p. 1535) Some might maintain that if principles addressing social housing and environmental enrichment belong in the core, so do principles relating specifically to other aspects of housing that can affect research animal

welfare and the importance of which is also implied by Principle VII, such as water and air quality, temperature, noise, and facility lighting. In my view these inclusions would be unwise because they might detract from the usefulness of the core in expressing very general principles, but some might disagree.

Even if a principle is implied by the core, but does not fall within it (such as the principle that animals should be provided fresh and clean air), it can still be a principle that HHAR must follow as carefully as any. Indeed, because of the power and broad applicability of general principles in assessing and guiding research activities, the articulation of successively more concrete ethical principles can be extended well beyond the ethical core, to various kinds of HHAR and various species, experimental methods, and ways of housing and caring for animals. Moreover, certain kinds of HHAR employ distinctive research methods and lend themselves to articulation of sets of ethical principles that are so central to these areas that they can be regarded as stating core ethical principles of *these* kinds of HHAR (Tannenbaum, 1999 [pain research]; Tannenbaum, 2017b [studies of epilepsy and seizure disorders]).

Presentation of the Core

The presentation of the ethical core of HHAR that follows first identifies and defends foundational and (non-foundational) basic core ethical principles that are *established* in the sense that they seem clearly correct and any practicable approach to HHAR must regard them as axiomatic. Unsurprisingly, these principles are virtually universally accepted by, or follow logically from principles virtually universally accepted by, the biomedical research community, the general public, and government authorities who regulate HHAR. The discussion also examines general principles that are *potentially emergent* for the ethical core of HHAR in the sense that they may well in the future, in some form, be regarded as belonging in the core. However, at least at present, these principles cannot be included in the core because they raise difficult issues that are as yet unresolved, or because there is not yet sufficient consensus regarding their precise content or underlying justification.

Established Core Ethical Principles and Supporting Facts

Established Foundational Core Principles and Supporting Facts

The entire enterprise of HHAR is motivated and ultimately justified by an incontrovertible fact, F1: *Many human beings suffer from diseases that shorten or end their lives; cause them significant pain, distress, discomfort, disability, fear, and anxiety; cause their families and friends great distress, anxiety, and sorrow; and have significant effects on the economy, by affecting the ability of disease sufferers to earn a*

living and by necessitating personal and societal economic costs to facilitate their health care.

F1 provides the impetus and support for a correspondingly foundational ethical principle, EP1: *It is appropriate—indeed obligatory—for human society to employ scientific research to study human disease, and to expend significant resources when necessary in this endeavor.* EP1 is so widely accepted and so obviously correct that some may think it does not need mentioning. However, consideration of the ethical use of animals in HHAR should explicitly acknowledge this principle and its importance, urgency, and great moral weight. There is little if anything that is more important for society to do than to attempt to prevent, alleviate, and cure human disease. And essential in the understanding of and ability to battle human disease is scientific research.

A corollary of EP1 is EP2: *The more important it is to study a human disease, the greater is the weight of this importance in a determination of the ethical appropriateness of studying the disease.*

Several factual truths and ethical principles lay the foundation for the appropriateness of using *animals* in the study of human disease. The first of these is EP3: *Humans are of greater worth and value than nonhuman animals*. The vast majority of people around the world accept EP3, and for most people, EP3 provides the support for EP4: *It is sometimes ethically appropriate to use animals for human benefit.* One can accept EP4 without accepting EP3. A utilitarian, for example, can argue that although there is nothing morally special about being human, some human uses of animals, including HHAR, are ethically acceptable (indeed obligatory) because these uses result on balance in more total pleasure, happiness or benefits for humans than suffering or detriments to animals (Frey, 1988). However, as a number of opponents of animal research appreciate, typically underlying EP4 is the view that humans are intrinsically more important and valuable than nonhuman animals and that therefore we may sometimes use them for our benefit. This is why opponents of using animals for human benefit (including in HHAR) argue that humans are not in virtue of being human of greater worth and value than nonhuman animal species (e.g., Cavalieri, 2002; Francione, 2009; Regan, 1983).

HHAR would be at best pointless and at worst ethically questionable were it not for another incontrovertible fact, F2: *The use of animals in scientific research can be an effective and indispensable tool in the study of human disease.* Critics of HHAR have claimed among other things that there is insufficient evidence that animal research has resulted in net benefits to humans (DeGrazia & Sebo, 2015; Rowan, 2012; Singer, 1975); that using animals to study human disease may have been valuable in the past but is being replaced by new scientific tools and techniques such as computer modeling and studies on humans (HSUS, 2021); and that animal research causes great harm to humans because it diverts resources from scientific research that, unlike animal experimentation, can advance the study of human disease (Akhtar, 2015; Greek & Greek, 2000). It is beyond the scope of this chapter to address such claims in detail. As is noted below, there is widespread agreement among animal researchers that more must be done to identify kinds of studies that are likely to contribute to the understanding of disease, and that more can be done

to improve scientific rigor, transparency, and reproducibility in HHAR. Nevertheless, it is absolutely clear that animal research has made essential contributions to the prevention, alleviation, and cure of many serious human diseases, and is likely to continue to do so for the foreseeable future (Botting & Morrison, 1997; Friedman et al., 2017; Gay, 1984; Genzel et al., 2020; IOM, 1991; Kinter et al., 2021; Kiple & Ornelas, 2001; Maurer & Quimby, 2015; Merrill, 1986; Phillips & Westerfield, 2014; Phillips et al., 2014; Quimby, 1998; Walsh et al., 2017; Warfield & Gay, 1984).

The foregoing factual truths and ethical principles support the principle that is the ethical foundation of HHAR, EP5: *It is sometimes ethically appropriate to use animals in scientific research to study human disease.* If it is sometimes ethically appropriate to use animals to benefit humans it must sometimes be appropriate to use animals in a way that will further arguably the most important of human benefits—the prevention, alleviation, and cure of human diseases that cause countless people pain and suffering, disability, misery, and death.

A corollary of EP4 and EP5 is EP6: *When scientifically and ethically appropriate, the study of a human disease should be conducted in animals before it is conducted in humans.* This principle is reflected in the provision of the post-World War II Nuremberg Code that medical research on human subjects "should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment." (Nuremberg Code, 1947, para. 3) EP6 does not imply that any animal species may be used to study any human disease. EP6 allows precluding the use of certain species (e.g., chimpanzees) to study any or certain diseases and requiring greater justification for the use of some species to study some diseases. As is discussed below, there is reasonable disagreement about the ethical significance in HHAR of species membership. In order not to foreclose such disagreement, EP6 holds that while investigators should generally attempt to first employ animals in HHAR, use of a given species in a given way must be not only scientifically but also ethically appropriate.

The broadest foundational core ethical principle relating to how animals are used and treated in any HHAR project is EP7: *There must be sufficient ethical justification for anything that is done to animals and for anything animals undergo or experience in an HHAR project.* Some readers may regard this principle as superfluous because it might appear simply to restate the general concern of animal research ethics, namely whether animal experiments or kinds of experiments are justified. However, EP7 as presented here can play a distinctive role in ethical assessment of HHAR. The great majority of discussions of the ethical appropriateness of animal research in general and of HHAR in particular focuses on the issue of whether any *harm* done to animals is justified. However, as is discussed further below, there is disagreement regarding what constitutes such harm. Many, but by no means all, researchers and commentators believe that most things that are done to animals in HHAR—including confining them in cages, preventing them from exhibiting all their natural species behavior, and killing them—do not in themselves constitute harm. In order not to foreclose relevant ethical discussion, it is important to

postulate that such things, and indeed anything done to or with the animals must be justified, whether or not these things should be regarded as harm or causing harm.

Because so much of current ethical discussion of HHAR focuses on whether and when this research causes harm to animals, it is important to recognize the presence in the ethical core of HHAR of the following two general (and self-evident) principles:

EP8: *Harm is an evil to something that can be harmed.*
EP9: *One must therefore have sufficient justification intentionally to cause it harm.*
From EP8 and EP9 follows EP10: *An HHAR project must not cause harm to animals without sufficient justification.*

Some readers familiar with the animal research ethics literature may be puzzled by use in EP10 (and EP11 and EP12 below) of the words "harm" instead of "pain or distress" and "justification" instead of "benefit to humans." Discussions in animal research ethics typically begin with the question whether the *likely benefits*—taken to mean probable effective medical treatments or approaches to human disease—justify any *pain or distress or other significantly unpleasant sensations or feelings* experienced by the animals. This is in my view a major mistake that limits ethical discussion. Although pain and distress and other significantly unpleasant experiences are harms to research animals when they occur, it should at least be open to debate whether they are the only harms that can be caused to these animals. Moreover, as is discussed below, it is unreasonable to limit justifications of HHAR to likely medical benefits. It is more helpful to phrase *foundational* core principles in terms of the more generic "harm" and "justification"—and then to identify ethical principles and supporting facts that address the issues of what more precisely constitutes harm and might justify its causation.

From EP8, EP9, and EP10 follow two additional foundational core principles:

EP11: *The greater the harm an HHAR project causes animals, the stronger must be the justification for causing this harm.*
EP12: *When an HHAR project is justified in using animals in any way that has the potential of causing them harm, the project must whenever possible prevent the occurrence of such harm, eliminate this harm if and when it occurs, and minimize this harm if and when in light of experimental aims it must occur.* Because harm to animals ought not to be caused without sufficient justification, any harm that is not necessary for, or an unavoidable consequence of, justified experimental aims and that can be prevented, eliminated, or lessened, is unjustified. It is important to acknowledge that EP10 cannot function independently of EP8 as a justification of an HHAR project, experimental technique, or way of using or caring for research animals. That a project or some aspect of a project causes minimized harm to the animals does not imply that this minimized harm is justified. There must be sufficient ethical reason to cause this minimized harm. It is conceivable that some project or aspect of some project that causes animals minimized harm would inflict sufficient harm, or a kind of harm, that is unacceptable.

Established Basic Core Principles and Supporting Facts

Animal Harm and Its Justification in HHAR

Basic (nonfoundational) core HHAR ethical principles as I understand them follow from and clarify foundational core principles. Because so much of current discussion of the ethics of HHAR, and many of the foundational core ethical principles identified above, center around harm to research animals, it is reasonable to focus deduction of basic core principles on principles that address the nature and justification of such harm.

Pain, Distress, and Other Significantly Unpleasant Sensations and Feelings as Harm

Whatever else might be included in the definition of "harm," there is universal support by all who conduct or engage in ethical assessment of HHAR (and other kinds of animal research) of a factual truth that has an evaluative component and therefore can also be classified as an ethical principle, EP13: *Pain, distress, and other significantly unpleasant feelings or sensations are harms or evils to animals when experienced by them, just as they are harms or evils to humans who experience them.*

There is also universal support of an incontrovertible fact, F3: *Most species used in HHAR are capable of feeling pain, distress, and other significantly unpleasant sensations or feelings, as independent experiences or as part of more complex emotions such as fear, anxiety, or boredom.* A great deal of scientific research has been conducted on understanding pain and distress in animals in general and research animals in particular (Carstens & Moberg, 2000; NRC, 2008, 2009). It may not be clear whether all species employed in HHAR can experience certain unpleasant sensations or feelings, or complex unpleasant emotions. It may not always be clear how various aspects of unpleasant experiences should count in quantifying their unpleasantness, for example, whether a long period of moderate distress should be regarded as equivalent in unpleasantness to a brief period of severe pain. Although much is known, much more remains to be learned about how unpleasant experiences in research animals can be prevented or minimized. However, it is clear that many animals used in HHAR can—and some sometimes do—experience painful or unpleasant sensations and feelings that, if not identical to those experienced by humans, can often be as painful or unpleasant. The best source of data in the US regarding research animal pain and distress are annual reports of facilities registered under the AWA by the USDA. According to the latest data as of the time of this writing, in fiscal year 2019, of the 797,546 animals used in AWA-regulated research (USDA, 2021c), 225,404, or approximately 28%, were used in procedures (such as surgeries) that could be painful or distressful but in which pain or distress was prevented by use of appropriate anesthetic, analgesic, or tranquilizing drugs (USDA, 2021a); and 49,422, or approximately 6%, experienced some unrelieved pain or distress (USDA, 2021b). (AWA reports do not

distinguish between HHAR and other kinds of animal research.) As noted above, the AWA does not cover and therefore does not ask for the counting of the number of mice and rats that experience pain or distress. However, there is no *a priori* reason to suppose that a higher percentage of these species experience pain or distress than do AWA-covered animals. Nor is there reason to suppose that a higher percentage of animals used in HHAR experience more pain or distress than do animals in other kinds of research. Nor is there reason to suppose that research animals used in the US experience more, or less, pain or distress than do animals in other countries that engage in serious legal regulation of animal research. Therefore, whether the number of animals used annually in research in the US is ten million, or 100 million, or somewhere in between (see f.n. 2 above), the number used in the US and other countries in HHAR that experience some unrelieved pain or distress is not insignificant.

Justification of Pain, Distress, and Other Significantly Unpleasant Sensations and Feelings

EP13 and F3 support the presence in the HHAR ethical core of the following two principles, which are more concrete applications of foundational core principles EP10 and EP11.

EP14: *Animals must not be caused pain, distress, or other significantly unpleasant sensations or feelings in an HHAR project without sufficient justification.*

EP15: *The greater the pain, distress, or other significantly unpleasant sensations or feelings animals are caused in an HHAR project, the stronger must be the justification for causing these experiences.*

The process of determining whether an HHAR project justifies any pain or other significantly unpleasant experiences it may cause animals is often called "balancing" or "weighing" the value of the project against the unpleasant experiences. This language is entirely metaphorical and does not identify considerations relevant to making this determination. These metaphors might suggest to some that the determination is utilitarian in nature, i.e., that an HHAR experiment is justified if and only if it will result on balance in more total benefits to all humans than pain and distress to animals used in the experiment. However, as is discussed below, the value of HHAR experiments that can justify using, and sometimes harming, animals cannot be identified with their resulting in benefits such as the prevention, alleviation or cure of disease. Moreover, the demand of utilitarians like Singer (1975) to the contrary notwithstanding, humans and research animals are not commonly viewed as equals whose pains and pleasures count equally. It is possible that an experiment that causes distress to a large number of mice, for example, and would help a relatively small number of humans with a moderately discomforting ailment would seem justified—even if the total distress suffered by the mice exceeds the

benefits to the humans. An experiment that would cause excruciating long-lasting unrelieved pain and suffering to relatively few cats, but would benefit a large number of humans who have a disease for which there are already reasonably effective treatments would likely seem unjustified—even though the total pain suffered by the cats would be exceeded by the benefits to the humans. To be sure, when it contributes to medical advances, HHAR almost always results in benefits to *very* large numbers of humans at the expense of far fewer animals. However, for the vast majority of people, determining whether the value of an HHAR project justifies any harms it might cause animals is not simply a utilitarian exercise but rather a consideration of whether, when a wide range of *varied* factors are taken into account, what is done to the animals is justified.

Importance of Studying the Disease

In determining whether an HHAR experiment that might cause animals pain, distress, or other significantly unpleasant experiences—or any other kind of harm—is justified, one clearly relevant consideration is the seriousness of the disease the experiment studies and the importance of discovering a prevention, amelioration, or cure of the disease. There are numerous factors that can be relevant to determining the importance of studying a given disease including: the number of people who have the disease; whether or to what extent the disease is life-threatening or fatal; the nature and extent of pain and distress or other significantly unpleasant sensations or feelings associated with the disease; whether, to what extent, and how the disease is transmissible to others; whether there are current effective treatments of the disease; the risks or side-effects of current treatments; whether and to what extent the disease is caused by choices in behavior or lifestyle; the economic cost to patients of available treatments; the extent to which the disease imposes financial costs on the health care system or the general economy; and whether studying the disease may contribute to understanding similar or other diseases. Often some of these (and other) relevant factors must be considered concurrently, and must be weighed against each other. This can make it difficult to assess the importance or comparative importance of studying a disease.

Scientific Soundne of the Study

That an experiment studies a disease it is important to combat does not however imply that the experiment has great value and justifies animal pain or distress or other harms. If the experiment seeks to answer questions that have no scientific merit, or addresses sound questions with poorly designed or executed methods, or is conducted by investigators who are unqualified or do not have adequate facilities and equipment to apply sound scientific methods to sound questions, the experiment

will not be valuable from a scientific standpoint.[4] It will not discover knowledge useful in understanding the disease. *Any* pain or distress or other harm it causes animals cannot be justified by its relevance to the study of human disease.

One of the most significant recent developments relating to the ethical conduct of HHAR have been measures taken in the animal research community to improve the scientific soundness of animal experiments (e.g., ACD, 2021; AMS, 2015; Cheleuitte-Nieves & Lipman, 2022; Festing, 2020; Macleod & Mohan, 2019; NASEM, 2020). These efforts acknowledge and are motivated by the recognition that some scientists in HHAR have not engaged in best research practices that enable their work to be reproduced or assessed by others. This has resulted in experiments that do not advance the study of human disease and thus can subject animals to pain and distress that is not ethically justified because it is not scientifically justified. Efforts to improve the scientific rigor, transparency, and reproducibility of HHAR projects include recommendations of inclusion of statisticians in the design and institutional assessment of experiments; greater attention to determination of adequate sample sizes; minimization of risk of investigator bias through use of sample randomization methods; improved knowledge and education of investigators regarding which kinds of animal models and studies have been or are more likely to be translatable to clinical medical advances; greater understanding of and attention to effects on experimental results of environmental conditions of animal housing and care; and use by investigators of standardized guidelines for planning, conducting, and reporting experiments that enable others to assess and when scientifically appropriate to reproduce experimental results. Among innovative suggestions for promoting scientific soundness of animal experiments have been proposals for researchers to register their experimental designs and results in a confidential repository that would allow for subsequent comparison of actual with intended or predicted results, and methods of reporting negative results that could prevent other investigators from conducting the same or similar unpromising experiments. Two sets of rules for planning, conducting, and reporting animal experiments that enhance scientific rigor, transparency, and reproducibility, the ARRIVE (Percie du Sert et al., 2020) and PREPARE (Smith et al., 2018) guidelines, are already widely used by animal researchers.

[4] Assessment of the scientific soundness of experiments is a difficult and complex task and is beyond the scope of this chapter to consider in detail. There are undoubtedly different reasonable approaches. The NIH, for example, asks reviewers of proposed projects seeking funding to appraise and score five primary factors: significance, investigator(s), innovation, approach, and environment. "Significance" and "innovation" relate to the quality of a project's scientific aims and design and its potential contributions to the understanding of an important disease; and "approach," "investigator(s)," and "environment" to the likelihood it will fulfill its goals (NIH, 2016a, 2018).

Likelihood of a Valuable Result

From EP10, EP11, EP14, and EP15 it follows that if an HHAR experiment does cause animals pain or distress, there ought if possible to be *something* of value that the experiment might discover that is sufficient to justify this pain or distress. Some argue that an HHAR project cannot justify causing animal pain or distress unless it is *highly likely* that the project *will* result in *medical benefits* for humans that outweigh the pain and distress (Rollin, 1992, p. 140). Proponents of this view commonly call "harm-benefit analysis" the process of determining how much pain or distress or other harms a proposed experiment will cause animals, what benefits it might produce for humans, how likely it will be to produce such benefits, and whether this likelihood of these benefits justifies the pain or distress or harms (AAALAC, 2020; Brønstad et al., 2016; Laber et al., 2016).

Several discussions demonstrate in detail why such harm-benefit analysis can be profoundly anti-scientific and indeed dangerous (Grimm et al., 2017; Niemi, 2020; Tannenbaum, 2017a). It is sufficient here to note briefly some of its problems. First, as is reflected in the NIH Mission Statement (NIH, 2017) quoted above, a great deal of biomedical experimentation is fundamental or basic, in the sense that it seeks to understand foundational, underlying mechanisms or causes that it is hoped might eventually explain a wide range of phenomena. Such research typically does not expect to quickly make discoveries with specific relevance to practical results, precisely because the research seeks to find causes and explanations of matters that are not yet well understood. Even when it is hoped that basic research will result in medical benefits, such results usually cannot be predicted, because typically it will not be clear how the findings of the research can impact human health until additional research is done or until investigators can determine how this and additional research can be applied to particular diseases. This can take years, sometimes decades, and must sometimes await future discovery of entirely new and sometimes unexpected or unpredictable knowledge or technologies (Comroe & Dripps, 1976). Second, it almost always cannot be known before an experiment is completed precisely what its results will be; if things were otherwise, it would not be necessary to conduct the experiment. Third, failure is an important element of the scientific method; that an experiment does not discover anything, or determines that a proposed hypothesis or prediction is incorrect, can be valuable because it can advance basic or clinical research by channeling experimentation in other directions.

Requiring all HHAR projects that harm animals to promise likely medical benefits would stifle the discovery of knowledge necessary for future medical benefits. To be sure, if an HHAR project *is* likely to result in significant benefits, this would count heavily in justifying its causing a proportionate amount of pain or distress or other harm in animals. It is therefore appropriate for investigators and those who oversee their work to ask about the potential for practical medical benefits of HHAR projects. However, likelihood of benefits cannot be a necessary condition for the justification of all projects.

It is reasonable, in assessing the value of an HHAR project that might harm animals, to consider its likelihood of producing *some* valuable scientific result. Whether

an experiment seeks to produce such a result, and how likely it is to produce such a result, are matters for scientists familiar with the area under study to assess. When it is unclear before an HHAR project is conducted what, if any, scientifically valuable knowledge it will discover, it will likely be the importance of studying a disease and the soundness of the science of the experiment that determines whether and to what extent the experiment may appropriately cause animals pain or distress. If, for example, an experiment that is scientifically sound will study a disease of great importance about which much remains to be learned, it may be reasonable to take the chance that something of value will be discovered—even if taking this chance might involve some animal pain or distress.

The foregoing considerations are summarized in core ethical principle EP16: *Contributing to the value of an HHAR project to be weighed against any pain, distress, or other significantly unpleasant sensations or feelings—or any other kind of harm—it might cause animals are (1) the importance of understanding and combatting the disease or diseases under study and of any means of prevention, amelioration, or cure that the project might seek to discover; (2) the scientific soundness of the project and the capacity of the investigators to undertake it properly; and (3) the possibility or likelihood that the project will achieve a valuable scientific result.*

It is far easier to identify ethical principles that seek to ensure the appropriateness of research techniques and housing conditions in ongoing or clearly justified HHAR projects, than to formulate sound rules that can assist in determining when projects are justified in the first place. (This might explain why, as noted above, the *US Principles* focus on the former and say very little about the latter.) Much work is needed to clarify further each of the three considerations in EP16, how heavily each should count in favor or against given HHAR projects or kinds of HHAR, and how they should be balanced against each other in determinations of the appropriateness of causing animals pain, distress, or other harms. Serious and sustained consideration of these matters may result in identification of principles that follow from EP16 and belong in the ethical core of HHAR.

Minimization of Pain, Distress, and Other Significantly Unpleasant Sensations and Feelings

From EP12 and EP13 follows what I call above the pain and distress minimization principle, EP17: *When an HHAR project is justified in using animals in any way that has the potential of causing them pain, distress, or other significantly unpleasant sensations or feelings, the project should prevent the occurrence of such sensations or feelings if possible, eliminate them if and when they occur, or minimize them if and when in light of justified experimental aims they must occur.*

As is emphasized above regarding EP11 and causing harm to research animals generally, that some aspect of an HHAR project causes pain or distress that is minimized does not imply that this pain or distress is justified. There must be sufficient ethical reason to cause this minimized pain or distress.

In their 1959 groundbreaking book, *The Principles of Humane Experimental Technique*, Russell and Burch articulated what has become the most commonly cited principle in ethical discussions relating to HHAR and animal research generally. Russell and Burch recommended that investigators employ what they termed "the 3Rs," three general ways of eliminating or minimizing pain, distress, fear, and other significantly unpleasant experiences in experimental animals.

> Replacement, Reduction, and Refinement. … Replacement means the substitution for conscious living higher animals of insentient material. Reduction means reduction in the numbers of animals used to obtain information of a given amount and precision. Refinement means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used. (Russell & Burch, 1959, p. 64)

Although citations to Russell and Burch are omnipresent in ethical discussions of HHAR, the 3Rs as they understood them are often misinterpreted (Tannenbaum & Bennett, 2015). Russell and Burch made clear that the *sole* aim of all 3Rs is the prevention, elimination, or minimization of pain and other significantly unpleasant experiences. (They termed "inhumane" any experimental procedure that causes animals unrelieved pain, distress, fear or other significantly unpleasant sensations or feelings. This term was not intended to express disapproval of all such procedures, but to emphasize that these procedures harm animals and should whenever consistent with experimental aims be avoided.) Although replacement and reduction are means of attaining this end, "refinement" for Russell and Burch refers to the broad range of techniques that address the minimization of these experiences directly. They had no problem with the use of animals in research and did not regard their use as a necessary evil that replacement or reduction function to mitigate. They did not, contrary to the opinion of many, define "replacement" as not using animals. By "replacement" they meant not using animals that can have unpleasant experiences during experimentation. Thus, employing completely anesthetized animals (a common practice in HHAR) is a form of replacement. Russell and Burch viewed reduction of the number of animals used in experiments as a way of causing less pain, distress, fear, or other significantly unpleasant experiences. However, they also emphasized that using too *few* animals could render an experiment scientifically unsound and result in unnecessary and therefore unjustified pain and distress (Tannenbaum & Bennett, 2015).

The 3Rs as understood by Russell and Burch are concrete applications of EP17. They clearly belong in the ethical core of HHAR and are designated here as EP18: *In preventing, eliminating, or minimizing pain, distress, or other significantly unpleasant experiences in research animals, investigators should employ replacement, reduction, and refinement as defined by Russell and Burch in The Principles of Humane Experimental Technique.*

EP14, EP15, EP16, and EP17 provide support for another established core ethical principle in HHAR, EP19, stated here in the language of the *US Principles*: *"The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered."* (US Principles, 1985, Principle III) If the species used in an

experiment is not appropriate for addressing questions the experiment asks, or the animals employed do not have characteristics that are useful in addressing these questions, the experiment will not be scientifically sound and any pain or distress the animals experience will be unnecessary and wrong. If more animals are used than is required for scientific reasons, and if these unnecessary animals experience pain or distress, there will be more pain or distress than is scientifically and therefore ethically justified. And if a project or part of a project, can be accomplished without using animals, the project or part of it will not cause any animal pain or distress.

The following established core principles of HHAR also follow from EP17, the pain and distress minimization principle. When applicable, language quoted from the *US Principles* is employed in stating these principles because of the widespread use, and in the US the legal status, of this document.

EP20: *"Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents."* (US Principles, 1985, Principle V)

EP21: *"Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure."* (US Principles, 1985, Principle VI)

EP22*: Procedures should include humane endpoints that prevent animals from experiencing unrelieved pain or distress that is not necessary for, or an unavoidable consequence of, achieving experimental aims.*

Methods of effecting such endpoints can include terminating a procedure before onset of pain or distress if experimental aims have been achieved; euthanasia of moribund animals that are not required by a procedure to remain alive; and euthanasia of animals that are not required to remain alive but will become moribund or will survive the procedure with significant illness or disability (Stokes, 2000).

EP23: *"The living conditions of animals should be appropriate for their species and contribute to their health and comfort."* (US Principles, 1985, Principle VII) *When consistent with experimental aims and individual animal health and welfare, social animals should be housed in species-appropriate pairs or groups and should be provided environmental enrichment that promotes species-typical behavior.*

EP24: "*Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.*" (US Principles, 1985, Principle VII)

EP25: "*Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.*" (US Principles, 1985, Principle VIII)

EP26: *In all stages of a project, and in all aspects of animal housing and care, all who handle, interact with, or affect animals shall do so as carefully and gently as possible, in accordance with species-specific and individual behavior and needs.* This principle applies not just to those who touch, move, or physically administer medicine or other care to animals in a housing facility, but also to those who are in the facility to observe animals or to maintain the cleanliness and general environmental conditions of the facility. The principle requires among other things avoiding making noise and causing vibrations that can result in animal distress or discomfort (NRC, 2011b, pp. 49–50).

Justification of Debatably Harmful or Nonharmful Practices

Although core ethical principles of HHAR require the justification and minimization of harm to research animals, there is some disagreement about whether certain common practices in HHAR harm these animals.

Killing Research Animals

For some time, the prevalent view in the animal research community has been that merely killing animals (i.e., killing without causing pain, distress, discomfort, or other unpleasant sensations or feelings) does not *harm* them because, it is claimed, they do not have a concept of life and a desire to live, or a concept or a fear of death (e.g., Cigman, 1981, pp. 53–59; Webster, 1994, p. 15). Others argue that even a painless death is a misfortune and harm for animals because it prevents them from having, and potentially enjoying, a future life (e.g., Harman, 2011; Regan, 1983, pp. 99–103). Although this is an interesting dispute, its resolution is not necessary to establish the ethical acceptability of killing research animals in appropriate circumstances. EP7 requires generally that there must be sufficient justification for *anything* that is done to animals in an HHAR project, whether or not it is characterized as harm or causing harm. Sometimes, indeed often, animals must be killed so that, at some stage in an experiment, or at its conclusion, their bodies, tissues, or cells can be examined. Sometimes they must be killed because this is the only way to prevent their experiencing pain or distress. Sometimes they must be killed because, due to disease, infirmity, or unsuitability for a study they cannot be used further.

The claim that killing animals in HHAR is wrong in itself simply is unlikely to be accepted by the vast majority of people. It is impossible for a society to accept killing animals to produce meat for human consumption (which many people enjoy but almost all could survive without) and reject killing animals in research that seeks to allow many people to live and enjoy the pleasures of life (including the eating of meat). Indeed, in light of the insignificance of the gustatory pleasures of meat-eating relative to the importance of conquering disease, an HHAR project is

likely to appear justified in killing animals even if it might add just a *small* amount of knowledge to the understanding of an important disease. The great majority of animals used in HHAR are either kinds of animals that already are killed and eaten by many people (such as pigs, rabbits, sheep, and fish) or are considered by many people of even lesser value and unfit for human consumption (such as mice, rats, and other rodents). As is discussed below, there is debate regarding whether certain species used in HHAR are of such high value that killing them (whether or not classified as harm) requires special or weighty justification, or is sometimes unacceptable. EP7 is sufficiently broad to allow for such debates, and for additional core or non-core ethical principles relating to killing or certain uses of these species.

Caging or Confinement

Some philosophers and animal welfare advocates argue that the inborn nature or to use the Aristotelian term "*telos*" of animals must be respected by people who use them for their own benefit (Rollin, 1992). According to this view, merely caging or confining animals, even in the absence of resulting unpleasant experiences, harms them because they are not allowed to behave in ways normal for their species. Among the problems with this view is that animals in their natural state frequently experience hunger, injury, pain, distress, predation, and painful death, which do not occur in the protected confines of research facility animal housing. It is also unclear why the promotion of *telos* is in itself obligatory, in light of the fact that much of modern medicine seeks to counter some of humans' natural, inborn tendencies, including our programmed nature to grow old and infirm and die. Laboratory HHAR projects require caging or confining animals so that they can be kept in appropriate numbers and conditions for research. It is conceivable that an HHAR project would require for scientific reasons the housing of animals in a way that would so interfere with their natural behavior that it would render the project unethical. However, aside from the fact that it would likely be the pain and distress these animals would experience that would invalidate the project, EP7 is sufficiently broad to enable taking into account the housing conditions of laboratory animals in determining a project's appropriateness, even if merely caging or confining the animals could count to some extent against it.

Potentially Emergent Core Ethical Principles

Potentially emergent core ethical principles as I understand them seem at least in part reasonable and correct and at some time may well be universally regarded as belonging in the ethical core of HHAR. However, these principles raise difficult or contentious issues that are as yet unresolved, or lack the consensus in the research community and general public necessary for inclusion in the core.

Adoption of Healthy Animals: Possible Core Justifications

Some investigators and HHAR facilities attempt to place with private owners or animal adoption agencies animals that are no longer needed in experiments and are sufficiently healthy and well-behaved to be kept as pets (Carbone et al., 2003). A number of US states have enacted laws that require research institutions to facilitate adoption of such animals, specifically cats and dogs (e.g., California, 2015; Nevada, 2015; Oregon, 2019; Virginia, 2021). The American College of Laboratory Animal Medicine (ACLAM), the body that certifies veterinary specialists in this field, states that it "fully supports the concept of adoption of healthy, post-study, research animals into long-term, caring private homes or farms that can provide appropriate and humane living conditions for these animals as pets." (ACLAM, 2017) It is fair to say that many researchers agree, provided animals are not removed prematurely from studies for the purpose of adoption. It is not clear whether ACLAM, laboratory animal veterinarians, or investigators believe that they are ethically *obligated* to try to place suitable healthy animals for adoption, or that this is an admirable practice that is an ideal and not an ethical requirement. It is also unknown at the time of this writing how many former research animals are adopted and how significant this practice is or is likely to become.

Even if one believes that HHAR investigators and facilities *are* ethically obligated to make suitable animals, at least cats and dogs, available to suitable new owners, it is unclear that a principle specifically requiring, or even just recommending, adoption belongs in the ethical core of HHAR. First, because the great majority of research animals are *not* alive or suitable for adoption at the conclusion of studies, it is doubtful that, unlike other research and animal care practices addressed directly in the core, placing animals for adoption is or will constitute a large proportion of the activities of investigators or facilities. Second, a principle relating to this practice requires a more general principle that supports it; it cannot simply be asserted as self-evidently correct. However, there is nothing in the ethical core of HHAR as thus far presented that supports an adoption requirement or recommendation. A requirement would not follow from the obligation to minimize pain, distress, or other significantly unpleasant experiences; one could accomplish this by euthanizing healthy animals no longer needed in studies.

There are several candidates for core principles that would support an appropriately worded adoption principle. One could identify in the core a principle that asserts that animal life is of value and that animals therefore should not be killed without sufficient reason. Most people surely agree that it is wrong to kill an animal if there is no good reason to do so (although they might disagree about what constitutes a good reason). Such a principle if stated appropriately would allow the current practice of euthanizing animals during or at the end of experiments when required for scientific reasons. A second possibility for a core principle that would support adoption would be the principle that when possible research animals should be provided pleasures or happiness in addition to freedom from unnecessary pain or distress. Such a principle would support adoption of healthy research animals on the

grounds that adoption could provide these animals pleasurable experiences. However, a requirement of such experiences raises serious issues, some of which are discussed in the next section. A third candidate for a core principle that many people would probably accept and that supports adoption, would be that investigators should be grateful for the contributions of research animals and thus should when possible give something back to them in return for their (albeit non-voluntary) service. This principle is not yet expressed universally in the animal research community. However, it seems defensible, if stated in a manner that would not compromise the ability of researchers to conduct scientifically sound and ethically justified projects. Such a principle would justify more than making animals available for adoption. A principle expressing gratitude to research animals would also provide justification, in addition to the obligation to minimize pain and other significantly unpleasant experiences, for EP23 through EP26.

Providing Pleasurable Experiences

As discussed above, many of the principles in the ethical core of HHAR relate to the justification and minimization of pain, distress, and other significantly unpleasant sensations and feelings in research animals. There has been emerging in the research community the view that these animals are also entitled to positive experiences—and not just because such experiences can prevent or lessen negative, unpleasant experiences. The NRC *Guide* repeatedly calls for research practices and animal housing that enhance animal "well-being," in addition to freedom from pain or distress. Indeed, it defines "refinement," which Russell and Burch regarded as a tool for minimizing negative experiences, as "modifications of husbandry or experimental procedures to enhance animal well-being *and* minimize or eliminate pain and distress" (NRC, 2011b, p. 5, italics added). The *Guide* also identifies as a goal of environmental enrichment not just preventing "abnormal brain development, physiologic dysfunction, and behavioral disorders," (p. 51), but also enhancing "animal well-being" and "psychological well-being." (p. 52) "Well-being" would appear to include sensations or feelings of satisfaction, contentment, and perhaps various pleasures. Rollin maintains that "all animals kept in confinement for human benefit" should be provided environments conducive to their psychological well-being and that the research community must "begin to seek animal-friendly housing, care, and husbandry systems that allow the animals to live *happy lives* while being employed for human benefit." (Rollin & Kesel, 1995, Preface, n.p., italics added).

It might seem obvious to some that it is more than ungenerous, that it is *wrong*, for researchers not to provide animals positive experiences as well as freedom from negative ones. However, as I have discussed in detail (Tannenbaum, 2002), serious issues must be addressed before an obligation to provide positive experiences is included in the core ethical principles of HHAR. It is not at all clear how terms like "satisfaction," "contentment," "pleasure," or "happiness" should be defined as applied to all species used in HHAR; whether and to what extent we can determine

that these species experience these mental states under various conditions of experimentation and housing; whether requiring pleasures or happy lives for research animals, assuming we know what this means and how to provide it, would hinder or preclude valuable research by greatly increasing its economic cost; and whether, if providing a "happy life" or even more limited pleasures for *all* research animals is obligatory, any experiment that must cause some unrelieved pain or distress, or is not consistent with animal happiness, might be unethical.

Including an obligation to provide positive experiences in the ethical core of HHAR would also likely require changes in the wording or interpretation of some current core principles, and would probably also require new core principles that could have significant implications. For example, if positive experiences are required in their own right, changes might need to be made to the statement of Principle VII of the *US Principles*, and EP18, that "*the living conditions of animals should be appropriate for their species and contribute to their health and comfort.*" "Comfort" connotes an important but nonetheless minimal mental state that would surely often prevent or alleviate distress if not also pain, but need not include greatly positive experiences such as pleasures or happiness. If living conditions must also provide pleasures, or certain pleasures, happiness, or a generally "happy life," more than is now provided to animals may be required. Perhaps not a great deal more, and perhaps not enough to preclude or affect scientifically valuable experiments. But until this and other possible implications of requiring certain positive experiences are investigated and considered, including in the ethical core of HHAR an obligation to provide positive experiences, or some kinds of positive experiences, could be extremely risky.

Stronger Justification for Use of Certain Species

Many animal researchers and members of the public appear to believe that it is preferable to conduct HHAR on some species than others. Mice and rats are favored animals in HHAR not just because many can be genetically engineered for desired traits (including possession of certain human diseases) and bred quickly in large numbers, but also because the public seems to have far less difficulty with experiments on these species than, for example, on cats or dogs (Ipsos MORI, 2018, p. 25). Researchers and those who oversee or regulate their work commonly ask whether experiments that propose to use dogs can be conducted instead on pigs. Most people are likely not bothered about experimentation on fish and frogs. For some people, certain species are either completely off-limits, or must be shown to be absolutely necessary for important medical advances. In 2016, the NIH decided no longer to fund new projects or renewals or revisions of ongoing projects involving chimpanzees, with the exception of projects involving non-invasive research such as "visual observation," and "collections of biological materials (e.g., saliva, oral or other cavity specimens, urine, feces, or hair) obtained voluntarily from a chimpanzee that has been trained through positive reinforcement to cooperate in the

collection." (NIH, 2016b) The NIH decision came after a 2011 report of a committee to study the necessity of the use of chimpanzees in biomedical and behavioral research appointed by the NRC Institute of Medicine (IOM). The committee recommended (NRC, 2011a) that chimpanzees be used only if the "knowledge gained is necessary to advance the public's health" and only if there is "no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects." (p. 4) The committee also stated that "imposing requirements for justifying the use of higher species is an implicit recognition that use of higher animals comes at higher moral costs." (p. 15).

I have called the belief that it is preferable to use some species rather than others in animal research "the relative moral cost view" (Tannenbaum, 2017a, p. 40). This view does not imply that pain and distress are less important to minimize and justify in certain species than in others. Nor does the relative moral cost view involve the reasonable claim that because of their mental capacity some species (e.g., nonhuman primates) may be capable of experiencing more pain or distress than other species, and research causing pain and distress in these animals may therefore sometimes require a higher value of experiments to justify this greater pain or distress. The relative moral cost view holds that a stronger justification—that is, greater value of a research project—is required simply to use or kill certain species, even if the research causes these animals no pain or distress. The relative moral cost view also holds that if it is necessary to cause animals a given amount of pain or distress, it is preferable to do this in some species rather than others.

The relative moral cost view raises difficult questions. If species are to be ranked, persuasive and consistent criteria are needed for ranking. There are a number of possibilities. For example, in speaking of "higher animals," the IOM report appears to suggest that the criteria to be used in ranking species relate to characteristics such as mental sophistication and complex emotions. These criteria may distinguish nonhuman primates from some other animals, but may not do justice to all discriminations many people seem to want to make. Doubtlessly many people think a stronger showing of the value of a research project must be made for using and killing dogs than pigs. What seems to distinguish pigs from dogs is not that dogs are "higher" animals, but that in many countries dogs are beloved pets and pigs are food. A number of criteria can be suggested for distinguishing among species in ways that support demanding a stronger showing of the value of research in using certain species, including whether animals exhibit self-awareness; their mental complexity; the complexity of their natural social behavior; and whether members of their species interact and bond emotionally with human beings (Tannenbaum & Rowan, 1985). These criteria support the widely-held view that using monkeys, cats, and dogs, for example, requires a stronger justification than using mice or rats. However, it is not clear how the cultural and historical preference for dogs over pigs would *justify* requiring a higher value of research for one of two species with comparable mental and behavioral capacities. Moreover, human attachment to dogs and cats would not account for special treatment for nonhuman primates, with which few people interact. If mental sophistication, human attachment, and other considerations are all relevant in determining the moral cost of using these and other species in research,

standards are needed for determining how much weight and relative weight these considerations should be given.

Second, if species are to be ranked, it must also be decided how many categories of ranking should be employed. It can be argued that if it makes scientific and ethical sense to rank species for the purpose of justifying their use, we should *separately* rank all species used in research. This might involve placing species separately along a spectrum, presumably with chimpanzees at the high end, and amphibians and fish, for example, far down the scale. One might then assign a different level of moral cost to research use of each species, and require a stronger justification for use the closer a species is located toward the chimpanzee end of the spectrum. As a demonstration of the difficulty of such ranking—and the possibility of disagreements among researchers and members of the public about where to place species on a scale of moral cost in research—the reader is invited to rank the following species used in HHAR: armadillos, baboons, cats, dogs, ferrets, frogs, guinea pigs, hamsters, macaque monkeys, marmoset monkeys, mice, octopi, pigs, rabbits, rats, sheep, squid, squirrel monkeys, and zebrafish. Alternatively, one could argue for various kinds of *grouping* of species in the same categories, for example, nonhuman primates in one group and all other species in another; or nonhuman primates in one group, cats and dogs in another, and all other animals in another group; or mice and rats in one group, and guinea pigs and hamsters in another group; or all these rodent species in one group; or baboons in a separate group from macaque monkeys; or baboons together with macaques and other monkey species, and so on.

If species are to be ranked, it must also be determined how much moral cost is associated with the use of each ranked species or group of species, so that it can be decided how much value an HHAR project must have to outweigh this cost. It might need to be determined whether certain ranked species or groups of species may be used in certain, but not other kinds of research. For example, it might be deemed appropriate to use monkeys in research aimed at understanding AIDS and COVID-19, but not in certain kinds of behavioral studies.

The relative moral cost view appears to be deeply engrained in the attitudes of the research community and society at large. It has, and will likely continue to have, significant effects on what kinds of animal experiments are conducted to study human disease. Therefore, if species ranking of some kind is to be retained and is scientifically and ethically defensible, the ethical core of HHAR should include one or more principles that would reflect and promote clarity and consistency regarding the ethical significance of species membership.

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Chapter 27
Ethical Issues Concerning Genetically Modified Animals for the Study of Human Diseases

Eduardo Rodríguez Yunta

Abstract The development of genetically modified model organisms for the study of human diseases may be beneficial in the research of causes and possible treatments, but there are serious concerns about animal welfare and safety issues that must be addressed. Guidelines and regulations for the use and care of genetically modified organisms are needed to improve their welfare. The appropriateness of genetically modified organisms suitable for modeling human disease should be evaluated, as well as an analysis of benefits versus harms. In establishing biotechnology using animal models for the study of human disease is important to listen to the public concerns of civilians so that research is subjected to public scrutiny.

Keywords Genetically modified animals · Ethics · Genetic engineering · Human diseases · Animal welfare

Introduction

Animal experimentation has been useful for a long time as models for human diseases. Due to the advancement in genetic engineering and the knowledge of the molecular base of human diseases, it is possible to introduce specific mutations or genetic changes that predispose or participate in disease into experimental animals, so that they can be controlled (Clarke, 2000; Santos de Dios, 2002). In these models, the symptoms, pathogenic mechanisms, disease process, and therapeutic approaches can be studied in a controlled way (Van Dyke & Jacks, 2002).

Genetic engineering allows redesign organisms adding new characteristics that generate more accurate and appropriate models for human diseases improving knowledge about therapeutic approaches. This may facilitate progress to make it more likely that research results could be transferred to humans. The use of

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genetically modified organisms may reduce the need to use larger mammals as models for certain diseases by the genetic refinement of smaller animals.

The advantage of animal models resides in that in general they are more simple systems than humans, specific actions may be isolated, generation times and life cycles may be shorter and ethically some difficult procedures are not possible in humans.

This chapter reflects on the ethical issues concerning the use of animals as models for human diseases. Animal models do not fully represent the human condition. Nature is altered by genetic modifications and there is suffering inflicted due to the conditions introduced. The use of animals in research for the benefit of human beings produces the moral responsibility to respect them since animals are capable of suffering. The practice is also questioned since animals are being used as instruments by human technical interventions so that they may be considered mere objects to serve human purposes ignoring their intrinsic value.

Genetic Modifications in Experimental Animals and the Study of Human Diseases

Genetic engineering techniques allow the introduction of genes from one species to another. A genetically modified organism is characterized by having a genome modified artificially without natural mating or recombination (European Union Directive, 2001). Genetically modified organisms could result from transgenesis or by specific changes resulting from removing genes or sequences (Knock-out) or addition of genes or sequences (knock-in).

Transgenesis

Transgenesis means the transfer of genetic material from one organism to another. Transgenics are genetically modified organisms whose genome has included genes from other species in their cells including germ-line so that changes are transmitted to following generations. The transfer of new genes has the purpose of producing valuable proteins for the traits looked for.

External DNA can be introduced by different techniques, such as:

1. Viral vectors such as retrovirus (dividing cells) or, lentivirus (non-dividing cells) (Osten et al., 2007)
2. Direct incorporation into cells outside the body by pronuclear microinjection, macro-injection, or microencapsulation in the zygote, which is transfer into the female uterus (Gordon et al., 1980) or sperm (Moisyadi et al., 2009). Offspring derived carries the transgene which will be inherited like any other DNA of the organism.
3. Cell fusion including protoplasts.

4. Homologous recombination in embryonic stem cells incorporating them into a blastocyst to produce transformed animals with the new gene introduced (Misran & Duncan, 2002; Gerlai, 2016). But, technically is difficult to obtain embryonic stem cells, being time-consuming, and expensive.

Genome Editing

In recent years, techniques of genome editing have emerged that can edit the genome of animals with progressively increasing efficiency. Genome editing has been defined as "the practice of making targeted interventions at the molecular level of DNA or RNA functions, deliberately to alter the structural or functional characteristics of biological entities" (Nuffield Council on Bioethics, 2005). The emergence of clustered regularly interspaced palindromic repeats (CRISPR) and the CRISPR-associated protein 9 has revolutionized genome editing due to its high degree of fidelity, relatively simple construction, and low cost. This technique allows scientists to modify the genomes of animals with considerable precision (Ledford, 2015) and few off-target effects (Sovova et al., 2017). Engineered nucleases can introduce genetic changes without creating transgenics not needing foreign DNA (Schultz-Bergin, 2018). The CRISPR/Cas9 system contains a single guide RNA molecule specifically designed to seek and bind a precise target sequence in the genome, and an associated enzyme, Cas9, that cuts the DNA at the bound site which is repaired by the DNA repair system of the cell, thus realizing a precise genetic modification.

Genome editing has as one of the possible applications to create new animal models to study human diseases (Ma & Liu, 2015). Some scientists believe that the use of genome editing in animals may create better models of human disease which may enhance research with new medicines, and therapies (de Graeff et al., 2019). In neurological disorders, genome editing may allow the use of other organisms as disease models different from primates (de Graeff et al., 2019). The use of genome editing may develop animal models modified to have less suffering by removing harmful recessive alleles (Eriksson et al., 2018) or by decreasing the occurrence of unwanted genetic effects (Combes & Balls, 2014). Genome editing has the advantage that it can be performed directly in the zygote or the embryo (Yang et al., 2013; Aida et al., 2015)

Applications of Genetically Modified Organisms in Human Disease Modeling

Genetically modified animals may be used in several applications related to human health, such as vaccine probes, drug development, antibodies, and hormone production, models for infectious diseases, the genetic base of human diseases, therapy design, fertility control, models for analyzing the effects of modulation, activation or suppression of gene expression concerning human diseases. Animals genetically

modified may be used as genetically defined models for human diseases, in which the mutations that predispose or participate in disease development can be controlled, and studied. The physiology, development, biochemistry, and relationship of genes with disease processes can be studied in the animal model. Also, it is possible to study the whole organism taking into account the complex interactions between organs and inside tissues. This allows following the process of the disease and developing and probing new therapies in experimental models. Human genes involved in disease may be introduced into the host animal genome so that they are expressed by specific promoters in the tissues to be studied.

Heritable disease models have been generated on the animals most frequently used such as mice, rats, and zebra-fish. Genetically modified mice have been used as models for human diseases and gene functions studied (Doyle et al., 2012). Examples are glucokinase genes involved in diabetes, myosin VII gene involved in deafness, genes involved in neurodegenerative disorders such as Parkinson and Alzheimer, Hprt Gene involved in Lesch-Nyhan disease, genes involved in cancer, genes involved in hepatitis.

Zebra-fish has also been a favored animal model for several human diseases, such as blood disorders, diabetes, muscular dystrophy, and neurodegenerative diseases (Bradford et al., 2017). Rats have been used as models for hypertension and diabetes (Szpirer, 2020).

The use of genome editing allows for specifically targeting any gene of interest in model organisms. CRISPR/Cas system has many applications in gene therapy through gene repair, targeted gene knockouts, gene disruption, or programmable RNA targeting (Doudna & Charpentier, 2014). Examples are mouse models of myeloid malignancies or cancer, zebra-fish models for hematological diseases, or hepatic cutaneous porphyria (Ma & Liu, 2015).

For the study of neurological disorders and some infectious diseases, primates have been favored as model organisms due to greater similarities to humans in the immune and brain system, but this may imply greater implications in animal welfare. The similarities to primates involve a greater responsibility not to inflict unnecessary suffering. For this reason, some authors favor the use of non-primate models (Quigley, 2007).

Ethical Issues

Research in Animal Models Findings Cannot Be Extrapolated Completely to the Human Condition

Some scientists argue that animal findings cannot be reproduced entirely for application in improving human health (Combes & Balls, 2014; Chen et al., 2015) and that this may induce risks in subsequent human research participants (Neuhaus, 2017). For some authors, animal models are not leading to better and safer therapies and in some cases, they may hinder the process due to misleading the research direction (Hunter, 2011). Animals suffer deteriorating conditions for being a model

of diseases that affect humans. Since animal findings cannot be reproduced entirely, human experimentation is still required. The laboratory cannot mimic entirely the complex nature of most diseases, encompassing not only genetic factors but also social, environmental, and nutritional factors. Data must be interpreted carefully since there are many limitations. Many drugs proved in animal models for therapy have failed to predict efficacy, safety, and toxicity in humans (McGonigle & Ruggeri, 2014). The effects of mutations involved in diseases may be significantly altered in animal genetics background. Also, the typical phenotype of human disease may not be observable in the animal model. However, many data obtained in animal experimentation is useful since there are neurological, biochemical, and pharmacologic similarities. Some research has been useful such as comparative anatomy, physiology, and pathology to understand disease processes, the contribution of genetic alterations in the development of diseases, or gene functions and their regulation in diseases.

Risks or Unwanted Consequences

One problem with the use of genetically modified organisms is the poor efficiency of the techniques used. There are risks of off-target effects due to difficulties in the techniques of producing transgenics which may affect animal wellbeing, mainly because the new genes are introduced in any region of the genome. The following risks have been identified in transgenesis: loss of function of a host gene (due to insertion mutations), inappropriate expression of the introduced gene in the host, adverse events by biologically active transgene derived proteins, increased difficulties in fetal development, parturition, and fetal and neonatal losses, and development of abnormal offspring (Van Reenen et al., 2001). When animal transgenics are created many may not fit the purposed research due to efficiency problems, some die, others experiment discomfort, some others have low birth rates with the desire genetic modification, while others suffer and maybe euthanized to end suffering (Colvin et al., 1996; Thon et al., 2002). The expected characteristics may not be developed in the required way.

The recent development of genome editing using the CRISPR/Cas9 system has improved on-target efficiency and decrease off-target effects (Chandrasekaran et al., 2017). Although more efficient, genome editing techniques may still cause off-target effects or mosaic mutations with inadequate gene targeting (Benz-Schwarzburg & Ferrari, 2016; Carroll, 2011; Ishii, 2017; Salomon, 2016; Bassett, 2017). The repair process exerted by CRISPR/Cas9 system generates small insertions or deletions at the break site and may affect distal genes as well. The use of somatic cell nuclear transfer cloning as the method of delivery for genome editing has been associated with embryonic losses, postnatal death, and birth defects (Bhat et al., 2017; Whitelaw et al., 2016), in some cells cancer, may be activated (Cradick et al., 2013). The tumor suppressor gene p53 maybe activated by the CRISPR/Cas9 when creating DNA breaks (Ihry et al., 2018; Haapaniemi et al., 2018). This gene is involved in the repair of DNA damage and if the damage is significant it may destroy

the cells containing the damaged DNA. Some authors consider that if p53 cannot fulfill its normal activities, damaged cells may grow as tumors (Ferrarelli, 2018)

The efficiency of the CRISPR/Cas9 system may be improved by using base editors which consists of chimera proteins composed of a DNA targeting module and a catalytic domain that modifies precisely DNA bases (Eid & Alshareef, 2018).

Impacts on Animal Welfare

Animal welfare has been defined by the World Organization for Animal Health (2010) as "the state of the animal, how an animal is coping with the conditions in which it lives".

The use of animal models in the study of human diseases impacts animal wellbeing by inflicting suffering due to human-created diseases to which they do not have the experience, many times interfering deliberatively in animal genome producing harm. Furthermore, animals in laboratories experience limitations in their biological and psychological natures, causing suffering due to not being able to satisfy basic drives, such as social interactions, mating, or breeding.

The process of transgenesis may carry many welfare issues. The generation of new genetically engineered animals may involve surgical procedures or even the sacrifice of some of them, a large number of animals may be required, many do not survive and very few have the genetic alteration of interest incorporated by transgenesis methods (Robinson et al., 2003). For example, producing zygotes in the generation of genetically modified organisms in rodents involves the induction of superovulation in females, whose zygotes are collected after mating, and these females may be killed or undergo surgery under anesthesia. The modified embryos are implanted into surrogate mothers who have been previously mated with vasectomized males. Inserting or removing DNA fragments may interfere with genetic homeostasis of animals which may affect their wellbeing in unpredictable ways. For example, transgenic livestock may suffer unexpected side effects such as lameness, susceptibility to stress and fertility maybe reduced (Laible, 2009). Fortunately, the current refinement of genome editing techniques has improved efficiency.

Regulations may help to reduce the suffering and increase monitoring of potential animal welfare impacts. Institutional Care and Use Committees have been established in most countries at research institutions for monitoring animal care and evaluating research protocols.

In the US, the Animal Welfare Act obliges animal laboratories to reduce suffering in animals used for research, treating them with human care. Of importance is the regulation of qualified personnel, proper sanitation, adequate housing, veterinary care, adequate nutrition and watering, adequate breeding, safe transportation, humane handling and treatment, minimizing pain and distress (www.aphis.usda.gov/ac/publications.html). However, the Act has been criticized for being weak, difficult to interpret, selective in its protection, with low resources, and scant implementation (Francione, 1995; Mendelson, 1995). Furthermore, the Act does not

include most species involved in genetic engineering research, resulting in that genetic manipulation is not being regulated.

In the European Union, Article 100 of the Treaty of Rome has issued directives to member states regarding limitations in biotechnology research whose objectives and interventions must be justified on ethical grounds. Each country must regulate biotechnological research taking into account these directives. Patents may be rejected by considering ethical basis.

According to the Royal Society of London, there is no qualitative distinction in terms of the welfare of animals between genetic modifications introduced by genetic engineering and those produced by artificial selection, chemicals, and radiation. The new techniques produce fewer welfare problems than older techniques and the areas of concern are identified faster (Royal Society, 2001).

On the other hand, studies on genetic modifications may lead to improvements in the understanding of physiology, genetics, and animal management which may help to improve the wellbeing of animals. Recent knockout experiments suggest that it is possible to reduce suffering in laboratory animals by genetic modifications creating welfare-enhanced animals (Shriver, 2015).

Limits Between Artificial and Natural

In the discussion about the social acceptance of genetically modified organisms, the differences between natural and artificial are important. Some authors are against the artificiality of living beings. Or consider that they transgress limits to what humans are allowed to. Some question that the genetic modification of living beings transforms their ontological status into artificial organisms able to reproduce, but becoming an instrument for humans (Bota-Arqué, 2007). The limits between natural and artificial become unclear. In the production of transgenics, new genes are introduced by the direct intentional intervention of genetic engineering technology, transforming the animals into technological products, making possible that some appropriate forms of life for commerce by patents. Genetic engineering may overcome biological restrictions among species, breaking insurmountable obstacles by intervening directly into the genome, for which we can say that animals are being "technified" (becoming technical). This allows for the patenting of these organisms. For others, becoming technical is not possible on ethical grounds and the patenting of animals is not justified since they are treated as mere objects subject to appropriation. An example is the first transgenic animal patent, the oncomouse, genetically modified with the propensity for developing breast cancer (U.S. Pat. No. 4,736,866, Harvard University, April 12, 1988). Researchers could study carcinogenesis and buy this oncomouse for research purposes. As a result, this animal becomes a scientific entity condemn to a life of extreme suffering. Patent laws require novelty, utility, and being non-obvious. The technical interventions provide novelty. Transgenic animals are a new kind of good and the legitimacy of accepting property rights for them is questioned. There are two general philosophical approaches to ethical issues in property rights exerted by patents (Thompson, 1992). The instrumental approach considers property rights a means for achieving fundamental goals for social

efficiency or economic growth. The labor approach considers property rights a fundamental human right protecting the liberty of creative inventions rewarding those who have labor and invest in the transformation from the natural state. Under the instrumental approach, property claims for genetically modified organisms provide an incentive for investing in research if there is a market and presume benefits for selling products and also because they are created for the fundamental goal of improving human health. Under the labor approach scientists or biotech companies are responsible for the creation of biotechnological products and processes, so they have the legitimate power to stipulate terms for their use or exchange provided there is no deception o coercion.

An anthropocentric vision considers that human beings have the power to manipulate other living beings, and under the globalization culture manipulations that produce benefits and profits are considered good for social development. But others think that there are limits, nature imposes limits and have also the power to modify humans, so that any modifications into other living beings affects also humans, including damage performed (Velayos, 1996). The ecosystem has moral relevance, acts as a unitary entity and every living organism is defined by its relations with other organisms and the environment (Lovelock, 1985). There is responsibility over the future generations. Due to the great power that human beings may exert above other living beings by altering them, there should be regulation of biotechnological applications. According to Hans Jonas (1995), the principle of responsibility towards following generations obliges to preserve the environment and biodiversity.

Some authors, worry that human beings do not have the right to interfere with animal natural history as is done by genetic modification techniques, but the genetic selection practice for centuries in farm animals also has change the natural history of animals (Royal Society, 2001). The only difference is that genetic modifications are faster and more precise, and they add new features not present in the species. There is a greater range of possible changes by transgenesis than conventional selection, but also there may be more risks involved.

Intrinsic Value

For some authors, the genetic modification of animals is immoral since it affects the intrinsic value or fundamental value of living beings or violates the integrity of nature. Beliefs of natural beings as sacred intervene in the reaction against the genetic modifications of animals (Velayos, 1996). Some are against crossing species barriers raising the concern that this may affect their integrity. It may affect even in not being able to recognize a genetically modified organism as their kind.

Animals have intrinsic value, although with different degrees according to species, they have some characteristics with moral substratum, such as they are capable of feelings, of improvement, sociability, cognition, they are being able to take decisions about experiences they like, and they have a life for which they care (Nutffield Council on Bioethics, 2005). For some authors, genetic modifications may affect

animal nature, for example preventing them from living according to their instincts by being made mere objects in the laboratory (Manesh et al., 2014). Some authors argue that genetic modifications of animals may affect their telos more when they lose their specific behaviors essential for what they are (Ishii, 2017). Telos has been adopted from Aristotle and refers to the fundamental nature of the animals, such as their essence and purpose in life (Rollin, 2003). For Rollin, telos contains a moral notion being partially metaphysical (defines a way of looking at the world) and partially empirical (it can be deepened and refined by empirical knowledge). Some authors consider that if biotechnology changes the animal telos then this is an indication of a limit that has been surpassed (Appleby, 1999). Others consider that behaviors and tendencies change over time and it is difficult to assign them to the essence of the animal (Shriver & Mcconnachie, 2018). Some modifications of animal telos have been made for centuries without genetic engineering such as the change of the telos of the wolf into the domesticated dog by human interaction. Disabilities inflicted do not necessarily affect the telos of the animal or make them worse off (Shriver, 2015; Shriver & Mcconnachie, 2018). Furthermore, conservation of the welfare of the animal by creating an adequate environment in the laboratory may help recover specific behaviors, so that it is ethically acceptable to change the animal telos so far as humans meet the new needs of the animal and the changes do not cause suffering (Rollin, 2015). For example, to change the nature of an animal so that it will live better in a cage, the change will lead to a better suite condition for laboratory animals diminishing their suffering due to social isolation, fear, and frustration that many animals have when living in confinement. For some authors, allegations about the loss of dignity may not be qualified since the Kantian concept of dignity cannot be applied to animals due to lacking moral agency and the capacity to exert self-determination (Heeger, 2015).

Schicktanz (2006) argues that what is altered by genetic modification of animals is the relationship with humans due to the asymmetry of power, genetic modification of animals increases the power of humans over animals.

Justification

There are two extreme positions. Under one vision, humans should not intervene technically in animals by genetic modifications due to their intrinsic natural value. Under another vision, there are no limits to human technical interventions by genetic modifications into animals so far as the technique can do it. Ethical Guidelines take a middle point, where human technical interventions by genetic modifications may be done in animals, but there are limits imposed by ethical implications, such as the welfare of the animals and safety issues due to off-target effects. The rationale to justify the use of genetically modified animals in the study of human disease is that the goal is to improve human health and diminish suffering in human beings, but this imposes moral responsibility to respect the animal, avoiding unnecessary suffering. There are benefits in understanding the process of disease and in finding new treatments, more effective and with lower cost.

The premise is that the value of laboratory animals is not absolute, but respect to animals obliges looking for ways for replacement, reducing the number of animals used in experimentation and diminish suffering (Rusell & Burch, 1959).

For some authors, the prospective human benefits should not be used to justify harm to animals (Greenfield, 2017). Many are contrary to animal experimentation and modification, but if they are not used, then all charges of research must fall into humans. Research must be performed first in animals with the intention to avoid irreversible damage in humans. Some research is very difficult and not ethical to be carried out in humans. For example, the research on the mechanisms, evaluation, and modalities of pain control, as well anatomy, morphology, and synaptic projections of pain requires animal experimentation without anesthesia, and in many cases euthanasia must be practiced (Short & Van Poznak, 1992).

Animal research must be evaluated and oversaw by Institutional Committees for the Care and Use of Laboratory Animals whose role is not only to evaluate the ethical, and scientific validity of research protocols but also to verify animal wellbeing and humanitarian treatment, taking into account the principles of reduction, refinement, and replacement (Goldberg et al., 1996; Rusell & Burch, 1959) (Table 27.1).

Table 27.1 Ethical issues concerning genetically modified animals for the study of the human diseases

Issue	Position against	Position in favor
Extrapolation to the human condition	Poor application to improve the human health condition	Data obtained by animal models experimentation are useful to understand human diseases processes and to find new treatments
Off-target effects of methods used	Poor efficacy of genetic modification techniques	Genetic modification techniques are being refined to avoid off-target effects
Animal welfare	Studies of human diseases in genetically modified animals affect their welfare	Some genetic modifications reduce suffering There is no qualitative difference between genetic engineering and artificial selection and chemical and physical methods
Technification of animals	There is an imposition of technology over genetically modified animals for human interests	The goal of using genetically modified animal models is to improve human health and diminish suffering. This justifies the need of the modifications inflicted
Intrinsic value	Genetic modifications of animals is immoral since it affects their intrinsic value or telos	It is ethically acceptable to change the animal telos so far as humans meet the new needs of the animal and the changes do not cause suffering
Patenting	Patenting of animals genetically modified is not justified since they are treated as mere objects subject to appropriation	Patenting is justified under an instrumental approach: mean for achieving fundamental goals for social efficiency and economic growth such as human health Or under a labor approach: protects the liberty of creative inventions rewarding those who have labor and invest

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Chapter 28
Of Mice-Rats and Pig-Men: Ethical Issues in the Development of Human/Nonhuman Chimeras

Mackenzie Graham

Abstract The modern biological definition of a chimera is a single organism composed of cells with multiple distinct genotypes. Chimeras combining human and nonhuman cells are invaluable for various kinds of research, providing a platform for the study of human cell development while avoiding the ethical issues involved in conducting this research on human subjects. There is also the possibility that human/nonhuman chimeras could one day be used to produce human organs for transplant. Yet human/nonhuman chimeras raise a number of unique ethical challenges as well. Critics worry that they are 'unnatural', or will cause a kind of 'moral confusion', or pose a threat to human dignity. There are also concerns about the kinds of treatment we might owe to human/nonhuman chimeras. For example, introducing human pluripotent stem cells into a gorilla blastocyst could result in the animal developing a 'humanlike' brain, or developing human behaviours or characteristics. Would we need to treat such a being as we do our fellow humans? This chapter examines various arguments concerning research involving human/nonhuman chimeras, and the implications of these arguments for research policy. I conclude that research involving human/nonhuman chimeras is not intrinsically morally wrong, though it may be morally impermissible in some cases. However, I criticize the standard approach to evaluating the treatment of nonhumans in research, arguing that the moral treatment of nonhuman animals, including human/nonhuman chimeras, depends on contextual factors, rather than their moral status.

Keyword Human chimeras · Non-Human chimeras · Ethics · Moral status · Regulation

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Introduction

In classical Greek mythology, the 'chimera' is described as a beast "in the fore part a lion, in the hinder a serpent, and in the midst a goat, breathing forth in terrible wise the might of blazing fire", and was considered "a bane to many men." (Homer, 1987). Today, chimeras exist outside the realm of myth, and play an important role in biomedical research. Yet their creation and use also raises a host of ethical concerns, making them 'a bane to many bioethicists'.

The modern biological definition of a chimera is a single organism composed of cells with multiple distinct genotypes. Human chimeras can arise naturally, such as when early-stage embryos fuse in utero and result in offspring with two distinct genotypes, or through medical treatment, such as when a patient undergoes an organ or bone marrow transplant (Madan, 2020). Cases of xenotransplantation, such as when tissue from a cow or pig is inserted into a human recipient undergoing aortic valve replacement, can also result in a chimera (Robert & Baylis, 2003). Animal-to-animal chimeras have also been created by fusing embryos from two different species or transplanting cells from one embryo to another. These include chimeras of sheep and goats ('geep'), quails and chickens, and different species of mice.[1]

Most of the discussion of chimeras within the bioethics literature has concerned human/nonhuman chimeras, which result from introducing human pluripotent stem cells into non-human animals at various stages of development (usually at the blastocyst stage). Pluripotent stem cells have the capacity to self-renew through division, and to differentiate into any cell type of the organism. These stem cells can be extracted from human embryos (a practice that has itself raised ethical questions, see Landry & Zucker, 2004), or produced by reprogramming already differentiated cells back into pluripotent cells (i.e., induced pluripotent stem cells) (Bourret et al., 2016). Human/nonhuman chimeras provide a platform for the *in vivo* study of human cell development, while avoiding the ethical issues involved in conducting this research on human subjects. This makes them invaluable for various kinds of research, including basic research on human cell growth, research on the development and function of the immune system, infectious disease research, cancer research, drug and vaccine development, and regenerative medicine (Sherringham, 2008; Levine & Grabel, 2017; Crane et al., 2019).

Additionally, there is the possibility that human/nonhuman chimeras could one day be used to produce human organs for transplant. One approach has been to genetically engineer the animal donor so that it cannot produce the desired organ, and introduce pluripotent stem cells into the unoccupied niche, with the result that the animal produces an organ made entirely of donor cells. (Waltz, 2017). For example, in a 2010 study researchers injected pluripotent stem cells from rats into mouse blastocysts in which the Pdx1 gene that is essential for pancreas development had

[1] Mules, created by breeding a female horse and a male donkey, are 'hybrids' rather than chimeras. A hybrid results from inter-species breeding, with each cell containing genetic material from both parent species.

been invalidated. The rat stem cells took the place of the deficient mouse cells, producing chimeric mice with a pancreas made entirely of cells from the rat donor (Kobayashi et al., 2010). Subsequent research using pig embryos injected with human stem cells have found limited success, with the resulting embryos containing roughly 1 in 100,000 human cells after 3 to 4 weeks of development (Wu et al., 2017). The hope is that eventually entire human organs might be grown inside human/pig chimeras, which would not only provide a means of reducing the current shortage of transplantable organs, but also mitigate the need for life-long immunosuppression in the recipient. Induced pluripotent stem cells could be derived from the potential recipient to create an organ that is genetically matched to them and that would not provoke an immune response.

Human/nonhuman chimeras are thus a useful tool for scientific research, and have the potential to provide significant benefit for patients in the future. They also raise familiar ethical concerns about research involving animals and research involving human embryos. Yet human/nonhuman chimeras raise a number of unique ethical challenges as well, including the spectre of crossing existing species boundaries. Critics worry that these entities are 'unnatural', or that they will cause a kind of 'moral confusion', or pose a threat to human dignity. There are also concerns about the kinds of treatment we might owe to human/nonhuman chimeras, if they come to possess certain properties or capacities characteristic of humans. For example, introducing human pluripotent stem cells into a gorilla blastocyst could result in the animal developing a 'humanlike' brain, or developing human behaviours or characteristics. Would we be morally required to treat such a being as we do our fellow humans?

Much of the existing regulation governing research involving human/nonhuman chimeras has taken a cautious approach, while also reflecting some of the underlying uncertainty about the nature of human/nonhuman chimeras. In the United Kingdom, the Human Fertilisation and Embryology Act 2008 prohibits keeping a 'human admixed embryo' (e.g., a human embryo altered by the introduction of animal cells) after the appearance of the 'primitive streak', or longer than 14 days (whichever is earliest). Similar laws existed in Japan until 2019, when new guidelines permitted human/nonhuman chimeras to be transplanted into surrogate animals and brought to term (Ministry of Education, Culture, Sports, Science and Technology, 2019). In the United States, there are currently no federal laws restricting the creation of human/nonhuman chimeras, although the National Institutes of Health continues to exercise a moratorium on federal funding for human/nonhuman chimeric research (Human Chimera Prohibition, 2005; Human-Animal Chimera Prohibition, 2016; Crane et al., 2020). Both Australia's Prohibition of Human Cloning for Reproduction Act 2002, and Canada's Assisted Human Reproduction Act 2004, prohibit the creation of chimeras by introducing animal cells into human embryos, but not by introducing human cells into animal embryos (although neither type of chimeric research can be federally funded in Canada (Tri-Council Policy Statement, 2018)). International guidelines issued by The International Society for Stem Cell Research (2021) recommend that research involving human/nonhuman chimeras should not be pursued if the resulting chimeras have the potential to form

human gametes, and research targeting the central nervous system or germ line should be subject to specialized oversight.

In what follows, I will examine the most prominent arguments that have been raised against the development of human/nonhuman chimeras. (While chimeric research involving two animals does occur, it is primarily the mixing of human and nonhuman material that has raised ethical concerns). I will then briefly consider the appropriate role of regulation in this ethical debate.

The Unnaturalness Argument

One of the most common objections to the creation of human/nonhuman chimeras is that they are somehow 'unnatural'. In its most basic form, the unnaturalness argument holds that there are objective, fixed boundaries between species in nature, and that these boundaries should not be crossed. The creation of chimeras is unnatural because it transgresses these fixed boundaries, and wrong because it undermines the integrity of these species groups. (Karpowicz et al., 2004, 2005; Sherringham, 2008).

This form of the argument is vulnerable to several criticisms. The first is that there is little evidence to support the idea that there are objective, fixed boundaries between species. Robert and Baylis (2003) point out that dozens of ways of categorizing species concepts are currently in use, usually determined by the particular explanatory or investigative context, with no general agreement about which way is correct. Depending on the definition one adopts, the same being may fall into different species categories. It is possible that fitting chimeras into existing species concepts might prove challenging, or even require novel ways of categorizing species, but it is unclear why this change in convention should itself pose a moral problem.

Further, research has shown that the boundaries between the conventional species categories are often fluid. Over long spans of time, species undergo fusion and fission, blurring any 'boundaries' between them. Bacteria and viruses also frequently transfer genes between organisms in a process called 'horizontal gene transfer' (Robert & Baylis, 2003). Accordingly, it can be argued that there are no such things as fixed species identities, at least from a scientific standpoint. Thus, if chimeras present a moral problem, it cannot be because they violate natural species boundaries.

However, the proponent of the unnaturalness argument need not argue that chimeras are morally wrong because they cross natural species boundaries. Indeed, it would follow from this that the creation of hybrid animals like mules, or even crossing species of plants like orchids, is morally wrong. Rather, all that the unnaturalness argument needs to show is that crossing species boundaries —even if these boundaries are based on scientific convention and somewhat fluid— is morally problematic in certain cases, and that the creation of human/nonhuman chimeras is one of those cases.

One possible approach to support the link between unnaturalness and wrongness is to appeal to the idea that mixing human and animal cells will have adverse

consequences for public health or the environment. For example, retroviruses contained in animal DNA could mutate and infect humans, causing disease to which humans are particularly vulnerable (Sherringham, 2008). However, this concern is mitigated when the source of the biological material is human, and the recipient is an animal embryo in a controlled laboratory setting, as would typically be the case with human/nonhuman chimeras. Environmental concerns have not received a great deal of attention, although there are various frameworks and guidelines regulating the use of animals in laboratory research that could presumably accommodate any specific environmental issues associated with chimeras. The wrongness of research involving chimeras is thus contingent on it producing negative consequences rather than strictly because it is 'unnatural'. Moreover, any potential negative consequences must also be balanced against the potential medical benefits of allowing research with human/nonhuman chimeras.

The Aristotelian Argument

Another possible approach is to adopt a kind of Aristotelian view, according to which all living organisms have appropriate ends or goals (i.e., a 'telos'), and an inner tendency to reach those goals (Karpowicz et al., 2004). This telos is the 'final cause' of the organism, that for the sake of which all the parts are made and conjoined, and provides an explanation of why it has –and indeed must have—come to be as it is. According to this argument, living beings are organized in order to achieve the ends that are natural, and therefore good, for them. Birds are made the way they are so they may fly, and thus, flying is a good for them; fish are made the way they are so they may swim, and thus, swimming is a good for them. On this view, what is good for the organism does not depend on its subjective experience; a bird need not suffer as a result of not being able to fly for the loss of flight to be an evil for it (Hauskeller, 2006).

The upshot of this argument is that it is morally wrong to tamper with nature in ways that might prevent living beings from achieving their appropriate ends, or pursuing their natural ways of flourishing. The problem presented by human/nonhuman chimeras depends on how we understand their natural ends. One might argue that in creating human/nonhuman chimeras for specific purposes (e.g., research, organ transplant), we impose certain ends on them, and exercising this sort of control over another living creature is morally wrong. Or, one might argue that the appropriate ends of the human/nonhuman chimera are not determined by the purposes for which it was created, but rather emerge from its natural capacities. Thus, creating human/nonhuman chimeras risks potentially creating an entity unable to achieve its natural ends, which would be morally wrong (President's Commission, 2003).

Teleology remains a controversial assumption in modern biology. Even if we accept the claim that the structure and behaviour of living organisms are dictated by internal 'final causes', it remains unclear what these final causes are, and thus, how

human/nonhuman chimeras might be prevented from achieving their appropriate ends (Karpowicz et al., 2004, 2005). Further, why should we think that an organism's natural state of being should carry any moral significance? For Aristotle, the answer to this question is that an organism's natural state of being is good for it, because whatever it is 'for the sake of which' the parts of an organism are made and conjoined *must* be good for it (Hauskeller, 2006). This intuition has some appeal. For example, we might think it is bad for an elephant to be confined to a small cage when we have the impression it is suffering as a result. But we might also think it is bad for an elephant to be confined to small cage even when we have the impression that it doesn't mind it, because we perceive the gap between what the elephant is now, and what it was 'meant to be' given its nature (Hauskeller, 2006). However, this intuition likely won't be convincing to those who do not already agree that what is natural for organisms is also good for them, and further, does not explain why what is good for another organism places any obligations on us as moral agents.

The 'Yuck Factor' Argument

At this point, the proponent of the unnaturalness argument might appeal to a different kind of intuition, an instinctive hostility that arises when contemplating the creation of human/nonhuman chimeras (Harris, 1998). This intuition is commonly referred to as 'the yuck factor', and is the same sort of feeling that provides the basis for proscriptions against practices like incest, bestiality, and cannibalism. The repugnance we feel towards human/nonhuman chimeras itself provides sufficient basis for concluding that chimeric research is morally unacceptable (Kass, 1998). Thus, despite not being able to provide a principled distinction between those cases in which crossing species boundaries are morally problematic and those that are not, proponents of the unnaturalness argument still claim to know that creating chimeras is morally wrong.

While we might question whether emotions or intuitions can provide direct evidence of our moral duties, it is clear that both are reflected in entrenched social norms prohibiting certain activities, or 'taboos' (Robert & Baylis, 2003; Karpowicz et al., 2004, 2005). Mary Douglas has argued that humans attach importance to classificatory systems, and shun those practices that threaten important conceptual boundaries. Taboos reflect this need to avoid mixing things from distinct categories, including human/nonhuman chimeras, which are neither clearly animal, nor clearly human (Robert & Baylis, 2003). However, these conceptual boundaries require justification. Indeed, many of the conceptual boundaries that have been reflected in taboos in the past (e.g., homosexuality, intersexuality, interracial marriage, even organ transplants) have shifted, as the basis for these conceptual boundaries have been re-evaluated. And, as we have seen, the conceptual boundaries that exist between species groups are based on convention, and thus could be subject to change. The historical and cultural context that once grounded the taboo against creating human/nonhuman chimeras may not take into account the reasons why

creating chimeras might be rightly pursued in the present (Karpowicz et al., 2005). Simply put, such taboos may need to change.

The Moral Confusion Argument

The arguments of the previous section have shown that we ought to be sceptical of the moral significance of crossing species boundaries. A different concern, however, arises from the mere *belief* that species boundaries are morally significant. Species categories play an important role in our common-sense morality, particularly with respect to our treatment of animals. Crossing conventional species boundaries is potentially threatening to the social institutions and practices that are predicated on the moral distinction that we draw between humans and animals.

In their seminal 2003 paper, Robert and Baylis argue that the creation of human/nonhuman chimeras is objectionable because "the existence of such beings would introduce inexorable moral confusion in our existing relationships with nonhuman animals and in our future relationships with part-human hybrids and chimeras." This is because, they maintain, people employ distinct frameworks for determining moral status (i.e., whether an entity's interests 'count' morally for its own sake): one for human beings, and one for all other entities. Human moral status is categorical, whereas the moral status of animals is contingent on other factors, including the attitudes or intentions of their human creators. This difference in moral status is taken to justify the different conventions that govern our behaviour towards animals. Human/nonhuman chimeras are threatening because it is not clear which framework for moral status to apply, and thus, there is no clear way of understanding our moral obligations to them. Would it be appropriate to kill and eat a human/nonhuman chimera? Would a human/nonhuman chimera be considered a piece of property? Which restrictions on biomedical research should apply, the relatively weak constraints we apply to animals, or the much stronger constraints we apply to humans? Accordingly, they argue, the creation of human/nonhuman chimeras "is sufficiently threatening to the social order that for many this is sufficient reason to prohibit any crossing of species boundaries involving human beings."

Furthermore, Robert and Baylis argue that human/nonhuman chimeras could generate confusion regarding our relationships to other humans, by forcing us to confront the possibility that being human is neither necessary nor sufficient for moral status. Many of our existing social institutions and practices —how we treat human embryos, how we treat patients in the vegetative state, how we treat those with severe cognitive impairments— are based on assumptions about the moral importance of simply being human. Because human/nonhuman chimeras challenge the importance of humanness for moral status, they challenge these existing institutions and practices.

Accordingly, the argument for prohibiting chimeras (or at least taking a precautionary approach to their creation) is prudential: we need to preserve and protect valued social institutions predicated on clear boundaries between humans and

animals, and more clearly delineate the grounds of moral status, before deliberately creating entities whose moral status is unclear.

Robert and Baylis explicitly state that they do not endorse or reject the moral confusion argument, but suggest that it can explain the public's opposition to human/nonhuman chimeras. However, as several commentators have pointed out, they offer no empirical evidence to support this claim (Rollin, 2003; Streiffer, 2003; Siegel, 2003; Charland, 2003). Setting this aside, however, we might ask whether there is any reason to think that human/nonhuman chimeras *would* create moral confusion, and if they did, whether this would justify taking the precautionary approach that Robert and Baylis advocate.

First, the claim that moral confusion might arise from "any crossing of species boundaries involving human beings" is an overstatement. As mentioned above, bioprosthetic aortic valve replacement has been occurring for decades (Head et al., 2017), with no confusion over whether the recipients are human. Similarly, not every chimera will threaten the boundary between human and animal. The most extensively mixed human/nonhuman chimeras to date have yielded embryos containing only a small fraction of human cells: 0.0001% when combining human and pig cells (Wu et al., 2017), and 4–7% human cells when combining human and monkey cells (Tan et al., 2021). At this stage, and for the foreseeable future, chimeras that would be truly confounding to the moral boundaries between human and nonhuman are purely hypothetical. Even if these hypothetical, category-defying chimeras were to be developed, it is unclear why uncertainty about how to categorize borderline cases like these would cause people to question their general commitments about moral status.

Second, the moral confusion argument is fundamentally a consequentialist one, meaning that the potential negative consequences of inviting a re-evaluation of our moral categories must be balanced against the potential positive consequences of developing human/nonhuman chimeras. On the one hand, while the medical benefits of these chimeras are largely speculative, it is not implausible to suggest that increasing the supply of life-saving organs for transplant might justify disrupting some of our long-held beliefs about moral status. On the other hand, revisiting the moral commitments that have led to the harmful and often cruel treatment of animals is arguably a positive consequence, rather than a negative one. While changing well-entrenched social institutions will always result in some negative consequences, these are often necessary to achieve moral progress. Indeed, Robert and Baylis themselves allude to the example of entrenched social institutions based on race, and how reflection on the moral significance of these categories (or lack thereof) was necessary to redress past wrongs. The risk of moral confusion was not a viable reason not to re-examine societal beliefs about the moral significance of race or gender, and neither is it a viable reason not to re-examine societal beliefs about the moral significance of species.

The Human Dignity Argument

Both the unnaturalness argument and moral confusion argument reflect an underlying concern about how the creation of chimeras might denigrate the distinctive value of both humans and animals. The importance of species integrity, the justification of certain taboos, and concerns about preserving traditional moral categories presume that there is something important about being human that needs to be preserved and protected, and that human/nonhuman chimeras threaten. One way of attempting to capture this important aspect of humanity is through the notion of 'human dignity'.

Several commentators have argued that the problem with chimeras is the threat they pose to human dignity. Karpowicz and colleagues, the main proponents of this view, argue that human dignity is "an unconditioned and incomparable worth", and that those with dignity are "uniquely valuable and worthy of respect" (Karpowicz et al., 2005). Dignity arises from possessing certain capacities, such as the capacity for reasoning and free choice, the capacity to set ends for oneself, to act for moral reasons, to use language, to participate in social relations, to develop a world-view, and to display emotional complexity. While none of these capacities is definitive of human dignity, they together set out a 'paradigm case' of what it is to have human dignity (Karpowicz et al., 2005).

There are a few problems with this account of human dignity. As Palacios-Gonzalez (2015) points out, defining human dignity in terms of the possession of certain psychological capacities implies that there are humans that do not possess human dignity (e.g., infants, those with cognitive disabilities).[2] Even if human dignity is based on the *potential* to have these capacities, this necessarily leaves out a proportion of human beings (e.g., those with congenital cognitive disabilities, or those in a permanent vegetative state). To avoid this conclusion, Karpowicz and colleagues claim that "because there is no clear agreement about just how many dignity-associated capacities a person must possess…human dignity proponents ascribe dignity to all humans" (Karpowicz et al., 2005). But this response fails to provide a consistent response in cases where a person clearly lacks the potential for *any* of the capacities associated with dignity, but is still clearly a human being (e.g., anencephalic infants).

Setting this issue aside, what problems are human/nonhuman chimeras thought to pose to human dignity? Karpowicz and colleagues argue that when the capacities associated with human dignity are "deliberately and wrongfully diminished or

[2] This definition also implies that there could be animals that do possess human dignity. Karpowicz and colleagues state "the family of capacities associated with human dignity seem to belong uniquely to human beings." If we take this to mean that only humans have any of the capacities associated with dignity, this claim is false; many kinds of non-human animals exhibit rationality, emotional complexity, or social relations. Or, if we take it to mean that only humans have a certain kind of combination of these capacities, this claim might be true, but implies that some humans lack dignity. Thus, if capacities determine human dignity, it cannot be the case that all and only human beings have dignity.

eliminated", human dignity is degraded or demeaned. There is thus a presumption against denying people with dignity the option of exercising their dignity-associated capacities (i.e., treating them as 'mere things'), as well as diminishing or eliminating these capacities themselves. (It is unclear if others have a positive obligation to facilitate the development or exercise of these capacities). Creating human/nonhuman chimeras denigrates human dignity by giving them some of the physical components "necessary for the development of the capacities associated with human dignity" but without allowing them to fully exercise or develop these capacities. Thus, the creator of the chimera "knowingly would diminish or eliminate the very capacities associated with human dignity."

We might understand this argument as claiming that we denigrate dignity whenever we provide the physical components necessary for the development of dignity-associated capacities, without also allowing for their exercise. However, this has some odd consequences. Any physical capacities that are necessary for an organism's survival will also be necessary for the development of dignity-associated capacities. Accordingly, any intervention that provides or restores physical capacities necessary for survival risks denigrating dignity. For example, placing an anencephalic infant on a ventilator gives it some of the components necessary for development of dignity-associated capacities, but does not allow their exercise (Palacios-Gonzalez, 2015). Yet it seems false that such a procedure eliminates or diminishes the infant's dignity-associated capacities. Similarly, suppose a healthy person suffers a catastrophic brain injury, and loses all dignity-associated capacities. Suppose also that a surgical intervention could restore some brain function (i.e., a physical component necessary for some dignity-associated capacities), but any dignity-associated capacities the person recovers would be highly diminished (Palacios-Gonzalez, 2015). Again, without the underlying physical components the person lacks dignity altogether, so it is unclear how *restoring* these components could diminish or eliminate dignity.

This is suggestive of a more general problem with the human dignity argument. When we create human/nonhuman chimeras that combine human and nonhuman functional capacities we do not deny dignity, but rather a being with dignity is created (de Melo-Martin, 2008; Palacios-Gonzalez, 2015). If the introduction of human stem cells into an animal confers dignity-associated capacities that would not otherwise be present, it is false to claim that dignity is eliminated or diminished. Conversely, if the introduction of human stem cells does not confer the dignity-associated capacities, then it is still false that dignity is diminished or eliminated, as it was never present.

It is also unclear why the creation of a human/nonhuman chimera would "diminish or wholly eliminate the possibility that humans could exercise the cluster of capacities and characteristics that are associated with human dignity" (Karpowicz et al., 2005). Why should the fact that a being with dignity simply exists have any effect on other humans' ability to exercise their dignity-associated capacities? Perhaps what Karpowicz and colleagues have in mind here is something similar to the kinds of worries expressed in the moral confusion argument: if a nonhuman were to possess a capacity normally associated with dignity (e.g., rationality), this

might 'devalue' that capacity, such that its exercise might be less associated with dignity in others. In this case, the problem would not be that the capacity cannot be exercised, but that it is no longer associated with dignity.

On this interpretation, the value of the dignity-associated capacities arises not from the capacities themselves, or the value they have to the being that has them, but from the fact that they are normally associated with human beings. This raises the question why those capacities that are associated with dignity when possessed by humans are not associated with dignity when possessed by nonhumans, and moreover, why those humans lacking the dignity-associated capacities still have dignity, simply because humans typically possess dignity-associated capacities.

Alternatively, we could interpret the above claim to mean that creating a human/nonhuman chimera would diminish or eliminate the possibility of *that chimera* exercising the capacities associated with human dignity, given that it will solely be treated as a means to others' ends. While it is plausible that creating a chimera and denying it the exercise of its dignity-associated capacities would present a moral problem, this is not a necessary consequence of chimeric research; the problem arises when a dignity-possessing chimera is not treated as a possessor of dignity. But this is not strictly an argument against creating chimeras, it is an argument against mistreating them once they are created. We might explain this mistreatment in terms of the chimera's dignity, but we might also explain it in terms of its moral status, autonomy, rights, or interests. While this is not a refutation of the human dignity argument so understood, it demonstrates a need for some account of why the moral problem is best explained in terms of dignity, especially given the challenges with defining dignity discussed above.

The Moral Status Argument

In the last section, we briefly considered the idea that research involving human/nonhuman chimeras might be morally problematic insofar as it results in the inappropriate treatment of the resulting chimeras. This is the focus of the moral status argument: research involving chimeras is problematic not because creating them is morally wrong, but because of the possibility that once created, the chimera will be treated in ways that do not respect its moral status.

The Mainstream Approach to Animal Ethics

The moral status argument is an application of what can be called the 'mainstream approach' in modern animal ethics, an approach that has had tremendous influence through the works of philosophers like Tom Regan (1985), and Peter Singer (1990). According to this approach, how animals should be treated is a matter of their moral status. Moral status is a way of demarcating those 'within the circle of our moral

concern'. Things within the circle matter morally, for their own sake. Things outside the circle do not.

To possess moral status, animals must have features that are relevantly similar to those in virtue of which humans have moral status. These features include, for example, sentience (i.e., capacity for pleasure and pain), rationality or other sophisticated cognitive capacities, being the 'subject of a life', and being party to an implicit social contract. (For an overview of the grounds of moral status, see Jaworska & Tannenbaum, 2021). Because many animals do have such features, failure to regard them as having moral status is irrational, and unjust discrimination. This discrimination manifests a 'speciesist' attitude towards animals, comparable to racist or sexist attitudes that ignore the moral status of certain human beings. It is irrational to regard difference of species, (or sex, or race), as a grounds for withholding moral regard, because these differences are morally irrelevant.

However, most adherents to the mainstream approach maintain that humans and animals do not require the same treatment. For example, Peter Singer (1993) argues that moral status requires the 'equal consideration of interests', but claims that beings with self-consciousness have the capacity for certain kinds of interests that merely conscious beings lack; this justifies differential treatment. For example, a bird is harmed much less by death than a human being because fewer interests, and interests of less complexity, are at stake. Of course, this suggests that we are able to represent the various interests that are at stake in a way that is countable and measurable. Does a major frustration of the moderately complex interests of a chimpanzee outweigh a small frustration of the highly complex interests of a human? It is not clear how we are supposed to make these kinds of comparisons.

One might also argue that moral status itself admits of degrees, such that the moral consideration one deserves is proportional to the possession of those properties that confer moral status (e.g., cognitive, emotional, and social complexity). Beings with rudimentary cognitive capacities merit some consideration of their interests, but less than would be accorded to the same interests of more cognitively sophisticated beings (DeGrazia, 2007). This raises a different sort of problem, however: what are we to do about the fact that small and relatively simplistic animals greatly outnumber large and complex beings like ourselves? Is it permissible to frustrate the simplistic interests of 10,000 mosquitos to protect the more complex interests of a single person? Again, it is unclear how we are meant to make the kind of comparative calculations necessary for a genuinely non-speciesist approach to animal treatment.

The Moral Status of Human/Nonhuman Chimeras

In any case, chimeric research is argued to raise concerns about moral status, insofar as it could result in changes to the physiological properties underlying moral status. In virtue of these changes, it is possible that a chimera might have greater moral status than the animal (or animal embryo) from which it was derived, and thus

warrant different kinds of treatment. Streiffer (2005) argues that research enhancing the moral status of chimeras must be evaluated against the life to which the chimera is entitled given its enhanced moral status, and not the life it would have had without enhancement. This presents a problem when research enhances the moral status of a chimera to that of a normal adult human (i.e., full moral status). As Strieffer argues, most regulation takes a fairly permissive stance towards the use of animals in research and allows for the sacrifice of their fundamental interests, provided there is a valid research objective. Conversely, human participants in research are entitled to substantial moral protections, owing to their moral status, including stringent prohibitions on harmful research without informed consent. If the subjects of chimeric research fall under the purview of animal ethics, the wrong set of moral considerations will be applied to them. As Streiffer (2005) states:

> sacrificing the fundamental interests of the chimeric research subject as they would have been sacrificed in any other animal research is the moral equivalent of sacrificing the fundamental interests of a fully functional adult human being…this makes status-enhancing chimeric research much worse than other biomedical research on animals, and on any plausible view, makes it absolutely unacceptable.

Of course, this outcome can be avoided by treating the subjects of chimeric research as their enhanced moral status requires. But, as Strieffer argues, this would be likely to frustrate the aims of chimeric research. The purpose of using chimeras for research is that it involves procedures that would be unethical if performed on a human participant. If the research in question could be performed in a way that was consistent with the chimera's enhanced moral status, then it could also permissibly be performed on a human participant. Because regular human participants would typically provide a better model from which to learn about human development, or test possible therapies for humans, it would be scientifically preferable to conduct such research with human participants rather than chimeras.

The moral status argument, at least as presented by Strieffer, seems to adopt a version of moral status in which the kinds of animals that might be used for chimeric research have less than full moral status (or else it would be impossible for their status to be enhanced by changes to their physiological properties). One possible explanation for this view is that humans have full moral status in virtue of their (potential to develop) sophisticated cognitive capacities. Could the introduction of stem cells to animals, or their embryos, affect the development of their cognitive capacities in a way that enhances moral status?

Because the regulations governing chimeric research in most countries currently restricts allowing chimeras to develop beyond a certain stage, this question is difficult to answer. For the kinds of research currently underway, however, the answer is likely to be no. Research suggests that it is highly improbable that multipotent neural stem cells could develop the cytoarchitecture necessary to support the functions that would enhance moral status in a nonhuman host, due to constraints like smaller skull size, shorter gestation period, and the effect of the surrounding cellular environment (Karpowicz et al., 2005; Crane et al., 2019). For example, most studies of human/nonhuman chimeras are conducted in mice or rats, the brains of which contain roughly 75 million and 200 million neurons respectively, whereas

the human brain contains roughly 86 billion. While multiple studies have found that human neural stem cells will survive, mature, and integrate with the host brain, none have reported an alteration to the neuronal architecture of the host brain, or alterations in behaviour (although many did not measure behaviour directly) (Crane et al., 2019). Thus, it is unlikely that even a majority of human neurons in a rodent brain would substantially alter the cognitive capabilities of the resulting chimera. Similarly, studies involving pigs and rhesus macaques (which possess brains containing roughly 2.1 billion neurons), have not demonstrated an observable alteration in chimera behaviour (Crane et al., 2019).

An important variable when interpreting these findings is the age of the host at the time the human stem cells are introduced, as the developing brain is more plastic to the integration of transplanted cells. For example, studies have shown that human fetal glial progenitor cells transplanted into demyelinated neonatal mice will integrate and out-compete endogenous mouse glia (Windrem et al., 2014), with one study finding that the resulting chimeras demonstrated enhanced performance on memory and navigation tasks compared to wild-type mice (Han et al., 2013). Therefore, while the current state of research provides limited evidence to support the idea that future human/nonhuman chimeras might develop enhanced cognitive capacities, much less cognitive capacities sufficient for enhanced moral status, this possibility cannot be ruled out.

Setting aside these empirical uncertainties, the moral status framework offers a principled argument against certain kinds of chimeric research, namely, that which enhances a chimera's moral status (without a commensurate change in its treatment). Fundamentally, it is the being's individual capacities that grounds their moral status, and thus, the treatment they deserve.

Criticisms of the Mainstream Approach

However, philosophers like Cora Diamond (1978), Mary Midgley (1983), and Alice Crary (2010) are highly critical of the mainstream approach to animal ethics on which the moral status argument is based, arguing that it both distorts our understanding of our relationships with other humans —relationships that are not based simply on a detached assessment of their cognitive capacities— and provides an unpersuasive ground for the ethical treatment of animals. Diamond argues that it is our practices which are at the root of how we conceptualize those individuals we interact with, and provide the grounds for treating them one way or another. She states:

> we can most naturally speak of a kind of action as morally wrong when we have some firm grasp of what *kind* of beings are involved. But there are some actions, like giving people names, that are part of the way we come to understand and indicate our recognition of *what* kind it is with which we are concerned.

On this view, 'human being' and 'animal' are not strictly biological concepts, but gain their meaning from the various ways that we think about and respond to those that fall under the concept. We can see this clearly in our treatment of dead human beings; specifically, in our refusal to eat them. This is not done out of respect for their interests or capacities (a corpse has no interests or capacities), but because being human *means* being something that is not to be eaten (Diamond, 1978).

As Monso and Grimm (2019) point out, the importance of practices is implicit in the arguments of the mainstream view. For example, on this view, it would be morally equivalent to subject a puppy to severe pain as it would be a human infant, insofar as roughly the same interests are at stake. Yet, without a background of established practices against causing pain to infants, the idea that we should also avoid causing pain to puppies has little force. (We could just as easily avoid inconsistency by disregarding the interests of both the puppy and the infant). Similarly, the reason the case against speciesism seems compelling is because it appeals to established practices against slavery, racism, and sexism. Yet, if we compared partiality towards the interests of our own species (speciesism), to partiality towards members of our own family ('familyism'), we might conclude that speciesism is justified in some cases, as 'familyism' surely is in some cases (Hursthouse, 2011). Thus, the moral relevance of features like sex, race, or species are not given *a priori*, but rather depend on context, which is inextricably bound up with our practices.[3]

By attempting to ground reasons for the ethical treatment of others entirely in empirical facts, capacity-based approaches strive to assume a neutral and 'objective' point of view. As Diamond articulates, this is an attempt to find "reasons which are reasons for anyone, no matter how devoid of all human imagination and sympathy". Both Crary and Diamond argue that assuming this impartial and detached perspective is neither possible nor desirable. Rather, our response to animals depends upon a conception of *human* life. Diamond argues that emotions such as pity are fundamentally involved in our conception of suffering and death, in coming to grasp both with what they mean and why they matter to those who experience them, including animals. Our treatment of animals is an extension of our moral response to other human beings. We might extend moral concepts to animals like respect, charity, justice, friendship, compassion, and pity, not out of respect for their cognitive capacities, but because we see them as sharing aspects of our distinctively human life. Without the involvement of human imagination and sympathy, and emotions such as pity, it is unclear why the fact that animals feel pain just as we do should have any meaning for us. This is supported by work in the field of moral psychology, which demonstrates that emotions are needed to move from moral judgement to action, and can also influence our moral judgements (Haidt, 2003;

[3] This is not to say that moral practices must remain unchanging, or cannot be criticized. Without the ability to criticize practice, we risk perpetuating morally illegitimate practices. But appealing to theory or principles is not the only way to criticize practice; most people are able to distinguish certain actions as morally right or wrong without appealing to a moral theory. Various accounts of our pre-theoretical moral practices have been given by Ross (2003), Hare (1981), and Dewey (2008).

Prinz, 2006). Leaving aside all emotion in one's theory of ethics belies our nature as highly emotional moral beings.

Like Diamond and Crary, Midgley criticizes the mainstream approach as paying inadequate attention to the contexts, facts, and details of our complex relationships with animals. Abstracted from the concrete relationships in which they obtain their meaning, talk of 'rights' or 'respect' is opaque and ambiguous. What does it mean to have respect for all animals, despite our having a connection with only a tiny number of them? Should I mourn the death of every animal, as I do my beloved pet, because they have equal moral status? More generally, Midgley echoes the notion that what counts as 'relevant' similarities between members of a group cannot be separated from what, in practice, people do regard as relevant. The person who extends to the birds in his garden the same regard he has long had for his pet dogs isn't noticing some hitherto unnoticed similarity between them (e.g., capacity for pleasure or pain). Rather, he is extending the attitudes and practices he previously held for pets, to birds. This is why people who lack the same level of concern for birds will be unmoved by the information that they have intelligence and feeling; they don't see this as a relevant similarity between birds and pets (just as the need for water is not seen as a morally relevant similarity between a human and a plant, or being subject to the forces of gravity are not a morally relevant similarity between a human and a stone).

Thus, while a capacities-based approach to moral status has the virtue of logical consistency, it achieves this at the cost of leaving out much of the complexity of our moral lives. The reason we care for a grandparent, an infant, a neighbour with a disability, a dead body, a pet, or an animal being used for research, might all be different, and might depend on the circumstances. By focussing only on the presence or absence of certain capacities, we ignore important factors that make a difference to our moral judgments. In the same way, a human/nonhuman chimera's cognitive capacities (and corresponding moral status) do not themselves provide a complete justification for treating them in certain ways. The fact that a being is cognitively sophisticated, or rational, or sentient, or even merely alive, may or may not be relevant for a particular moral decision.

Alternative Grounds for the Ethical Treatment of Human/Nonhuman Chimeras

How might we ground our treatment of animals, including human/nonhuman chimeras, without appealing to moral status? Both Midgley and Rosalind Hursthouse (2006) argue that moral concern for animals need not be grounded in their possessing specific traits, although these traits may nevertheless be relevant for how we treat them. On Hursthouse's view, application of virtues and vices to our treatment of animals can provide action guidance without assuming that human life or interests are more valuable than those of animals. For Midgley, much of what is wrong

in our treatment of animals is that it exemplifies cruelty, greed, indifference, and other human vices. Many of the ways we currently treat animals —either as a means of food production or research— are obviously unacceptable: confining them to small spaces, keeping them in isolation (or too-close proximity to their conspecifics), subjecting them to painful experiences, or otherwise causing them distress or terror. Stopping or avoiding these practices is an urgent duty, and applies equally to the creation and use of human/nonhuman chimeras as it does animals.

Does it follow that it is wrong to create chimeras, or use them for research? Not necessarily, if it can be done in a way that avoids cruelty, self-indulgence, or indifference to their suffering. This suggests that, for example, chimeric research investigating the development of human cell differentiation in chimeric embryos would likely be morally permissible, whereas using chimeras as live animal models for the study of disease may not. What about using chimeras as a means of developing human organs for transplant? If such a procedure could occur without causing the chimera significant suffering (e.g., if a human/pig chimera had one of its 'human' kidneys removed, and could go on living with the other), this seems permissible. A more challenging case is one in which saving or drastically extending the life of a human being through an organ transplant would come at the cost of the chimera's life. I would argue that killing an animal, or human/nonhuman chimera is not necessarily cruel, self-indulgent, or lacking compassion. Thus, in some cases, killing a human/nonhuman chimera is morally permissible. Doing so to save or drastically extend the life of a human being will typically be one of those cases. At the same time, if the production of the organ required significant suffering on the part of the chimera (e.g., if chimeric organ donors were raised in something like 'factory farms'), this might not be acceptable, even to save a human life.

Regulating Chimeric Research

This chapter has focussed primarily on the ethics of research involving chimeras, but it is important to note that much of the debate concerning chimeric research has taken place within larger discussions about public policy. While many of the regulations mentioned above cite concern about the ethical issues raised by research involving chimeras, sound public policy depends on more than just consideration of ethical issues. It must also, among other things, account for public opinion, be practically and politically feasible, be broadly enforceable, be consistent with individual legal rights, and remain neutral with respect to certain kinds of values. Thus, while the ethical issues discussed in this chapter are critical to understanding what is at stake in the debate about chimeric research, devising sound public policy will require careful attention to these further considerations.

Accordingly, it is significant that the use of chimeras in research is part of a much larger practice of using animals in experimentation, one that is well-established in a powerful and deeply entrenched and interlocking set of institutions. In this respect, it is useful that chimeric research is a relatively novel practice, and that existing

regulations have taken a cautionary approach. These regulations may be more amenable to change than those governing the use of animals in research more generally, despite the fact that, I have argued, the use of chimeras in research rests on many of the same moral considerations as the use of other animals.

What possible form might such regulation take? One possibility is to prohibit any research involving chimeras, or to limit their development to a certain threshold (e.g., prior to the emergence of a functioning nervous system, or consciousness). While this would avoid any risk of cruelty or unethical treatment, it would severely limit the potential benefits of chimeric research. A different possibility would be to prohibit the development of chimeras that could develop humanized brains (Koplin & Savulescu, 2019). While this would prevent the possibility of certain kinds of harms to the chimera (i.e., those for which human-level cognition is necessary), it ignores the considerable range of harms which a chimera might suffer that does not require a humanized brain.

Rather than restricting chimeric research through regulation, a more promising approach is to rely on oversight committees to approve or reject specific research projects involving the development of human/nonhuman chimeras, either at a national or institutional level. This oversight process would require the development and application of a framework which takes seriously the welfare interests of chimeras, and how they may differ from their animal counterparts (Hyun et al., 2007).

Conclusion

This chapter has considered various objections to the creation of, and research involving, human/nonhuman chimeras. The unnaturalness argument raises concerns about crossing natural species boundaries, or frustrating the natural ends of animals, as well as the 'yuck' response that many people have to the idea of mixing humans and animals. While aspects of this argument are resistant to conclusive refutation, they rest on assumptions that are unlikely to be convincing to those who do not already oppose chimeric research. The moral confusion argument is claimed to underlie public opposition to chimeric research, although this has yet to be substantiated by empirical evidence. Moreover, the upshot of the argument —that moral confusion ought to be avoided— is itself open to doubt. The human dignity argument claims that creating human/nonhuman chimeras poses a threat to human dignity, by diminishing or eliminating the capacities associated with human dignity. However, it fails to explain how creating human/nonhuman chimeras would impact an individual's dignity-grounding capacities. Finally, the moral status argument maintains that creating chimeras is permissible only insofar as the enhanced moral status of the resulting chimera is respected. While there are empirical questions regarding precisely the kinds of research likely to enhance moral status, this argument is also susceptible to wider concerns about the grounds of moral status.

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Chapter 29
Animals in Research in the Pharmaceutical Industry

Margaret S. Landi

Abstract Since early Greek times, animals have provided knowledge critical to understanding human anatomy, physiology, disease injuries, development of medicines, vaccines, diagnostics and much more. The questions asked and the experiments designed have changed over time; most dramatically with increased genetic and immunologic insights of the past 20 years. In research within the pharmaceutical industry animals have been important in the discovery of new medicines and treatments. In animal models, new modalities are studies for their ability to turn on or off a receptor, to understand target and off target effects, induce mechanisms of actions and other investigative questions, tied to clinical questions and trial design. Recently the translatability between preclinical (animal) and clinical (human) studies have been questioned. This paper will review why animal models are important in drug discovery using select pharmacologic models, a brief review of the importance of animals and the brutality and outcomes of vivisection, and the problems of translation and bioethical questions about the use of animals in drug research.

Keywords Animal studies · Human health · Pharmaceutical research · Governance · Pharmaceutical industry

Animals as Models for Humans

The linkage of contributions non-human animals (from now on referred to as animals) to the understanding human animals (from now on labeled humans) must never be underestimated. Humans have relied on the imperfect translation between themselves and animals to increase insight into the workings of "bodies" over millennia. (Franco, 2013; Hajar, 2011) Though not understood at the time, conservation in mammalian biology led to the successful early studies in anatomy and

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physiology. What follows are exemplars of the thoughts and importance of animals throughout history, though not a contiguous history.

Aristotle is credited as the first to recognize that it was possible to increase knowledge about human anatomy from animals (Ogle, 2014). More modern insight into human physiology and anatomy from animals often references the cardiovascular work of William Harvey, active in the 16th and 17th centuries (Schultz, 2002); (Bates, 1992). Harvey's well documented work on the "heart as a pump" required vivisection of animals with functioning circulatory systems. He did his comparative anatomy with human cadavers, but the *in situ* circulatory activity was in intact larger animals (Shackelford, 2003). For those wishing a more thorough review on the importance of animals models through the centuries, please refer to the article "A Brief History of Animal Modelling" (Ericsson et al., 2013).

Prior to the next jump into the more modern era for drug discovery in pharmaceutical research, one should explore more of the importance of animal studies in human health. A common metric of the success of animal models often used is the number of the Nobel Prize awards given in Physiology or Medicine. Since 1901, 186 of the 222 awards have involved studies with animals (Nobel Prize Winner 2020, fbr.org, accessed 20 Jun 2021). Examples include the 1901 development of diphtheria antitoxin using guinea pigs, the 1945 discovery of penicillin and its curative effects using mice and the 2020 award for the discovery of Hepatis C, using chimpanzee models (Alter et al., 2020; Baptista et al., 2021). Though as one will read there has not been as much change in models over the past 20–30 years as one may envision, the use of chimpanzees is an example where change has happened and happened rapidly. Chimpanzees were used as a model for many diseases specifically because of their role as "our closest non-human relative"(Olson & Varki, 2003). Some of the research was successful, some not. However, as the 2011 report "Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity" showed, the presumptions that chimpanzees were still needed as research models was not accurate. In fact, the committee (of which I was a member) could only find one area of the dozens discussed where we could not agree that chimpanzees were no longer needed, and that was in the study of prophylactic Hepatitis C research. All other areas, where chimpanzees played a role, could be done with other animals and in a few cases, non-animal models (Council, 2011; Kahn, 2012). For this reason, the Committee did not recommend a full ban, but created principles to which studies would be critically reviewed prior to star. These principles were: (1) The knowledge gained must be necessary to advance the public's health; (2) There must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects; and (3) The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats. Despite the rigid principles, in 2015 years the NIH did invoke a full ban on federally owned chimpanzees.

The long, and by many factors, successful history of animal modeling is one reason pharmaceutical research or drug discovery relies on the use of different

efficacy models. Prior to discussing specific models, what follows is a short review of how animal studies are handled in most US pharmaceutical companies. If a company is not using covered species, e.g. is using only *Mus musculus* and *Rattus norvegicus* or chickens and is not AAALAC-I accredited and does not receive PHS funding, there is most likely no protocol review of any animal studies. Fortunately, most companies do have protocol reviews by the Institutional Animal Care and Use Committees (IACUC), the legally accountable institutional body for review of animal studies. Another differences is that studies approved within a pharmaceutical work do not undergo the equivalent of an independent scientific review, or grant review. It is up to each company to decide how and when to ensure peer review.

The type of models depends on the focus of the specific pharmaceutical company, independent of size. If a company is working in the field of immunological diseases, a wide variety of models may be employed. Two examples are collagen induced model arthritis (CIA) for studies of rheumatoid arthritis (RA) (Miyoshi & Liu, 2018) and experimental autoimmune encephalomyelitis (EAE), a classic model for multiple sclerosis (MS) (Glatigny & Bettelli, 2018). The CIA and EAE models are both older models which have been refined over the years to improve study design, but they are not a replication of a human disease in an animal, rather they reproduce aspects of the disease phenomenon in animals (Kaklamanis, 1992; Ransohoff, 2012). Both these models are primarily done in rodents and remain controversial. It is not possible to create a small rodent "human" with MS or RA, rather, they are an experimental induction of certain aspects of either disease. The principle investigator and their teams must know the limitations of the model and not over interpret results (Roep et al., 2012).

For companies doing oncologic research, a very commonly used model in mice is the patient-derived xenotransplant (PDX) model (Chateau-Joubert et al., 2021; Meehan, 2019). Simply stated, a PDX model is when tumor cells from a patient are implanted into a humanized mouse or immunodeficient mice. The former carrying human cells and the later, lacking a functioning immune system. The use of PDX models has become an industry practice and there several repositories and consortiums standardizing the nomenclature and availability of these models. In addition to PDX models, genetically altered animals (Dunn et al., 2005; Törnell & Snaith, 2002) and the paradigm shifting CRISPR/Cas9 technology (Chaudhary et al., 2018) are also used in drug discovery research, but not to the degree these technologies are employed in academia.

The above is a brief review of a few models used in drug discovery. Models explored in pharmaceutical research will depend on their therapeutic areas of interests. Other examples are pain models, models of diabetes, models of COVID-19(SARS-CoV-2), infection disease models; the list is a long as the diseases and conditions that afflict humans (Gregory et al., 2013; King & Bowe, 2016; Muñoz-Fontela et al., 2020).

Vivisection and Governance

While this chapter has centered on where animal models have played a role in the discovery of new pharmaceutical agents, it is important to recognize the interests and concerns on the use of animals in research. Societal fears for animals used as experimental models have existed since animals have been surrogates for humans. The statement "the science of life is a superb and dazzlingly lighted hall which may be reached only by passing through a long and ghastly kitchen" is often attributed to the scientist Claude Bernard, 1813–1878 (Noble, 2008). Dr. Bernard who is recognized as the Father of Physiology for his work on internal control processes, recognized the brutality of vivisection his work required. It is interesting to note that his wife, Marie Francoise Martin, is credited for launching France's first antivivisection society (Régnier, 2013). Vivisection, which is the practice of animal experimentation without the use of use anesthetics or analgesics, causes great pain and distress but has been recognized as integral to the growth of anatomical, physiological and eventually medical knowledge of those early eras (Bates, 2017). One often cited example of the brutality of the period contrasted with benefit of the outcome is the work of John Hunter, who in the eighteenth century conducted groundbreaking studying aneurysms in animals and cadavers (Beekman, 1936). In fact the magnitude of the vivisection and its outcome was starkly declared by the nineteenth century physician author, Andrew Wynter (1819–1876) who stated, that Hunter's work alone had been worth "the destruction of a whole hecatomb of dogs" (Bates, 2014). The cruelty of vivisection not surprisingly led to antivivisection movements across much of the Western world. Movements started in the UK and continental Europe, but also arose in the US in the nineteenth century in Philadelphia (Finsen & Finsen, 1994). These and similar movements continue today.

The goal of the antivivisection movements is to create, repeal or change laws and regulations governing the care of animals. Not surprisingly in the English speaking world, the first law to protect animals, was the UK 1876 Cruelty to Animals Act (Finn & Stark, 2015). The imperfect law was a direct response to the rise in antivivisection protests. The 1986 Animal Scientific Procedures Act was a later UK law specifically governing laboratory animals (Hollands, 1986). In the US, outcry was over stolen pets ending up in research laboratories under surviving or in some cases, perishing, under deplorable conditions. The concentration camp like conditions were described in two articles, one in Sports Illustrated (Nov 29, 1965) and a cover story in Life in 1966. The US public responded with more letters regarding the fate of these animals than those of soldiers in the ongoing Viet Nam war. Congress took action quickly and The Animal Welfare Act of 1966 (PL89–544) was signed by President Johnson on Aug 24, 1966 (Adams & Larson, 2016; Schwindaman, 1999). Two major laws separated by almost 100 years between countries with a long history: one written from a prevention of cruelty approach and the other the promotion of welfare.

Animals as models for humans was, and still is, a global practice. However, the laws, regulations, rules, policies, and practices differ widely. The UK is the only major English-speaking country to regulate animal research with project and personal licenses. Most other countries, including the US, have training requirements but not licensing requirements (Griffin & Locke, 2016; Guillén, 2017; Guillén et al., 2017; Olsson et al., 2017; Rivera et al., 2018; Vasbinder & Locke, 2016). For the pharmaceutical industry the lack of standardization is handled by use of accreditation bodies, such as AAALAC-International (Gettayacamin & Retnam, 2017) and company policies or principles. Depending on the strategy of a pharmaceutical company, anywhere between 10–100% of its animal work may be outsourced. Most companies are international and work across many different countries. AAALAC-I provides a way to harmonize practices to ensure quality animal care and use programs, including (though not limited too) training, occupational health, veterinary care, and animal welfare, while endorsing professional judgement and performance standards. In addition, many pharmaceutical companies have their own core principles that must be followed at all internal sites, regardless of country, and all sites where work is externalized. These principles may be written into contracts with external vendors. Below is an example of institutional core principles:

(a) Access to species appropriate food and water.
(b) Access to species specific housing, including appropriate temperature and humidity levels.
(c) Provision of humane care, and a programme of veterinary care through guidance of a veterinarian.
(d) Animal housing that promotes 'normal' behaviours minimizes the development of abnormal behaviors.
(e) Adherence to principles of replacement, refinement, and reduction in the design of in vivo or ex vivo studies with processes to optimize animal use and to ensure effective population management.
(f) Supported by a relevant scientific justification/rationale, approved by an institutional ethical review process, and subjected to independent scientific review.
(g) Commitment to minimizing pain and distress to the animal during in vivo and ex vivo studies.
(h) Work is performed by staff documented as trained and competent to conduct the procedures for which they are responsible.

Essentials of Translation

The concern about insults to animal welfare of research animals continues, but more recently, challenges about the science itself are increasing. Numerous published papers demonstrate failure of translation from an animal model into a successful

treatment for humans. Prior to the development of the PDX mouse model, described above, cancer research from animal studies to patients had a greater than 90% failure rate (Mak et al., 2014), and these failure numbers are not unusual. There is an ever-growing pile of publications criticizing the lack of translatability of animal models (Ferreira et al., 2020); (Karp et al., 2020); (Shaffer, 2021); (Macleod & Mohan, 2019).

Why has change proven to be so hard? There have been changes in technology, improvement in health, monitoring of studies, but the use of efficacy models is still a cornerstone of much drug discovery work. Decisions on and design of animal models have roots deep in both tradition and science (Kooijman, 2013; Veening-Griffioen et al., 2021; Yasinski, 2018). This may seem like an odd statement, since science must stay current and methods and technology are ever changing, but at the heart of a scientist's education is a pattern akin to that of a master craftsman (the principle investigator), educating and training their apprentice (doctoral student) and journeyman (post-doctoral student) (Barefield, 2017). This anchoring in past tenants with new technologies is one reason why transability failure has become magnified and change has proven difficult.

One can explore what is needed for a quality animal model and/or a quality study. Words consistently now related to "quality models" are translatability, robustness, repeatability, reproducibility, transparency, rigor, and others. What is common is the need to ensure a study design is not an exclusive experience of one lab or one team of investigators. The hypothesis may be unique, but the design needs to be repeatable and reproducible, aligned with scientific principles (Crabbe, 2016). In pharmaceutical research, especially, the need for translatability between humans and animals is the critical consideration.

There are major themes emerging important for translatability and rigor in animal studies; most of these are articulated in the document "ACD Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research (nih.gov)" (accessed 10 Sep 2021).

One major consideration is to ensure not only expertise in statistics for well-designed studies, but also clear dialogue between the researcher and statistician. Statistical input must happen before a study starts, not at the end. A biased study, one where the study is not blinded and the animals/groups are not randomized, is another large contributor to poor study design (Denayer et al., 2014; Festing, 2020; Frommlet, 2020). It is also important to recognize that science does not operate in isolation. Scientists and members of the animal research community must be willing to interface with the public to not only explain the importance of research but the specific import of a model of a disease or syndrome. Standardization of reporting in publications is acknowledged as critical for reproducibility of studies, in fact, this is key to the foundation for reproducibility in studies. What is often referenced is "Animal Research: Reporting of *in vivo* Experiments (ARRIVE)" guidelines (Kilkenny et al., 2010). First released in 2010 by the National Center for the 3Rs (NC3Rs) in the UK, the ARRIVE Guidelines had suggested 20 factors to be included in publication of *in vivo* experiments. The 20, while highly accurate, were daunting

both for author and publisher. More recently the NC3Rs has release what is labeled the ARRIVE 2.0, sometimes called the "Essential 10" (Kang, 2021; Percie du Sert et al., 2020). The ten elements are easier for authors to include and for journals to publish and increase the ability to reproduce the published experiment; helping to mitigate the ongoing reproducibility crisis.

Another way to replicate, as much as possible, a disease or mechanisms of disease in animals is to consider the 3 areas of validity in models. Face validity is the alignment of the animal model with the human phenotype, "does it look right"? Construct validity, considers if the etiology is the same in the animal model as it is in people? Predicative validity, queries if it translates from animals to humans? A model rarely demonstrates all validities and the validity may be strong or weak. Clearly for animal research in pharmaceutical drug discovery predictive validity takes precedent (Tadenev & Burgess, 2019). An exemplar of failure are studies in Alzheimer's. In most of the models' study, the "reason to believe" was tied to "construct validity"; face validity being very difficult to measure in rodent species for this diseases. The 99% translation failure rate points to the lack of predicative validity (McGonigle & Ruggeri, 2014; Tadenev & Burgess, 2019); (Veening-Griffioen et al., 2019). However not all studies have translation failure. The "animal rule" in place in the US is a regulatory mechanism where an animal is known to be predictive of a human response and human testing is not needed; the best example of this is primarily in infectious diseases (Snoy, 2010).

Ethics of Translatable Models

Even with improved model quality, that is models that are more translatable, more specific questions need to be explored for drug discovery in the quest to find new medicines, but the challenge remains; should animals be used at all? At most pharmaceutical industries animal studies undergo review by the IACUC. At IACUCs there are two main aspects of the study discussion, from an ethics standpoint; this is in addition to the in-depth discussions on specific aspects of study design and delivery. The two areas deliberated are the harm/benefit analysis (HBA) and the 3Rs (Everitt & Berridge, 2017; Silverman et al., 2014). In harm/benefit analysis, harm is generally quantified for its real or potential compromise to the animal's welfare by the experiment itself or aspects of the study (Grimm et al., 2019). These can be modified by application of the conventional definitions of the 3Rs; replace an animal with a non-animal system, reduce the number of animals that experience a harm or refine the study to lower harm. The recent introduction of the contemporary approaches to the 3Rs does bring broader context and allow for better application of a 3R strategy, but in the US they are still not part of the IACUC conversations (Clark, 2018). The cornerstones in animal research discussions continues to be that of the 3Rs; replacement, reduction, and refinement in animal studies published in 1959, Russell and Burch's *Principles of Humane Experimental Technique* (Hubrecht

& Carter, 2019). The second part of harm/benefit analysis, benefit, is much harder. Benefits are often listed by the principle investigator and accepted with little discussion of push back. This can lead to templated ways of working and stymie discussions and debates needed to enhance translatable models.

In the debate on the need for animals in research there are two extremes, which we will not explore here. One; we should never use animals (Bruers, 2015) and two, animals have not rights other than humane care (Feinberg, 2017). Rather this paper will present what the author believes is the current balanced bioethical approach, the work by Beauchamp and DeGrazia; *Principles Research Ethics* (Beauchamp & DeGrazia, 2020). In their treatise, Beauchamp and DeGrazia posit 3 claims: (1) sentient animals have moral status and are therefore not properly regarded as mere tools of research, (2) the only possible justification for (non-therapeutically) harming beings with moral status—including animal research subjects—is the prospect of substantial and otherwise unattainable social benefits and (3) permissible harming of animals in research is limited by considerations of animal welfare. Aligned with these claims are two core values: social benefit and animal welfare. Within each core value are 3 principles and for a study to be "morally justified by scientific purposes" all 6 principles must be met. Under social benefit there are the principles of (1) no alternative method, (2) expected net benefit (of the work) and (3) sufficient value to justify harm. The principles of (1) no unnecessary harm, (2) basic needs (are met), and (3) upper limits to harm, are tied to the core value of animal welfare. Though the principles are listed here, the reader is referred to the reference for more in-depth information in the *Principles of Research Ethics.* The importance of these 6 principles is that they can prompt discussions on bioethical questions beyond those normally investigated and they also provide a way for different communities who care about animals to have a common ground for discussions on the ethics of animal research (Beauchamp & DeGrazia, 2020).

Summary

Animal models, despite the differences between humans and animals, continue to play an important role in the development of new treatments, whether medicines, vaccines, or other modalities. The weakness of models is multifactorial, though at its basic, is tied to inaccurate development and/or over expectations of the model. Lack of robust study design, including statistical analysis, blinding and randomization, poor peer review and failure to ensure face, construct and predictive validity all play a role. When designed well, e.g. understanding the specific question and use of the right model to answer the question, animal models give us insights that cannot be gathered in humans. In the recent and ongoing pandemic animal models played key roles in both understanding the disease and development of treatments and vaccines (Pandey et al., 2021; Veenhuis & Zeiss, 2021).

Over time, we have seen change in model types; such as, banning of chimpanzees by NIH in 2015, overall downward trends in animal numbers and specific

reductions in dogs and cats over the past 20 years (Kinter et al., 2021). The large species where the trend is reversing is in macaque monkeys, where demand is increasing due to pandemic and other research areas. Challenge of prediction failure in efficacy studies in pharmaceutical research continues to be an issue. Ways to improve model quality and translatability are continuing to be reported and documented. Relevant questions continue to be asked; will "complex in vitro models" or microphysiological systems be more translatable and allow replacement of animals? Why does update of replacement technologies seem so slow? Interestingly, there is dramatic reduction occurring in animal numbers in the regulated space due to replacement with non-animal methods, especially in vaccines. A recent example is the replacement of rabbit pyrogen testing with a monocyte-activation test to measure pyrogenic content of a vaccine. This success involved scientists, regulators and required changes in country specific pharmacopeia with acceptance of this non-animal assay (Valentini et al., 2019).(Studholme et al., 2019) (Avila et al., 2020).

As a whole society, still endorses the need for new medicines and treatments, and our changing ecological systems and present and future pandemics speak to this need. However, the tensions and questions about what the right models are, how to design the right study, what is the right way to do the study, the best way treat the animals in studies and what is the correct ethical debate, still exist. Harm/benefit analysis (HBA), where harm can be modified as an outcome of a 3Rs discussion is the basis of most "ethical debate" in institutional forums. Though the new contemporary definitions of the 3Rs are useful, HBA and the 3Rs do not go far enough for ethical discussions; work by Beauchamp and DeGrazia take us further toward the "correct" ethical debate, but we are not there yet. The incentive for independent scientific review in pharmaceutical companies differs than academia and is tied to more clinical translation, but it is inconsistently applied across companies.

Where does this leave the future of efficacy models in drug discovery? For most pharmaceutical companies, the target species are humans. Animal studies are used to answer questions and to predict if the asset will be useful for humans. No amount of work in a non-human will fully answer that question. For now, animal models remain the cornerstone, but this is slowly changing. To increase translatability, more use of non-animal methodology is being considered and applied. Better understanding of genetics, increased access to human tissues are all being sought, by many companies. Like all parts of the company, pharmaceutical biologists are under time pressures and have milestones to meet. We need to labor on change in parallel with the working chevrons and when we know we can stop the animal study and use the non-animal method; we must make it happen. This should be recognized in the company, promoted externally, and published with links to increase translatability and non-animal methods. We can govern the desire for change ourselves and work to improve translatability, increase application of non-animal methods, work for better treatments – it may not seem so, but it is possible.

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Chapter 30
Use of Animals in Toxicity Studies

Andrew N. Rowan

Abstract Ethical aspects of the use of animals in the safety testing and risk evaluation of the hundreds of thousands of industrial chemicals are briefly discussed. By and large, everybody agrees that such use of animals is ethically challenging, and that safety testing and risk evaluation should be carried out without animals wherever and whenever feasible. The trends in the use of animals in laboratories in Great Britain are described with particular focus on the use of animals by commercial laboratories in Great Britain (primarily by pharmaceutical and chemical companies). Animal use in laboratories stabilized during the years of the genetically modified (GMO) mouse "revolution" but is now again starting to decline as the hoped-for breakthroughs from GMO mouse research have not met expectations. In addition, new biomedical technologies (e.g., human organs-on-a-chip, human organoids, high-thruput test systems and sophisticated artificial intelligence algorithms) are beginning to dominate chemical safety assessments. The new technologies promise to replace animal safety testing within the next 10–20 years if regulatory inertia can be overcome. Ultimately, the ethical challenges are being overtaken by technological innovations that will lead to an end to most or all use of animals in safety testing and risk evaluation.

Keywords Animals · Toxicity studies · Welfare · Regulation · Ethics of toxicological testing

Introduction

Various ethical traditions have been applied to the determination and understanding of the moral status of animals over the past 50 years. These analyses include various virtue-based, consequentialist, and deontological approaches, as well as discussions

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about the importance and relevance of particular characteristics such as animal cognition, animal personhood, and animal sentience (i.e., the ability to experience pain, distress, suffering and pleasure) when addressing the continuing challenge of how humans should treat animals (see Rowan, 1993). For the most part, both supporters and critics of laboratory animal use couch their arguments about the appropriate use of laboratory animals in utilitarian (consequentalist) language but there are also deontological elements (i.e., various rules such as "do not experiment on conscious but paralyzed animals") and virtue elements (for example, appoint virtuous and qualified people to ethics committees reviewing the use of animals).

Consequentialist arguments tend to dominate. Supporters of animal use argue that the benefits (to humans) of animal studies outweigh any costs (usually referencing animal suffering and death rather than economic costs). Opponents of animal research argue that some, or all, experimental use of animals is too costly in animal lives and suffering and is, therefore, not justified. In theory, it should be possible to determine which side is correct by the careful evaluation of costs and benefits, but the two sides mostly argue past one another and point at examples that support their position. The estimates of costs and benefits are also usually couched in very general terms.

Toxicity testing tends to be different to basic and applied biomedical research. In general, there is now widespread agreement that subjecting animals to such testing would be unethical if there were adequate non-animal alternatives. However, there is still considerable difference of opinion when it comes to determining if available non-animal test systems are, indeed, adequate. In addition, the adequacy of non-animal test systems is a moving target as biomedical technology generates new approaches to identify the hazards and risks of chemicals and consumer products for people and the environment. Nonetheless, it is no longer outlandish to expect to see an end to animal testing in the next 10–20 years.

In 1980, very few toxicologists would have agreed that there were adequate non-animal replacements for animals in toxicity studies. In 2021, there is much broader agreement that adequate alternatives for many animal tests are already available or will be available in the next 10–15 years (cf. Collins et al., 2002; NRC, 2007). In 2013, the EU Cosmetics Regulation of 2009 prohibited the marketing of any cosmetic product that had been tested on animals (cf. Knight et al., 2021). Major consumer product producers (e.g., Unilever, Procter and Gamble, and L'Oreal), who have spent 40 years developing alternatives to animal tests, have recently agreed that they can test the safety of cosmetic products and ingredients without the use of animals (for example, see the corporate members of the Animal-Free Safety Assessment Collaboration, AFSA, 2021) and have also begun supporting legislation enforcing no animal testing of cosmetics products in many countries around the world.

An examination of the ethics of toxicology testing using animals therefore has to consider not just the various arguments about the appropriate moral status of animals and how humans should address that moral status, but also the arguments about the availability of new technologies to determine human and environmental safety and the extent to which those technologies are as good as or better than the

traditional animal tests conducted to establish safety and risk. First, we should establish just what is happening as regards safety testing on animals and the current trends in such testing.

History of Laboratory Animal Use and Animal Testing

The widespread use of laboratory animals is a twentieth century phenomenon. Relatively few animals were used in laboratory studies in the nineteenth century but even that very limited use of animals in research laboratories launched the modern antivivisection movement (French, 1975). Using the annual reports on animal use in Great Britain published by the UK Home Office one can track laboratory animal use by laboratories in England, Scotland and Wales from 1887 to the present (Fig. 30.1).

The annual reports on laboratory animal use produced by the UK Home Office have evolved over the past 133 years but nevertheless provide a useful guide to how laboratory animal use has changed in this time. The most significant reporting change occurred in 1987 when the Home Office switched from enumerating "Experiments" to "Procedures" (Home Office, 1987). In both cases one *Procedure/Experiment* has been considered to be almost equivalent to the use of one animal. *Procedures* include laboratory animal breeding whereas *Experiments* did not. In 1987 when both were enumerated there were 23% more *Procedures* than *Experiments*

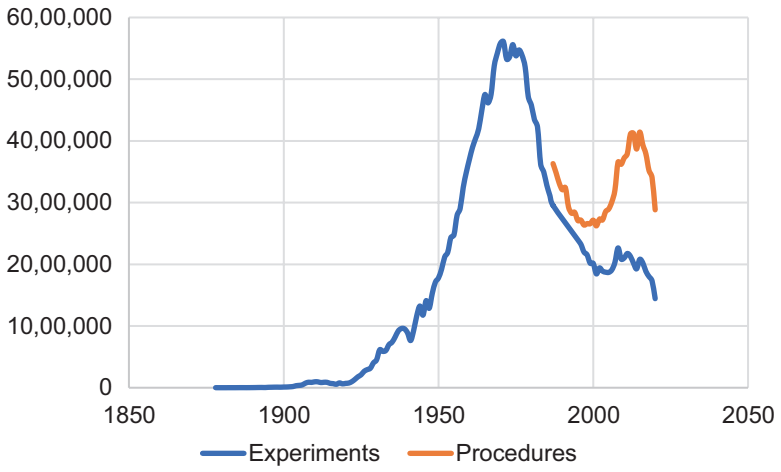

Fig. 30.1 Laboratory animal use in Great Britain: 1887–2020. (The Home Office in the United Kingdom has produced annual reports of laboratory animal use in Great Britain since 1887. In 1986, the law governing laboratory animal use was changed and the Home Office reports – Statistics of Scientific Procedures on Living Animals are now produced under a mandate from the Animals (Scientific Procedures) Act 1986 (Home Office, 1987). Recent reports (since 2001) are available at https://www.gov.uk/government/collections/statistics-of-scientific-procedures-on-living-animals. Older reports are available in UK National Archives)

The graph of laboratory animal use in Great Britain can be divided into approximately six different periods (see Rowan, 1984 and Rowan et al., 1995 for further discussion of early developments in animal use). The first period lasted from 1887 to the end of the First World War when relatively few animals were used in laboratory experiments. The second phase began after the discovery and therapeutic use of insulin in 1922. Animals were used in large numbers for the quality control and standardization of individual batches of insulin as well as for other therapeutic agents. The third phase started in 1935 when the first sulfa drug was identified in experiments on mice followed by the development of penicillin as a miracle drug in 1942. These events (development of insulin, the sulfa drugs and penicillin) launched the modern pharmaceutical industry. The subsequent search for new drugs led to a major expansion of laboratory animal use which peaked in the 1970s in Europe, the United Kingdom and the United States.

The fourth phase began in the mid-1970s when laboratory animal use in Europe, the UK and the USA began to fall as fast as it had risen from 1940 to 1975 (see Fig. 30.1). Given that most of the rise in animal use occurred in commercial laboratories, it is perhaps not surprising that most of the subsequent fall in laboratory animal use would also be driven by changing practices in commercial laboratories (Fig. 30.2). From 1950–1975, large numbers of laboratory animals were employed in screens searching for potential new drug entities. But, from 1975 onwards, these animal screens gave way to more mechanistic and targeted approaches in the search for new drug entities. Today, the use of animals by the pharmaceutical industry in Great Britain has fallen by around 75% since its peak in the mid-1970s even though expenditures on pharmaceutical research and development have increased several-fold since 1975 (Rowan, 2021).

The fifth phase in laboratory animal use was driven by the development of the new gene-editing technologies that permitted the creation of very specific mouse models of human disease – the Genetically Modified Organism (GMO) revolution. The development of these specialized strains of mice led to institutions maintaining large mouse inventories. By 2015, around half of all procedures (two million) recorded by the Home Office involved mouse breeding while the other two million procedures involved the actual use of animals in experiments. This trend can be seen in Fig. 30.2 with the rapid increase in the number of animal procedures in non-commercial laboratories from 2000 to 2015.

We are now in the sixth phase of laboratory animal use. The number of animal procedures have again begun falling after reaching a 2015 peak. The initial expectation was that the special strains of genetically modified mice would lead to a host of new breakthroughs. However, the actual results have been relatively disappointing. In 2013, a former NIH Director commented that the reliance on mice rather than human studies had been a mistake (cf. McManus, 2013, quoting former NIH Director Elias Zerhouni). Then, in 2019 in the United Kingdom, a major center for genetically modified mice announced that it would be shifting away from such mouse models to new research technologies involving human cell organoids and organs-on-a-chip (Else, 2019). That announcement was followed by the UK Medical Research Council announcing it would be closing another major mouse breeding

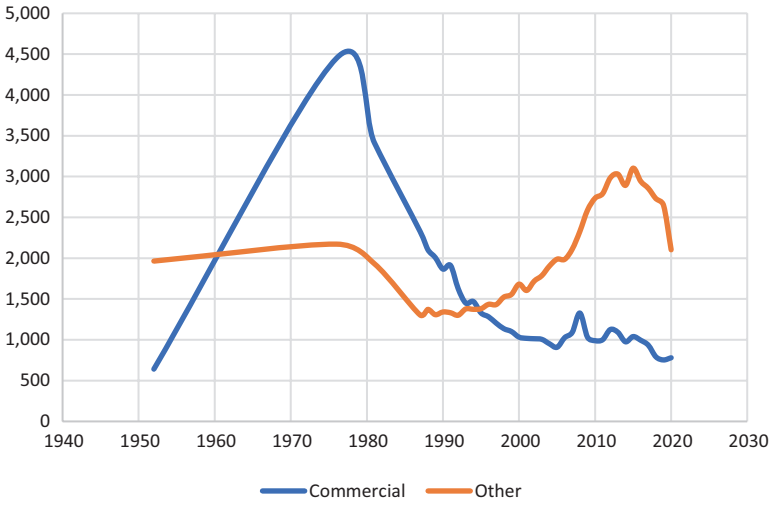

Fig. 30.2 Great Britain: Use of laboratory animals by commercial and other laboratories ('000 s of procedures)

facility in the UK. It is possible that the big drop in laboratory animal procedures in the last few years in Great Britain reflects a shift away from the breeding and use of genetically modified mice.

Animals in Toxicity Testing

In the USA, the first systematic toxicity testing conducted on behalf of public authorities in the first decade of the twentieth century used human volunteers. Dr. Harvey Wiley's famed Poison Squad consisted of 12 young males who were the subjects of feeding experiments conducted between 1902 and 1904. The substances fed to the human experimental subjects included benzoate and formaldehyde. All were present in the American food supply (Lewis, 2002).

In 1927, Trevan devised the LD50 test as a way of standardizing biological therapeutics (Trevan, 1927). In this test, fifty to a hundred animals are dosed with the test substance at sufficient concentrations so that approximately half die within 2 weeks. From this, a median lethal dose (lethal dose 50%) with statistical confidence limits can be calculated. The LD50 test was then pressed into service as a basic toxicity measure for all chemicals. At one point, a Canadian toxicologist became so caught up by the measure and perhaps its false promise of precision, that he ran feeding experiments to determine the rat LD50s of egg whites dissolved in distilled water and then determined the LD50 of distilled water alone as a control (Boyd & Godi, 1967).

Various poisoning scandals in the 1930s led to a steady expansion of animal use in toxicity testing. In the 1930s, Lash Lure, an eyebrow and eyelash dye, was so toxic that a number of users were blinded or disfigured (Lamb, 1936). In the same decade (1937), the mixing of a sulfonamide elixir antibacterial solution in a toxic solvent led to the deaths of more than one hundred people. Both of these events contributed to the passage of the Food, Drug, and Cosmetic Act of 1938, which was intended to make sure that drugs and other chemicals were safe for human use (Lehman, 1955). In 1962, following the thalidomide tragedy, in which many infants were born with severe deformities, Congress tightened standards again with the Kefauver Amendment, which required that drugs should not only be tested for *safety*, but also that the companies should prove that their drugs were *effective* before they would be allowed onto the market.

By the end of the 1980s, an estimated 10%–20% of all laboratory animals were being used in a variety of safety and quality control tests for a wide range of agents and products including drugs, vaccines, cosmetics, household cleaners, pesticides, and other products (Rowan & Loew, 2001). The most thorough testing was reserved for products used in or on foodstuffs and for drugs that would be taken for long periods of time, such as the cholesterol-lowering drugs. These agents are subjected first to a number of acute animal tests lasting less than a month and then to sub-acute animal tests lasting a month to 3 months and then finally to chronic animal tests lasting more than 3 months. The cost of a full-scale battery of animal tests runs into multiple millions of dollars and a complete battery can take four or more years to complete.

Scientific and Regulatory Dissatisfaction with Animal Testing

Since 1995, there has been a substantial decline (around 70%) in the number of animals used in laboratories for drug discovery and toxicity testing (see Fig. 30.3). The decline has been driven by several factors. The pharmaceutical industry has been moving away from animal models for drug development and testing because such models have become less useful in identifying potential new drugs (FDA, 2004; Rowan, 2021). Animal advocates also continue to press companies and regulators to move away from a reliance on animal tests. Finally, animal studies are time-consuming, expensive and are increasingly recognized as not being particularly good at predicting human toxicity risks.

There have been substantial increases in funding devoted to develop alternative testing methods over the last 30 years. Multinational companies, in particular those producing cosmetics and household products, such as Procter & Gamble, Unilever, and L'Oreal have devoted hundreds of millions of dollars toward the development of new approaches for safety testing of their products. The goal has been to address their concerns about human safety without using data from animal tests. Total research funding on alternatives (new methods development) probably amounts to at least $75–100 million a year and there have been many remarkable developments in new technologies and methods to identify human hazard and risk without relying

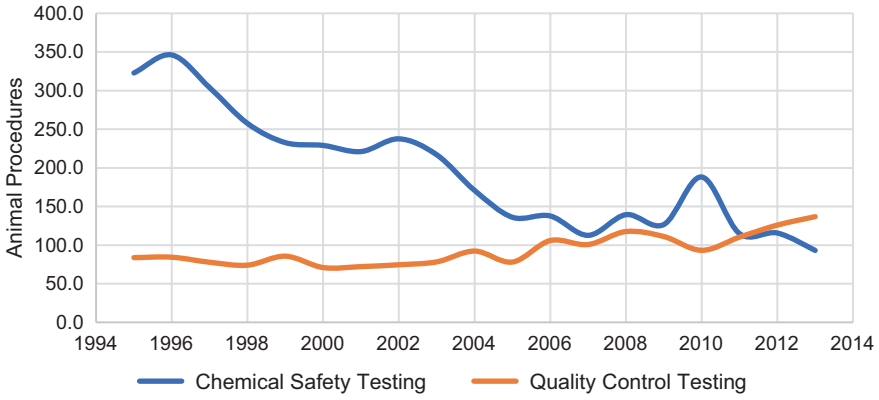

Fig. 30.3 Animal procedures for safety testing and quality control in Great Britain: 1995–2013. (Data taken from Annual Reports of laboratory animal procedures produced by the UK Home Office. The report structure changed in 2014 so it is not possible to extend the above graph to include the reports from 2014 to 2020.)

on animal testing. Meanwhile, the past few years have seen a growing dissatisfaction, probably influenced by the technical developments in toxicology, with the predictive power of animal tests for human risk assessment.

For example, in 2005, officials in the European Union launched the European Platform for Alternatives to Animals, or EPAA, to support and track progress toward the ending of laboratory animal use. In 2007 in the United States, an expert panel of the National Research Council, convened at the request of the U.S. Environmental Protection Agency (EPA) to determine what toxicology would, and perhaps should, look like in the twenty-first century, concluded that the future of toxicology would be based on non-animal methods (NRC, 2007). Since its publication, the US EPA has continued to pursue alternatives and recently announced its intention to end the use of mammals in safety testing by 2035 (Grimm, 2019). In 2016, the NIH Director, Dr. Francis Collins, announced at a congressional budget hearing that he expected most animal use for drug development and testing to be replaced by non-animal methods within 10 years (Rowan, 2021). Meanwhile, in Europe, the Netherlands national committee for the protection of animals used for scientific purposes (NCad, 2016) produced a report that concluded that the use of animals for regulatory safety testing could be phased out by 2025.

The immediate reaction to the NRC, 2007 report, "Toxicity Testing in the 21st Century: A Vision and a Strategy" was negative. But, in 2008, the US National Institutes of Health, the US National Toxicology Program, and the US Environmental Protection Agency signed a memorandum of understanding to pursue the goals laid out in the NRC report. A few years later, the Society of Toxicology launched what became a series of "Future Tox" meetings that examined the prospects for nonanimal methods. At the second of these meetings, in 2014, the attendees focused almost entirely on how one might achieve a new non-animal toxicology rather than whether the goal was realistic or when it might be achieved (Future Tox, 2014; Rowan, 2015).

Although the toxicological literature is now replete with peer-reviewed papers that identify exciting non-animal methods to identify human hazard and that raise doubts about the usefulness of animal test data for human risk assessment, there are many who still cling on to animal testing. Inertia, especially as found in regulatory agencies, requires considerable effort to overcome. The idea that data from animal tests is somehow preferable to non-animal data is exemplified by the following example.

In 2000, an expert panel of toxicologists reported that the ability of animal test data accurately to predict human toxicity ranged from 43% for rodent studies to 63% for non-rodent studies to 71% when both rodent and non-rodent results were combined (Olson et al., 2000). Therefore, the best predictive outcome for the animal testing paradigm was 71% when a range of species were used in the toxicity studies. However, for the most part, toxicological studies are conducted in the rat and in one non-rodent species – typically a rabbit, dog, or primate. Therefore, in practice, one might expect routine animal testing to predict human toxicity somewhere between 50–60% of the time. The analysis by Olson and his colleagues is often cited to support the value of animal data (cf. Vogel, 2014). In contrast, when non-animal testing approaches are evaluated, the ability to predict human outcomes around 50% of the time is considered inadequate (Thomas et al., 2012).

Thus, a 50–60% predictive capacity (little better than a coin-toss) is acceptable (and even good) when obtained in animal studies but is unacceptable when produced from *in vitro* systems. The predictive "success" of the animal studies comes after over 80 years of "improvement" of animal test methods that have attempted to increase the ability of such tests to predict human outcomes. The EPA Toxcast program that Thomas et al. evaluated in 2012 had only been active for little more than a decade. The Toxcast program has continued to evolve and improve and, by 2035, when the EPA proposes to end all mammalian toxicity testing, one would assume the non-animal methods would be performing much better than the twentieth century animal tests.

Economic & Time Factors

While relevance—that is, prediction of toxicity and/or effectiveness in humans--is a very important outcome in the toxicology laboratory, there are other factors that also need to be considered in deciding whether one should continue to focus on animal studies or switch the emphasis to a new approach as proposed in the 2007 NRC Report.

A complete battery of animal toxicity studies to identify the major risks to humans from a chemical in the environment takes a long time to complete (3–5 years per chemical) and is expensive (several million dollars per chemical). The global laboratory capacity to conduct such studies is also relatively limited. In 40 years, for example, only around 600 chemicals have been subjected to the standard carcinogen bioassay in mice and rats. At that rate (15 chemicals tested per year), it would

take 2000 years to test the 30,000 chemicals registered by the European Chemicals Agency in Finland. By contrast, the new robot-testing systems installed at the US National Chemical Genomics Center (NCGC) outside Washington, DC can test almost 1500 chemicals at 15 different concentrations every 2 weeks in around 200 different non-animal test systems. Just one robot system (there are three at NCGC) could, in theory, test all 30,000 chemicals in under a year. If the non-animal tests have approximately similar ability to the animal tests to predict human hazards and risks (as indicated by Olson et al., 2000 and Thomas et al. 2012), a decision to switch to non-animal approaches should happen immediately because of the huge time and cost advantages of non-animal test systems.

The high-throughput robot testing systems generate huge amounts of biologically-relevant data in a very short time. While there are still many questions about what these data might mean for human risk assessment, it is reasonable to predict that the powerful computing systems currently available can, and will be employed to discern patterns in the data and then begin to make more accurate predictions of human hazard and risk. In fact, Luechtefeld et al. (2018) recently reported that they have developed an algorithm that predicts human risk better than a basic set of short-term animal tests. This algorithm is now being marketed by Underwriters Laboratories (see https://www.ul.com/services/predictive-toxicology-solutions) and, reportedly, several governments have expressed interest in using it in regulatory decision-making.

Even if the non-animal test systems do not predict human toxicity quite as well as the animal tests, their speed should tip the scales in their favor. Do we really want to wait 2000 years to test the current 30,000 chemicals in common use?

The Ethics of Toxicological Testing

It is widely agreed that the use of animals in studies that poison them to the point of death or kill them for pathological studies if they have not yet died, is morally problematic if not obviously wrong, all things considered. Today virtually everyone agrees that it would be preferable not to do toxicity studies in animals if they are unnecessary in light of available alternatives. It is generally recognized that there are compelling scientific, economic, and practical arguments against continuing such animal studies as the new technologies come online and are refined to produce more predictive results. The real question now is not *if* but *when* we should stop undertaking the animal testing that still occurs.

Regulators and toxicologists continue to argue that we need to validate the new systems before abandoning animal testing. However, this argument begs two questions. First, the animal studies have rarely been subjected to any validation, so why should they be given a free pass when the alternatives are not? One validation study conducted over 40 years ago of the Draize eye irritancy test found serious problems with the test (Weil & Scala, 1971). Second, what data should we use to validate the new tests? The human toxicity data are limited and the animal data do not present a

satisfactory benchmark. From any reasonable ethical perspective, we ought to accept the need to:

(a) End animal testing promptly (with a few possible exceptions) but perhaps continue for a few years to require animal tests AND non-animal tests on the same chemicals to guide the transition to non-animal methods;
(b) Invest much more heavily in the new paradigm outlined by the National Research Council in 2007 and then embraced by toxicologists in Europe, North America, and, increasingly, other parts of the world; and
(c) Begin to educate government regulators on the benefits and pitfalls of the new paradigm so that regulatory decision-making will take full advantage of it, leading to quick and more reliable policy decisions.

In the last few years, the U.S. Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) has been actively engaged in seeking non-animal alternatives for the so-called "six-pack" of animal acute toxicity tests – dermal lethality, oral lethality, inhalation lethality, eye irritancy, skin irritation and skin sensitization. They are very close to achieving this goal. Recently, a consortium of teams engaged in producing computer models to predict the oral lethality of chemicals has concluded that a consensus artificial intelligence algorithm can be used in place of animals to predict the LD50 (the lethal dose that would kill 50% of a population) (Mansouri et al., 2021). In addition, the use of rabbits to predict the pyrogenicity of medical solutions and devices as well as various chemicals has, in the last few years, fallen dramatically (from around 160,000 a year in 2008 to 35,000 in 2017 in the EU) because of the availability of satisfactory non-animal alternatives (Hartung, 2021). It can be concluded that the use of rabbits for pyrogen testing is now unethical. In fact, the non-animal alternative has been available for two decades but was not being employed and its slow uptake (accelerated recently by political pressure) reflects the large time-gap between the development, acceptance and finally implementation of alternative methods (despite widespread agreement that non-animal systems should replace animal testing wherever possible).

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Chapter 31
Ethical Issues from the Use of Animals in the Cosmetics and Fashion Industries

Darryl R. J. Macer

Abstract This chapter examines some of the ethical issues associated with the persistent use of animals in the fashion and cosmetic industries. There are some cultural differences in the construction of what is considered a human need and what is luxury or simply a desire. Fashion and cosmetics are examples of *self-determination, and people* may also express their membership of a particular gender, indigenous or ethnicity through their fashion. There is discussion of opposition to the killing of animals for fur clothing, and consideration of both the fur trapping industry and factory farm production. Particular issues are also raised through the killing of endangered animals and environmental pollution from tanning industry. There are also animals used for research aimed at increasing the productivity and efficiency of animals to produce fibre and safe ingredients for the cosmetic industry. The desire to dress attractively, and fashionably, is universal and applauded in most cultures, but our use of animals also shapes our moral community, and may also lead to legal reform.

Keywords Animals · Cosmetics industries · Fashion industries · Non-medical animal testing · Industry and captive animals · Animal rights

Introduction

Throughout human evolution people have been in relationships with other animals around them as companions, sources of food, labor, security and clothing. If we use more economic language we can say that "consumers", both human beings, as well as members of other species, have used other animals to provide both goods and services. The fashion industry global trade value is over 100 billion U.S. dollars per year (Ferreira, 2016). All our relationships have ethical implications, and the use of

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animals by human beings has a long social, biological and spiritual heritage (Macer, 1998). In this chapter we will explore some of the ethical issues that especially relate to cosmetics and fashion that may at times go beyond the provision of necessities for life and may be associated with luxury. Are there times when the pursuit of luxury as an expression of autonomy be unethical?

Let me start with a quote from Ovid written over two millennia ago, which reflects some of the variety of similar opinions over the cosmetics and fashion industries we can also find today. He wrote:

> Listen and learn, dear girls, how to improve your appearance,
> By what methods to keep beauties you want to preserve.
> Cultures the word – thereby the briers die out in the farm lands,
> Culture produces the grain out of a bountiful soil,
> Culture improves the taste, if the flavor of apples is better;
> From the graft of the tree opulent richness is born."
> "When the mother, red faced, and perched on a stool or a high chair,
> Kept the work going along, spinning with calloused thumb,
> Folded the lambs and the ewes her daughters had driven to pasture,
> Split the kindling, and lugged heavier logs for fire.
> Daughters, in our own day, are frail and delicate creatures,
> Fonder of brighter array, garments embroidered with gold,
> Hair perfumed, and set an every conceivable fashion,
> Rings on their fingers, and wrists dangling with bracelets and charms,
> Necklaces brought from the east, and earrings heavy with jewels –
> Double their weight, and one ear hardly could carry the load.
> Nothing is wrong with all this, dear girls, if you're trying to please us:
> Even the men in this time cultivate elegant style. (Ovid, *The Art of Beauty*, lines 1–6, 13–23 1960).

Firstly, we can say that nothing changes under the sun. If the pursuit of ethics is happiness, or eudaemonia, then is there anything intrinsically unethical about the pursuit of beauty? Many of the most highly regarded human achievements as listed by the Convention Concerning the Protection of the World Cultural and Natural Heritage (1972), are expressions of beauty. The reference to culture by Ovid is also something that will be explored further in this chapter, and is particularly relevant because of the debates between cultural relativism and universalism in ethics. Ovid also gave examples of the contrast between more basic needs such as food, clothing ("spinning"), warmth, and items such as jewelry and imported products "from the East".

The demarcation of needs and desires is not always so easy to draw, and as Ovid wrote, in the end the pursuit of beauty is not just to please oneself but also to please others. The question of the continuity between the popular uses of cosmetics and fashion in ancient populations, current indigenous populations and other persons and communities living in the current modern age, will be explored with reference to consideration of whether modern industry is somehow morally different? I would argue that there is little moral difference between the modern fashion industry to the traders and merchants of the past, except perhaps in the number of persons affected.

Culture of Needs and Desire

All living organisms are biological beings, and share a common and intertwined biological heritage. Humans are members of the species *Homo sapiens*, one of the millions of species alive on the planet Earth. Fundamentally when it comes to the use of other animals by humans, we must ask whether that particular use of animals raises ethical issues and how we might want to assess such ethical issues because we are moral beings. Other chapters in this volume reference the development of ethical approaches to animal use, which usually start with the reduction of suffering caused by our moral choices. Suffering can be defined as prolonged pain of a certain intensity (Regan, 1983), and it is claimed that no individual can suffer who is incapable of experiencing pain. The capacity for suffering and/or enjoyment has been described as a prerequisite for having any interests (Singer, 1976).

There are a range of different approaches to bioethical issues amongst different people (Macer, 1998). Some doubt that there are any particular ethical issues in the exploitative relationship that human beings find themselves in as products of evolution because we are a carnivore and a top predator in most ecosystems. Typically, they will argue that since we have canine teeth, it is our natural ontology to eat meat.

For this first group of people the fact that clothing is essential for our human survival, especially in cold climates, means that the use of animal pelts from deer or bears that were captured and killed for food, is simply making use of parts of a living animal. They could also raise the point to those who object to the use of animals for clothes, to say that it would actually be disrespectful and a waste not to use parts of an animal that you killed for food.

They would also probably say that when it comes to the use of the larvae of the silk moth to produce silk specifically that these are just insects which are not sentient. We can see this example has consequences for the followers of different religions, some Christian or Buddhist monks would use silk clothing especially in cold winter climates, whereas Jain monks would only use cotton clothing because it comes from plants and not animals. Although as far as we know insects do not feel pain, the techniques used to extract silk consist of placing the cocoons in hot air, steam or boiling water in order for the silkworm to die without damaging the silk thread.

Some animals are targeted for their fur rather than as food. Trappers see their work as moral, as Musgrove and Blair (1979) write:

> It has become fashionable in recent years to avoid such strong words as trapping, killing, bleeding, and shooting, but this approach is not ours. Trapping is an honorable profession, and we will refer to trappers as trappers. "And when it comes time to kill a trapped animal, we will be honest in our terminology their too." To those who disagree with this outlook we offer no apologies. We are convinced that fur trapping is both necessary and humane. Trapping is necessary from a game management aspect to animals to maintain a balance between wild animals and their habitat.

Some other voices, especially among the bioethics community, ask questions such as whether humans are a special form of life, different from other living creatures

that generally only harm others when they need to for their survival? Although annoyed hippopotamuses reportedly kill about five hundred humans globally every year, making them one of the deadliest large animals, most sentient animals only kill for self-protection or food.

For this second group of people, they may consider that the use of the pelts of animals that were being killed for food, might become ethical by a utilitarian calculation that it was better not to waste parts of the animal. Some may also accept the rationale of ecological balance used by the fur trappers above. Some argue from a deontological perspective may place particularly high moral status on certain species and encourage the use of alternative sources of fibre to make clothes.

The concept of "do no harm" or non-maleficence, which has a basis at a more fundamental level - the level of being alive, argues against hurting any living organism. If we are going to harm life, a departure from the ideal of doing no harm and love of life, it must be for a good motive (Macer, 1998). Such a motive might be survival, and we can see this as natural - all organisms consume and compete with others. Plants compete with each other for space to grow, animals eat plants or other animals, bacteria and fungi also compete for resources and space - sometimes killing other organisms and other times competing without direct killing.

Destruction of nature and life by humans is caused by two human motives - necessity and desire. Basically, it is more ethically acceptable to cause harm if there is necessity for survival than if it is only desire. This distinction is required ever more as human desire continues to destroy the planet.

Intrinsic values are something that exist without another person assigning value to something. We could also consider intrinsic value as some experience which has value in itself without any instrumental reference by others. To perceive something of intrinsic value we need to have an object of value, whether it is the bone thrown to a dog or a ball thrown to a child, the object becomes of value. It becomes of value even if we cannot be conscious of the value or talk about it, as you can see from the reaction of the animal to the removal of the object that they have interest in.

A particularly important source of fibre for clothing is wool, which is shorn from sheep in the spring so that they will be cooler in the summer and it naturally grows back for winter months when they need it as a thermal protection themselves. Sheep farming has a long tradition, being also mentioned by Ovid in the quote cited above. I have not made a calculation of the amount of wool that could be harvested from the pelts of animals killed for food as opposed to just shearing of sheep. The pelts of sheep are also fashionable and used as rugs in a number of both ancient and modern societies. It seems to be ethically justified if you're going to kill the sheep for meat that you also make the sheep skin as a useful product.

However, vegans will prefer to use a fibre from plants such as cotton or hemp, as opposed to one made from animals, such as wool or silk (Choi & Lee, 2021). Vegan materials used in so-called vegan fashion include acrylic, bamboo, cotton, hemp, jute, linen, modal, nylon, ramie, rayon, and spandex. Sometimes the environmental consequences of use of vegan materials in fashion and food may not be ideal, as seen for example in the environmental costs of production of almond milk in water scarce environments compared to cow's milk. Having said that, the wool scouring

industry does use a lot of water. More thorough environmental impact assessment, including analysis of the harms to animals, should be research priorities in these areas.

The leather industry relies on animals such as cows, buffalo, sheep, deer and kangaroo, for example. Around 95% of the leather used globally is a side product of the meat and dairy industries. The tanning industry will be discussed later. Basic footwear in many parts of the world has used leather for centuries and continues to do so. Unless people will give up eating beef, which is against the global trends which clearly predict significant global increases in beef consumption (Kanaly et al., 2010), our focus should be on making the tanning industry more environmentally sustainable.

The motive for using animals also alters the morality of their use in some religions, suggesting these concerns have a long history. All religions display examples of the use of cosmetics and even particular fashion codes are used for priests, nuns and monks. Animal sacrifice for worship is used in Islam, but they would generally condemn scientific research or battery farming. Vivisection is allowed under circumstances where there is no pain or disfigurement and if other animals benefit (Macer, 1998). The use of animals in science is under the same moral codes as applied to humans. Even though the animals possess a lower consciousness, Islam says animals know their own mode of prayer and psalm, a voluntary act of praise. The killing of any breathing beings, except for food or religious sacrifice, is high on the list of deadly sins. Hindus, Jains and Buddhist believe that we will be reborn as another living animal, which creates their bond of caring and compassion for animals. So they will reject animal sacrifice, even though the sacrifice of an animal won't kill what is essential, in the reality, the soul, of that animal.

Christian scriptures and traditions accept animals do have valid claims upon us. Animals cannot be viewed simply as expendable raw materials for our designs, they do not exist simply to serve us, the doctrine of creation is opposed to anthropocentric notions. The use of animal sacrifices does not mean animals should be sacrificed for the selfish pursuits of humans, the practice of animal sacrifice was to bring God into the focus of human hearts in place of their own selfish desires, and was not necessary after the birth of Christ. The tradition of the Roman Catholic church is to regard animals as means to human ends, and the moral objections to cruelty on animals are more concerned with fear that those inflicting pain will contract habits of cruelty, something also seen in Kant (Macer, 1998). The contrasting attitude of St. Francis of Assisi, to talk of sister cows or brother dog, is a picture which is appealing to those with a more biocentric view.

Who should judge whether a practice is a need or a desire? If we live in cold climates the use of an animal fur as warm clothes is a need rather than a desire. If we go outside in the cold catching food, gathering fuel for the fire, or water, and so on, it is usually a necessary excursion. Can we then criticize a socialite who likes to venture out in the cold winter to attend parties? If it is a business dinner, necessary for employment and gathering an income is this more justifiable compared to a birthday party? Is wearing a fur coat a necessity for a homeless person on the streets at night, but not for someone who lives in a warm house? What about in times of

natural disaster? A fur coat can be a life safer. The principles of balance and context seem critical here, but even more fundamental is whether anyone can limit our autonomy.

Animals such as ostrich, peacocks, doves, geese and turkeys are some of the few species that have been involved in the feathers trade (Ferreira, 2016). These are not all from dead animals, and a percentage of the world's supply derives from birds plucked alive. The plucking of feathers is painful and damaging for the animal, and it may be repeated every 6 weeks. The brutality in which these feathers are plucked can lead to serious wounds that are usually taken care off without anesthesia and dirty materials.

Some indigenous tribes find particular spiritual meaning in some feathers, and in USA use of bald eagle feathers, a protected species, is limited to Native Americans, on the grounds of religious freedom. Thus not all feathers are produced through industrial processes, and these are retrieved from dead or molting eagles.

Autonomy, Fashion and Cosmetics

One of the basic ethical principles is autonomy or self-rule. The cosmetics industry is linked to a number of complex mental traits (Haiken, 1997), but is ubiquitous. Both the International Covenant on Civil and Political Rights and the International Covenant on Economic, Social and Cultural Rights include these words: "*All peoples have the right to self-determination. By virtue of that right they freely determine their political status and freely pursue their economic, social and cultural development.*" Throughout history people have chosen fashion, cosmetics, jewelry, and other habits to express their individuality. They may also express their membership of a particular gender, indigenous or cultural ethnicity. This freedom of expression is enshrined in the Universal Declaration of Human Rights (1948), and most national legal constitutions.

We should demonstrate real harm if we limit someone's autonomy and their self-determination. Fashion is associated with social, financial and cultural factors of a society, and is not a mere indication of personal taste. Women are freely wearing clothes nowadays that commonly used to be worn by men only such as trousers, and men start to wear feminine clothes, such as skirts and dresses, more and more each day. There was some fashion which physically hurt people that have been used during history. From ancient Mayans making holes through people's teeth to put jewels in it to sixteenth century's high heels which were 50 centimeters high, or some harmful modern surgeries. If you hurt yourselves as a consenting adult, we may have less objection to it. The fashion industry however is linked to some dangerous psychophysical conditions such as anorexia nervosa, that can also cost people their lives.

A well known example of abuse through fashion choices is foot binding in China. Having small feet was a beauty standard among Chinese women since the tenth century A.D.. Therefore, some people tightly fastened girl children's feet at a young

age to prevent the natural growth of the feet. In those cases, their feet got strange forms that even made walking hard and painful for them. They only could take short steps. This cruel fashion remained present until the mid twentieth century when after a lot of efforts, it finally became illegal.

Use of both live and dead animals as fashion accessories is seen all around the world. The pet industry has also promoted various accessories for pets for the ubiquitous dog walkers, with additions of carriages and clothes for cats and other pet animals to accompany people in their social encounters. These are also being encouraged by growth of social media.

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Fur Protests

Opposition to the killing of animals for fur clothing have always been one of the most violent protests in fashion industry. Wearing clothes made from animal's fur used to be almost universally popular but in the 1970s the efforts of Animal Rights Organization (such as PETA and Greenpeace), as well as certain celebrities and animal rights activists, saw the clothing which once were a synonym with luxury and high culture change to become out of favor. Furs used to be associated as an indication of socio-economic class and sometimes even were displays of higher moral and cultural status compared to the working classes. After these protests furs

became symbols of an unnecessary "slaughter" which is now highly regulated in some countries under different conditions.

The animal rights organization, People for the Ethical Treatment of Animals (PETA) lobbied against some fur manufacturers to reduce fur use for some years (Ann & Paulins, 2020). Media campaigns by Greenpeace and associates against the killing of baby seals in the Arctic changed public opinion, and even made Greenpeace a household name. As a source of animal fur the videos of baby seals clubbed to death in the wild changed many peoples' minds.

As a result, the majority of furs used today come from factories. The most common animals used are foxes, rabbits, minks, chinchillas and otters. There are still efforts made against industrial fur factories, similar to industrial meat production. Although there were reductions for some years in the sales of fur-based clothes from the 1980s for several decades, in recent years in Western Europe and North America we can see a return of fur into many clothes (Ferreira, 2016).

Over half of the fur factories globally are in Western Europe (Ferreira, 2016). It is estimated that about one hundred million animals die each year just to be turned into a fancy clothes and accessories (Humane Society International, 2021). As they write:

> Around one hundred million animals are bred and killed on intensive fur farms specifically to supply the fashion industry with not only traditional fur coats but, increasingly, real fur trim for hooded jackets, and real fur pompoms used on hats, gloves, shoes and a range of other clothing and accessories.

Given this demand, we can say that there are still millions of consumers who choose to buy products with animal fur, and not only those who live in cold climates. The protests have peaked at different times in different cultures, first in North America and Western Europe, and later in parts of Asia. In Japan, some campaigners domestically and internationally forced some clothing brands to announce that they will no longer use fur. Between 2006 and 2016 the import of furs into Japan was reduced by 80%. In Japan, still some 1.6 million pelts were imported annually in 2016 (Sivakami, 2019). We can also see decreased attention on the fur trade as environmentally minded protesters have shifted their attention to climate change.

The use of reptile skin accessories has been reduced in most countries and the trade in animal skins decreased significantly. Most of this was due to the enforcement of CITES. Overall a market analysis of 15 case studies is Cavusoglu and Dakhli (2017).

Industry and Captive Animals

Overall the word "industry" has often been associated to excesses of global capitalism and exploitation of the poor throughout colonization that expanded with the industrial revolution. However, trade is a basic relationship that we can see even

among pre-human species through the evolutionary strategy of tit-for-tat and reciprocal altruism. As industry developed, and with increasing populations, trade has increasingly separated the relationships between consumers and producers. The development of specialization in production of particular trade products and consumer items is seen throughout human history and can be particularly useful still today to support particular communities and tradesmen. The whole fabric of social structure is based on trading and industry. From a biological perspective we have to balance both the benefits and harms of industrial approaches to the provision of goods and services.

If any readers have grown your own animals in your backyard, or even on your farm, for food, you may have experiences of a less than ideal, and even the downright painful, execution of the animal as an amateur slaughterer. Although there are concerns about some meat abattoirs due to unethical practices, the industrial system also offers offers human society an opportunity for a more ethical and humane killing of animals in a systematic process then that which could occur through the killing of animals in everyone's backyard. If you are going to eat an animal, it is consistent with ethical principles of minimizing pain to kill with less pain and suffering.

In the modern "meat works" sentient animals are executed painlessly, and for over half a century in New Zealand and Australia producers have attempted to avoid stress because it results in elevated adrenaline which will make tough meat in animals, which will lower the price of the meat and thus reduce profits for the meat producers. The production of fur and animal skins also benefits from a professional approach (Musgrove & Blair, 1979), and if our society supports the killing of animals to produce fur or skin, ethically the same standards of reduction of cruelty to animals should be applied.

Non-invasive farming and research on captive animals leads to pain, suffering, and deprivation arising out of the manner in which research animals are kept (Rollins, 2009). Factory farming of animals for fur can mean that normally "social animals are kept in isolation; burrowing animals are kept in stainless steel or polycarbonate cages; and, in general, animals' normal repertoire of powers and coping abilities", their *teloi* or natures (Rollin, 1982). Animals used in research probably suffer more from the ways in which they are kept for research than from the invasive manipulation they are exposed to within research (Rollins, 2009). This argument could be used to argue that it is better to have animals enjoying their life in the wilderness rather than a factory farm. A utilitarian calculus could be applied to balance years of suffering through deprivation of a natural environment, versus perhaps a day being trapped in a steel animal trap until the trapper executes the animal. There are also efforts to modify the types of trap that are used, or the mode of killing. The steel-jaw trap is banned in some countries, but is still a favorite method of trappers in Canada, USA and Russia (Plannthin, 2016).

Killing of Endangered Animals and Environmental Concerns

Although there have been many ethical concerns expressed about the research involving animals in the testing of cosmetics and luxury products, the extensive use of cosmetics as commercial products, and the use of products produced from animals in the fashion industry, involve a significantly larger number of animals. It is not only the sheer number of animals that are used, but some of the fashion industry also utilize endangered, and/or wild animals which raise particular concerns that may not have been explored in the other chapters in this book.

Some exotic and endangered species such as snakes, lizards, crocodiles and elephants- became endangered due to the high demand for their hide. The list of animals use by the leather industry also includes frogs, sharks, dolphins, camels, mules, cats and birds (Plannthin, 2016). Opposition to the killing of endangered animals for fur, or crocodile, snake skins, turtle shells, and so on, has been supported by international laws such as the Convention against Trade in Endangered Species (CITES) which protects endangered animal's species. Some of the animals including crocodiles, snakes, turtles, and so on, became endangered because of the cosmetic and fashion uses of their body parts. The success of CITES reflects that growing public morality to value biodiversity for its own sake (Bosworth et al., 2012). A number of studies have also shown the value of targeted species for both human and non-human communities (van der Ploeg et al., 2011).

Many clothing brands offer non animal-based leather these days. Some are trying to replace animal products with herbal alternatives such as cactus leather which is also sustainable and environmental friendly.

In the nineteenth century it was popular for fashionable ladies to wear corsets made from whale baleen to keep their body shape thin as a cosmetic fashion style. The baleen found in some whale species was particularly useful as a material and was widely used. It is however debatable to say that baleen was a major reason for the killing of whales, because whale oil was the greater economic product. In the end alternative materials in the clothing industry could replace baleen. In addition, dietary changes may have actually made it easier for people to keep a thinner shape of a body of a woman in accordance with the prevailing social fads at the time, and the increasing attention to healthy diets and exercise.

The tanning industry uses a number of chemicals that can harm both the workers and the environment. In the case of the use of skins from animals killed for their meat, we could argue that the animal was already dead and using the leather will add to the benefit ratio against the harm caused from the loss of life. However, while chemicals are avoided in the killing process so that the meat is not contaminated because of food safety standards, the skins are treated with chemicals which may create both noxious gases for employees, and dangerous run off with carcinogenic and teratogenic compounds for both people and other organisms. As Ferreira (2016) writes:

> Employees from tanneries lack laws and regulations to protect their rights and interests, and most are liable to get in contact with chemicals such as lime, tanning liquor, acids, solvents

> or chromium that, when inhaled, create lung irritation, obstruction in the airways and can increase the chances of developing cancer, asthma, bronchitis or pharyngitis, among others. When in contact with skin, chromium can cause erosive ulceration and allergic dermatitis.

Some of these compounds persist in the environment. Since reduction of chemical residues costs money, this work is often done in developing countries and/or in jurisdictions that will minimize the costs as much as the regulatory environment allows. The majority of major fashion brands have closed many European, Japanese and American tanneries and moved to countries where labour is cheaper and environmental standards are weaker. There are number of poorly regulated tanneries that contaminate the water and soil of these regions (Plannthin, 2016). Even in some countries, such as India, which has had laws to protect against the pollution caused by tanneries since the 1980s (Jacob et al., 1997; Lavanya & Venkatakrishnan, 1997), the enforcement of laws remains weak. This short-term vision of protection is unethical, and environmental protection and health and safety standards are important ethical requirements for ethical fashion. There are also environmental consequences in the farming of animals for fashion industries, relating to water use and agricultural run-off as well.

Research and Development of Modified Animals and New Products

There are also animals used for research in cosmetics and fashion. Research aimed at increasing the productivity and efficiency of animals to produce fibre and ingredients for the cosmetic industry is conducted, in the same way as used for food production. There has been a long history of breeding of domestic animals targeted at different roles, and the wool industry has focused on production of different qualities of wool fibre. The breeding, treatment and manipulation of other lifeforms as producers of market products occurred over centuries.

There are also techniques used in the wool industry that can cause suffering to animals. One is mulesing ("the cutting of flaps of skin from the breech and tail of the lamb with a scalping to create an area of bare and stretched skin"), which is used to prevent infections. This may often be carried out without anesthesia (Ferreira, 2016). Selective breeding and modification to overproduce wool make the animal unable to shed its fleece, which can provoke death from heat exhaustion, and make them completely dependent on humans, which leads to mulesing (Plannthin, 2016).

Some research includes feed trials, metabolic studies, and the development of bioreactors (in which animals are genetically engineered to produce particular substances of potential commercial value). The creation of genetically modified animals has become routine. While in medical research we must try to balance the pain caused by the benefit to humankind or other animals (Porter, 1992), for people who dismiss the "need" for cosmetics and fashion, this balancing will be more difficult (Macer, 1998).

There are economic reasons to make faster growing animals, or using animals as bioreactors. To make a chicken lay an egg full of interferon, a protein that can treat some cancer, is novel, but not beyond the daily use of animals. In analogous ways, products for cosmetic use can also be produced. Ethically, if such proteins can be made in soybeans for similar cost it is better, and if the substance can be delivered to the body by eating only beans - that would be a great advance.

The testing of various consumer goods for safety, toxicity, irritation, and degree of toxicity is an industry in itself. Such testing includes the testing of cosmetics and industrial chemicals, as well as the testing of drugs for toxicity, carcinogenesis (production of cancer), mutagenesis (production of mutations in living bodies), and teratogenesis (production of monsters and abnormalities in embryo development) (Rollins, 1982). Eventually laws may restrict this, and in 2018 California banned the use of animals in cosmetic testing (Wang et al., 2020).

There are consumer brands within the global cosmetic industry, such as Bodyshop, that have marketed their policy choice not to conduct new animal tests for product safety to considerable commercial success. In 2012 the Japan Anti-Vivisection Association (JAVA) won a LUSH Prize in Consumer Awareness category for it's boycott campaign against the Japanese cosmetic giant Shiseido. It was unusual for Japan to have Street Protests which led the company to announce an end to Animal Testing Program for products. Nevertheless, unlike the European Union Animal Testing ban there are no laws proscribing the practice (Sivakami, 2019).

Cultural Diversity, Ethics of Destruction and Shaping a Moral Community

The desire to dress attractively, and fashionably, is universal and applauded in most cultures. Although for some years there were campaigns against the fur trade that saw some persons throw paint onto other person's fur coats, these acts of destruction are unethical and rightfully illegal in most countries. The use of ivory keys in pianos, and in ornaments is becoming illegal in a growing number of countries.

Despite attempts over time for a ban on the use of animals for cosmetics and fashion, finding a middle ground is important for the construction of a bioethical mature society. Peter Singer (1976) argues that pains of the same intensity and duration are equally bad whether felt by humans or animals, and we should not be prepared to inflict pain on other animals that we would not bear ourselves, unless there is some overwhelming justification for it. For some people cosmetics and beauty do not justify the use of animals.

The origins of our selfishness and altruistic (giving) behaviour are fundamental to how we behave. Excessive concern with personal autonomy could be called selfishness, and there is obviously a balance between too little recognition of autonomy which is against the dignity of a person, and too much which can clash with justice. Autonomy should not be the most valuable principle of bioethics, even if it is the most dominant feature of human behavior (Macer, 1998).

Confucius in the *Analects* wrote that the presence of *jen* (human-heartedness, the extension of acts of affection, patience, and understanding) designates a human being as opposed to an animal. *Jen* is an embodiment of goodness, wisdom, and courage in a descending order of importance (*Analects*, 14:30), and in the widest sense it refers to a person who possesses the virtues of kindness, gentleness, humanness and unselfishness (6:28). If we can find these characters in animals then we could say that they too possess *jen*, a similar concept to altruism and love.

Perhaps our moral guide can be to look at animals themselves. Frans de Waal (1996) looked at the origins of right and wrong in different animals. Sympathy is a character at least seen in dolphins and whales. Dolphins have been videoed saving companions by biting through harpoon lines and hauling then out of fishing nets. The sympathy shown by whales to other members of their pod once injured is used by whalers, so that once one sperm whale is harpooned, other members of the pod will encircle the boat trying to help the injured companion, while the whalers will find it easy to kill many more. Sympathy in this case means both recognizing someone else's pain, empathy, and doing something about it. Culture specific tool use and language has been observed in different communities of chimpanzees and bonobos as evidence of learning not in genes. Tit-for-tat deals between leaders and supporters reminiscent of human politics has also been observed in other primates (Macer, 1998).

We may all agree that animals can suffer, but the question is how much does it matter? In the International Bioethics Education survey in 1993, in response to an open question, 8% of teachers in Australia and 7% of teachers in New Zealand, spontaneously mentioned that they had concerns over the use of animals in cosmetic tests, and that more students had also raised this as an issue (Macer et al., 1996). Less teachers in Japan mentioned this. However, in other comments it was clear that the majority of the public no longer clearly support for use of animals for cosmetic development. Recent public opinion surveys find that only about half of persons in Western Europe consider that the use of fur is unethical (Ferreira, 2016).

An often neglected group of persons who are affected by the fur industry are the employees of factories who need to become psychologically adjusted to routine killing of animals (Ferreira, 2016). Even if humane killing is performed not everyone can routinely kill animals. Socially it is also not always a desirable profession. In Japan for example, the equivalent of the the untouchable community, people who worked in the killing of animals usually came from social class/caste called the burakumin or ni-hin (literally translated as "non-human") (Macer, 1998).

Legal Evolution and Recognition of Animals

Modern legal systems developed in Europe during the eighteenth and nineteenth centuries. These systems resulted from the capital market economy, together with the ideologies such as individualism and liberalism, unified state power and modern bureaucracy as its foundations. Technological innovations require a re-examination

of the fundamental legal concepts of humans and nature which have formed the premises of the modern law up until now (Kitagawa, 1998). The debates on cosmetic industry, endangered animals, and research on animals have also been important in the evolution of laws to protect animals.

Under modern law, persons are treated equally as legal personalities, each possessing the capacity to hold rights. The modern law regards the person's intention and activities as the most significant element of law. Contracts and wills are built based upon such a presupposition. Land, resources, animals and plants are all conceived of as things which, as the object of a subjective right, may be owned by a person. Attention should be paid to the legal ramification of the conception that animals and plants are viewed as "things" in law. All creatures except humans are categorized as "things." This dichotomy is an unbridgeable one under the modern law. Kitagawa (1998) and others argue that the time has come for us to introduce a new concept called a "life unit" which is, in the world of microorganisms, the fundamental element of the third legal order and which is an addition to the existing legal dichotomy of "persons" and "things." Upon successful building of the "life unit" concept, it becomes feasible for us to begin constructing the new legal system of the "life unit." In this new legal order, a "life unit" will not necessarily be recognized as a new subject of a right, nor as a new thing. This legal order for the "life unit" and its constituents may require a complexity of new legal norms. When our intention is not to sacrifice other beings in order to safe our life or the life of a sick child, but only to look good at a party, the legal justifications weaken substantially. Although it took some decades, the evolution of laws to reject cosmetic safety testing in animals in the USA does represent a significant milestone in the balancing of human need and desire.

The so-called "moral" and social acceptance of a technology evolves over time (Tortora, 2015). Fashion and cosmetics also evolve over time, and what is "normal" changes over time. There are some fashion brands that promote their policy of not using fur from animals, for example Stella McCartney's "Fur-free fur" (Ferreira, 2016). While they do use silk and wool, they reject animal testing and use of fur and leather. Some other mass market brands promote reduction of animal products in fashion, such as Bodyshop and H&M, for example. Many exotic products are still used in the luxury fashion and cosmetic industries.

Although some proponents against the use of animal products in the fashion industry argue that we should all wear either plant based products or synthetic clothes. There are not just a few bioethically minded persons who would consider it more ethical to wear natural fibre compared to synthetic fibers and products. CITES and education against the use of endangered animals has been successful to reduce the use of some species. What we may all agree upon is that we need to protect our environment and find a better ethical balance in the use of animals in the fashion industry, but the recovery of the fur industry in recent years suggests that animal products will continue to be widely used in fashion in this millenia, as they have been in past millenia.

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Chapter 32
Is It Time to Phase Out the Use of All Nonhuman Primates in Invasive Research?

Bernardo Aguilera and Javiera Perez Gomez

Abstract The use of some nonhuman primates in invasive research—unlike that on animals more generally—has been severely restricted or banned in much of the world. This trend toward severe restrictions or bans raises the question: Has the time come to end invasive research with *all* primates? In this chapter, we offer an overview of the main ethical questions surrounding the use of primates in invasive research, evaluate some of the leading arguments in favor of and against such research, and propose some ethical recommendations for conducting this research. As we argue, the case for phasing out the use of primates in invasive research is not as straightforward as some might think. Stringent restrictions must be adopted if scientifically and ethically justifiable invasive research with primates is to continue.

Keywords Nonhuman primates · Invasive research · Ethics of animal research · Moral status of primates · Three-Rs

Introduction

The use of nonhuman primates (hereafter, primates) in invasive research has come under increased scrutiny in recent decades.[1] This is especially true of great apes, a subgroup of primates that has virtually been phased out of invasive research in much

[1] We will understand 'invasive research' as research that is potentially harmful and not primarily aimed at benefiting the individual animal. Thus, veterinary research that serves a therapeutic purpose, as well as research that is purely observational (e.g., some behavioral studies) will be outside of our scope.

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of the world; but it is also true of primates more generally. The European Union (E.U.), for example, has imposed stringent restrictions on the use of all primates in invasive research, and recent regulatory initiatives suggest a similar trend in the United States. This chapter offers an overview of the main ethical questions surrounding the ethics of using primates in invasive research, with a special focus on primates other than great apes. We evaluate some of the leading arguments in favor of and against such research and propose some ethical recommendations. Our focus is on three key incommensurable concerns that invasive research with primates must deal with: the moral standing of primates, the scientific and medical value of invasive research with primates, and the harms and costs to which primates are subject.

Defenders of the ethical permissibility of invasive research with primates—like defenders of the ethical permissibility of animal research more generally—have historically appealed to traditional utilitarian frameworks. There, the idea is that invasive research is justified as long as its potential benefits to human beings outweigh its harms to primate research subjects. Today, this line of argument often accompanies the implementation of Russel and Burch's 1959 "Three-Rs" framework, which seeks to minimize the pain and distress that animal research subjects experience, while at the same time allowing the relevant research objectives to be met, by *replacing* animals used in research with non-animal models, *reducing* the number of animals used in research, and *refining* procedures so that animals experience less harm (Russell & Burch, 1959; Schuppli et al., 2004).

While the Three-Rs framework continues to be the dominant framework in debates on the ethics of animal research in general, recent decades have seen a call to also include in such debates deontological considerations—that is, considerations involving the notion of personhood, the notion of rights, the notion of limits to permissible harm, among others. This call finds particularly strong support in debates on the ethics of invasive research with primates, who, like humans, possess complex cognitive, experiential, and social capacities. Appealing to these capacities, some authors maintain that the degree of respect and protections normally afforded to human research subjects should be extended to primate research subjects (see, e.g., Carvalho et al., 2018)—an active and controversial issue in animal ethics debates.

This chapter argues that the case for extending such a high degree of protection to all primates used in research is not as straightforward as some might think. Given primates' cognitive and experiential capacities, there is reason to believe that the moral status of some primates—specifically great apes—is higher than the moral status of other primates such as, for example, rhesus macaques. Furthermore, a strong case can be made in support of the idea that primate research models of human biology and disease are sometimes necessary for obtaining highly valuable scientific knowledge. Nevertheless, as we argue, stringent restrictions must be adopted if scientifically and ethically justifiable invasive research with primates is to continue. These should include, at the very least, carrying out maximally careful cost-benefit analyses, sharply limiting experiments involving severe harm, and

developing specific criteria for meeting primates' basic needs on the ground. Although we believe exceptions to these restrictions can hardly ever be justified, we end by considering some conditions under which such restrictions might be lifted.

Background

Let us begin by examining some data surrounding some of the various types of research that have been conducted on primates, as well as some of the policies that have been adopted worldwide in response to such research.

The vast majority of animals used in invasive research are rodents (>95%); primates comprise less than one half of 1% of such animals (SCHER, 2009; Grimm, 2018; Taylor & Alvarez, 2019). A large number of primates used in research are Old World monkeys, especially rhesus macaques and cynomolgus macaques (Cauvin et al., 2015). New World monkeys—especially marmosets—and prosimians are also used in research, but less frequently. Moreover, primates are either wild-caught or purpose-bred. According to a 2015 estimate, 158,780 procedures involving monkeys were conducted that year worldwide (Taylor & Alvarez, 2019).

Most primate research is conducted in the U.S., China, Japan, Brazil, Canada, the U.K., France, Germany, India and South Korea (Taylor & Alvarez, 2019). While the number of primates used in the United States has remained stable (US Department of Agriculture, 2021), the last decade has seen a decrease in the use of primates in the E.U. (European Commission, 2017). Trends in the use of primates in research in Asia are uncertain since most Asian countries where such research is conducted do not have requirements to report numbers of animals used in scientific experiments. Nevertheless, there appears to be a rise in the use of primates in invasive research in China, the leading supplier of primates on the international market (Zhang et al., 2014).

Worldwide, primates are primarily used in biomedical research and the neurosciences (Phillips et al., 2014; Cauvin et al., 2015; Friedman et al., 2017). Biomedical research includes studies involving toxicology, endocrinology, reproductive biology, neurology, genetics, and cancer, as well as the production of vaccines and medications for human diseases such as acquired immunodeficiency syndrome (AIDS) and hepatitis (Phillips et al., 2014; Friedman et al., 2017; Bhogal et al., 2005). Neuroscience research with primates aims at understanding the mechanisms of brain function and processes that underlie a variety of human brain disorders (Buffalo et al., 2019).

As we mentioned above, the use of great apes—a subgroup of primates—in invasive research has virtually been phased out across the world. It is worth noting, however, that this has resulted not from regulations that prohibit the use of primates in invasive research, but from regulations that only limit such use. For example, in the E.U., Directive 2010/63/EU, one of the most stringent legislative frameworks

for the use of animals in research in the world, permits invasive research with great apes in cases in which there is "a life-threatening, debilitating condition endangering human beings […] and no other species or alternative method would suffice in order to achieve the aims of the procedure" (p. 35). Similarly, in both the U.S. and Japan, the use of great apes for invasive research has come to an end without a law effectively banning it (Kaiser, 2015; Matsuzawa, 2016).

In the case of primates other than great apes, restrictions are also common, but less strict. For example, the E.U. Directive mentioned above imposes several stringent conditions on using primates in research. In particular, it allows only procedures "undertaken with a view to the avoidance, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical conditions in human beings" that "cannot be achieved by the use of species other than non-human primates" (Directive 2010/63/EU, p. 40). Moreover, it restricts the acquisition of primates from the wild along with the overall severity of the procedures carried out on such primates, sets forth specific requirements for the care and accommodation of primates in research facilities, and proclaims a commitment to undertaking periodic reviews to examine the possible replacement of primates in research. In the U.S., the Animal Welfare Act specifies husbandry and housing conditions adequate for primates other than great apes, but exemptions from these standards are permitted when required by a research proposal approved by the appointed committee at a research facility. A similar lack of restrictions is seen in the U.S. Office of Laboratory Animal Welfare Guide on Vertebrate Animals, which briefly notes that the use of primates in research "should be thoroughly justified" if they are to be used in lieu of "less highly evolved or simpler animal models" (NIH, 2021). In Japan, regulations on primate research appear to be even less restrictive, and in China, some regulations specific to primates require giving special justification for using them in research and providing "retirement" care for them (Ogden et al., 2016).

Yet, despite these more permissible regulations regarding the use of primates other than great apes in research, support for stricter regulations seems to be on the rise. Studies of public attitudes towards animal research suggest that people tend to disagree more with the use of primates than with the use of other animal species in research (Bradley et al., 2020). What's more, in the U.S., in 2015, Harvard University closed its national primate research center—one of eight in the country—for "strategic" reasons, and, in 2019, the U.S. House of Representatives approved a spending bill that would require the National Institutes of Health (NIH) "to accelerate efforts to reduce and replace the use of nonhuman primates with alternative research models." (Reardon, 2019). Meanwhile, emerging local regulations in some European countries appear to be strengthening restrictions on the use of primates in research even more—regulations that would strengthen the already stringent legislative framework of the E.U. Directive mentioned above (Zimmer, 2018).

Is this trend towards stricter restrictions justified? Given the global acknowledgment that great ape research subjects should enjoy protections almost equivalent to those enjoyed by human research subjects, should similar protections be extended to all primates? To address these questions, let us first consider the moral status of primates.

Primates' Moral Status

A being has moral status when its welfare deserves moral consideration in its own right—independently of how it might affect the welfare or interests of *human* beings. Here, we will assume that the notion of welfare relevant for moral status is *experiential* welfare, such that only animals who can subjectively experience whether things go well or badly for them deserve moral consideration in their own right. In the context of animal research ethics, this implies that sentient animals have moral status and therefore their interests ought to be taken into account when trying to morally justify research that causes them harm.

Moral status can be understood as a threshold requirement for moral considerability; yet in the academic literature as well as in the phrasing of research regulations, it is often claimed that some animals deserve greater moral consideration, or have higher moral status, than others (Jaworska & Tannenbaum, 2021). For example, animal research regulations often require using 'less sentient' animal species whenever possible (Tannenbaum & Bennett, 2015). Call this view the 'graded view' of moral status. In accordance with the graded view, many authors claim—often implicitly—that great apes possess a higher degree of moral status that justifies granting them special protections when compared with other primates (e.g., Prince et al., 1989; Reynolds, 1995; Fenton, 2012). The near global consensus that invasive research with great apes, but not that with other animals or even other primates, should be phased out is consistent with this view.

For the purposes of this chapter, we will assume that some graded view of animal moral status is plausible. On this view, human interests can be served by means of experiments that affect the interests of animals with lower moral status—at least under certain conditions and with adequate justification. Furthermore, we will not be challenging the view that great apes have a high level of moral status that might even be comparable to that of human beings—a view that is often supported by claims about the sophisticated and human-like cognitive, experiential, and social capacities of great apes (Aguilera et al., 2021).[2] On this view, research standards applied to persons, such as respecting their autonomous choices and protecting those incapable to provide informed consent, should be extended to great apes—at least to some significant degree.

Defenders of the view that great apes have a moral status that is comparable to that of human beings or persons normally remain agnostic as to whether the same reasoning applies to primates other than great apes. This is due to a lack of sufficient evidence to support cross-species comparisons and to the fact that the relevant capacities are not 'all-or-nothing', but, rather, vary in degrees. However, it is important to note that great apes are known to outperform other primates in various important cognitive tasks: for example, in terms of self-awareness (e.g., mirror self-

[2] A related, but more elaborate view is that great apes possess these capacities to an extent that qualifies them as persons, or what some have called 'near persons', or 'borderline persons' (Varner, 2012; DeGrazia, 2010).

recognition tests; see Anderson & Gallup, 2015; de Waal, 2019), self-control (a supposed key condition for autonomous action, along with intention and understanding, see Beauchamp & Wobber, 2014; Miller et al., 2019), mind-reading (Krupenye & Call, 2019) and the capacity to exert control over memory retrievals (Bobrowicz et al., 2020).[3]

In our view, the preceding suggests that on a graded view of moral status, it would be reasonable to place primates other than great apes somewhere between nonprimates and great apes, such that they would be less suited than great apes to fit into the category of personhood, and would be harmed and wronged to a lesser extent than great apes in similar invasive procedures. This view, however, is not inconsistent with the view that deontological considerations should play a role when ethically evaluating in the case of *all* primates—whether great ape or other—at least to some significant extent. After all, it is beyond doubt that *all* primates have a high level of moral status. This suggests that researchers face a strong burden of moral justification if they wish to carry out invasive research on primates.

Justifying Primate Research

Critics of Russel and Burge's "Three-Rs" framework have claimed that this framework overlooks important deontological considerations in animal research ethics and that it does not ensure that the value of scientific research is sufficient to justify harms caused in animal research (Ferdowsian et al., 2020; Strech & Dirnagl, 2019; Würbel, 2017). In part echoing these concerns, Beauchamp and DeGrazia (2019) have proposed a more comprehensive ethical framework which sets out six principles grouped in two "core values": 'Social benefit' and 'Animal welfare' (Fig. 32.1). So long as a research study meets these six principles, the authors maintain, it is ethically and scientifically permissible. In this section, we offer some insights into

Core values	Social Benefit	Animal Welfare
Principles	No Alternative Method	No Unnecessary Harm
	Expected Net Benefit	Basic Needs
	Sufficient Value to Justify Harm	Upper Limits to Harm

Fig. 32.1 Framework for animal research ethics. (Beauchamp & DeGrazia, 2019)

[3] Arguably, some chimpanzees have even met the diagnostic criteria for post-traumatic disorder (Ferdowsian et al., 2011).

the question of whether current invasive research with primates might satisfy these requirements. Because such assessments must ultimately be addressed on a case-by-case basis, the discussion will center around two questions based on the core values of Beauchamp and DeGrazia's framework: Could the social benefits that result from invasive research with primates scientifically justify the harms that such research causes primates? And, could such research be done under acceptable standards of primate welfare? As may be clear by now, we believe that the answer to both of these questions is 'Yes'—albeit with some substantial qualifications.

Social Benefits of Research

It is widely agreed upon that in order to scientifically justify the use of primates in invasive research, this research must be necessary for attaining highly valuable social benefits. According to scientists, examples of such benefits abound: given the high degree of similarity between primates and humans, primates have been used to further our understanding of the human brain and the development of therapies to treat mental, neurological and neurodevelopmental disorders, including Alzheimer's, Parkinson's, schizophrenia, depression, autism, and stroke (Friedman et al., 2017; Sughrue et al., 2009; Feng et al., 2020). Primates have also been used in the development of interventions against a number of viral infections, including Zika, Ebola, and Marburg, (Gardner & Luciw, 2008; Nakayama & Saijo, 2013; Friedman et al., 2017) and in the development of vaccines against diseases such as yellow fever, polio, Covid-19, among others (Barnhill et al., 2016; Chang et al., 2021). Other noteworthy examples of potential valuable research with primates include the prevention of negative pregnancy outcomes (including, e.g., miscarriage, stillbirth, and premature birth) (Friedman et al., 2017) and the potential to create human-monkey chimeric embryos that may have applications for regenerative medicine (including, e.g., the generation of organs and tissues for transplantation). (Tan et al., 2021).

In light of this record of scientific achievements, scientists have come to consider primates excellent models for particular biological and medical phenomena (Sughrue et al., 2009; Phillips et al., 2014; Mitchell et al., 2021; Feng et al., 2020; Friedman et al., 2017; Barnhill et al., 2016). This consideration is supported by a variety of recent reports by major governmental and nongovernmental organizations alike. For example, a 2016 U.S. NIH report concluded that the use of nonhuman primates is still critical in some research areas (Abee et al., 2016). This verdict was seconded by a 2017 Johns Hopkins University-funded panel on the necessity of the use of primate models in research (Beauchamp et al., 2017) aiming to replicate the 2011 Institute of Medicine's process applied to chimpanzees (which, in contrast, concluded that most current use of such animals for biomedical research was unnecessary). Similarly, a 2017 European Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) report at the request of the European Union arrived at the conclusion that primate research is essential for scientific progress in a number of important areas (SCHEER, 2017).

Nevertheless, there are doubts regarding the alleged social benefits of primate research. At least some of these doubts originate in skepticism regarding the validity of using primates as a model for human biology and disease. As critics note, despite their similarity with humans, experiments with primates often fail to predict drug or disease response in humans (see, e.g., Shanks & Greek, 2008; Thew, 2012). This worry is strengthened if one considers claims that there is a "reproducibility crisis" in science: often the outcomes of studies, including animal experiments, cannot be replicated by carefully designed studies using the same methods (Begley & Ioannidis, 2015).

But these worries of validity and reproducibility may not be as strong as they purport to be. First, the "reproducibility crisis" is a challenge that is currently faced not only in research with animals, but also in science more generally, with some critics arguing that a "science is in crisis" narrative may be an overstatement (see Fanelli, 2018). Second, at least according to the 2017 Johns Hopkins University-funded panel mentioned above, among research projects with primates, there is only a "small proportion (approximately 9%) of research programmes from which no clear scientific, medical or social benefit had emerged" (Beauchamp et al., 2017, p. 1). Thus, while this need not suggest that primate models are always appropriate for the study of human diseases, it does suggest that research with primates can, at least sometimes, yield good enough results to be scientifically justified.

Doubts regarding the alleged social benefits of primate research are also based on concerns that it is difficult to weigh such benefits in relation to the harms that such research causes to primates. In particular, some critics worry that balancing the harms and benefits of animal experiments involves comparing uncertain and often incommensurable data, and that the result is always arbitrary (Arnason, 2020; Arnason & Clausen, 2016). This concern, however, can be disputed. Even though cost-benefit analyses are complex—especially in the context of measuring harms and benefits to sentient subjects—and even though there is much room for improvement (Grimm et al., 2019), these concerns need not entail that all such analyses will be arbitrary. Indeed, arbitrariness and incommensurability concerns can also be raised with respect to biomedical research more generally (including human research), but opposing all such research on grounds that cost-benefit analyses are always arbitrary would be misguided. One might think that with hard work and careful analyses, reasonable judgments regarding the weight of benefits and harms may nonetheless be developed (see, e.g., Grimm et al., 2019). In any case, as the discussion from Sect. "Primates' Moral Status" suggests, the high moral status of primates calls for carrying out maximally careful harm-benefit analyses to justify invasive research with them.[4]

[4] Most Institutional Animal Care and Use Committees (IACUCs) may not actually be prepared for doing such maximally careful analyses (Carbone, 2020, p. 51). The allocation of more resources and the creation of specialized IACUCs to evaluate protocols that involve primates, might be needed to accomplish this goal.

Another worry raised by critics of invasive research with primates is that even if primates are good models for research, and even defensible cost-benefit analyses for invasive research with primates can be devised, alternative models exist or could be developed.[5] Indeed, as some argue, given primates' moral status, using and seeking alternative methods seems to be an ethical imperative that encroaches upon the scientific permissibility of such research. This thought is reflected in Fig. 32.1 above, specifically in the Principle of No Alternative Methods: that the "use of animal subjects must be the sole ethically acceptable way to address a research problem whose solution offers the prospect of a social benefit" (Beauchamp & DeGrazia, 2019, 6). According to this principle, researchers have an obligation to not merely consider alternative methods, but to actively and thoroughly search for possible alternative methods and forgo the use of animals when a scientifically viable alternative becomes available. It is noteworthy that in line with the trend toward extending stricter protections to primates used in research, the E.U. Directive mentioned above takes some concrete steps in that direction: it expresses a commitment to conducting periodic reviews of research programs in an effort to reach the total replacement of animals, with special emphasis on replacing primates.

As we have been suggesting, given that primates are sometimes suitable models for invasive research, the scientific case for phasing out their use in invasive research is not conclusive. Nevertheless, as we argued in Sects. "Background" and "Primates' Moral Status", the high moral status of primates places a heavy burden on the scientific justification of such research. Justifying such research would seem to call, at the very least, for carrying out maximally careful harm-benefit analyses and for actively seeking alternative research models.

Primate Welfare

Invasive research with primates often requires causing them a variety of physical and psychological harms—harms that may not be justified given that primates are highly sentient creatures. Thus, even if a sound scientific rationale for using primates in invasive research could be provided, more is required for *ethically* justifying such research.

The kinds of harms that primates are subject to in invasive research can range from minimal to severe. How a specific harm is classified will vary (Smith et al., 2018), but generally speaking severe harms are those that arise from invasive studies

[5] Note that moving directly from studies on lower animals (e.g., rodents) to studies on humans—instead of experimenting on primates as an intermediate step—has several drawbacks, including imposing a much greater risk on human research participants. Note, also, that studies may take longer to conduct or could be less controllable than studies on primates. See Phillips et al., 2014; Sughrue et al., 2009; Barnhill et al., 2016.

that involve prolonged suffering, suffering that cannot be treated or remedied, or even premature death.[6] More concrete examples of severe harms include major and irreversible neurological damage due to the induction of stroke, paralysis due to the severing of nerves, challenge studies for highly lethal viruses, and studies that induce sepsis and septic shock (especially when analgesic and anesthetic drugs are avoided due to their potential to confound experimental outcomes) (Arnason & Clausen, 2016; Lilley et al., 2015). There are also a variety of less severe harms associated with other aspects of research: for example, harms resulting from transport, social isolation, food and water deprivation, withdrawal from drugs, repeated surgeries, among others (Conlee & Rowan, 2012; Honess et al., 2004; Kagira et al., 2007). And even if some of these harms are categorized as moderate or mild, when repeated within or between protocols, they can cause cumulative harm that may nevertheless be severe.

In our view, given the moral status of primates, experiments involving such severe harms can hardly ever be ethically justified—even when confronted with the prospect of high social value. This point finds further support in one of Beauchamp and DeGrazia's principles: The Principle of Upper Limits to Harm (see Fig. 32.1), which holds that "animal subjects must not be caused to endure severe suffering for a lengthy period of time" (Beauchamp & DeGrazia, 2019, 12). This principle thus moves beyond mere refinement methods to avoid pain and distress and suggests that a limit to the level of permissible harm should be established (see also Arnason & Clausen, 2016; Walker, 2016).[7] Thus, if this is true for animals in general—that is, animals with varying degrees of moral status—then it is especially true for primates, given their high moral status.

Experiments involving mild and even moderate harms may constitute a different story, however. At least under certain conditions, such experiments may well be ethically justified. One such condition is if primates' basic needs are met—not only in research settings, but also beyond. This idea is at the core of Beauchamp and DeGrazia's Basic Needs Principle (see Fig. 32.1). But it is important to be specific about what these needs might be in the case of primates. Because primates have a high degree of complexity in their cognitive, sensory, and social abilities, meeting their basic needs would seem to involve putting primates in a physical environment that allows them to play, socialize, and carry out other activities that might support

[6] It is controversial whether the harm of premature death should be assessed as 'severe.' In the case of great apes, however, studies that resulted in the death or euthanasia of them were forbidden even before research with great apes was phased out. Given the high degree of moral status that primates have, and in particular their capacity for self-consciousness, we believe that a similar position should be taken in the case of primates used in invasive research. But a detailed defense of this point is a project for another time. See McAndrew and Helms (2016).

[7] As we explain below, Beauchamp and DeGrazia admit exceptions to this principle. In our view, however, appropriately applying this principle to the case of invasive research with primates would leave outside the scope of ethically permissible invasive research with primates' studies that involve severe and long-lasting harms.

normal development. This point is worth stressing, as it may require special attention on the ground. Reports exist that at least on two large facilities, "primates spent an average of 53 percent of their lives housed alone. In many instances, a metal shape hung for a month on the bars of a metal cage was deemed to constitute adequate 'enrichment'" (Conlee & Rowan, 2012, p. 32). It would be difficult to argue that such experiments met primates' basic needs. Thus, developing appropriate and evidence based criteria that ensure that primates' basic needs are actually met is an ethical imperative.

Now, implementing efforts to meet primates' basic needs may come at a cost. Indeed, increasing welfare and other requirements (e.g., the creation of specialized Institutional Animal Care and Use Committees or IACUCs) may turn out to be quite expensive and may contribute to a phasing out of research that uses primates, not for ethical reasons but due to prohibitively high costs. This worry is not unfounded; it was mainly for financial reasons that the NIH forwent controversial experiments with rhesus monkeys in 2015 (Grimm, 2015). Nevertheless, it should be noted that a concern that raising the costs of primate research will lead to the phasing out of such research is not a reason to forgo fundamental ethical principles such as the Basic Needs Principle. Rather, it is a reason for allocating more funding to such research so that the requirements of welfare and social value discussed above can actually be met.

One final point. Beauchamp and DeGrazia believe that there are ethically justified exceptions to the principles they propose. For example, in their view not meeting basic needs of animals or causing them some harm can be permitted "when doing so is necessary for and morally justified by the social and scientific goals of research involving animals" (Beauchamp & DeGrazia, 2019, p. 20).[8] But, as we have been arguing, primates constitute a special case among animal research subjects. Even if their moral status is not high enough to be on a par with that of great apes or humans, it is higher than other laboratory animals. This suggests that it may be difficult to justify exceptions to the Upper Limits to Harm and the Basic Needs principles when it comes to research involving primates. Specifying the conditions under which such exceptions would be justified is a project that is well beyond the scope of this paper, but it is worth noting that an intuitive case can be made for thinking that such exceptions may be ethically justified if and only if: (a) a failure to meet these principles is temporary, and (b) primate subjects are compensated for such violations. Examples of such compensation may range from allocating more play or social time on days in which violations occur, to sending primates to well-funded sanctuaries when they are no longer needed in research.

[8] It is worth noting that they do acknowledge that in the case of the principle of Upper Limits to Harm, exceptions correspond to "rare cases of extraordinary urgent social need" (Beauchamp & DeGrazia, 2019, p. 20).

Concluding Remarks

While we are sympathetic to the current trend towards imposing greater restrictions on the use of primates in invasive research, we have argued that there are reasons to resist phasing out the use of all primates in invasive research. This is in part because primates other than great apes seem to have lower moral status than great apes and are thus less suited to the category of personhood than great apes. But it is aso because invasive research with primates is, in many cases, much too valuable to be renounced. Nevertheless, as we have also argued, if scientifically and ethically justifiable invasive research with primates is to continue, tougher restrictions—with far less room for exceptions than are currently afforded—must be adopted. More specifically, maximally careful cost-benefit analyses of such research should be carried out, alternative research models should be actively sought, limitations on experiments causing severe harm should be enacted, and specific criteria for meeting primates' basic needs on the ground should be developed.

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Chapter 33
Growing Human Organs Inside Animals

Julian Koplin and Neera Bhatia

Abstract This chapter considers the prospect of generating human organs within chimeric animals comprised of a mix of human and animal cells. Although seemingly farfetched – the term 'chimera' even means, in some modern usage, a "mere wild fancy" or "unfounded conception" (Oxford English Dictionary (n.d.) 'chimera | chimaera, n.', OED Online. Oxford University Press. Available at: https://www.oed.com/view/Entry/31708) – recent research into interspecies blastocyst complementation is paving the way toward growing human organs inside of human-animal chimeras, potentially within the not-too-distant future Zheng et al. (Development 148(12), 2021). These human-animal chimeras promise important advances within regenerative medicine and medical research. They also raise some profound bioethical issues, which we survey below.

Keywords Human organs · Animals · Human-animal chimeras · Chimeric transplantation · Ethics regulation

Chimeras: From Mythology to Science

The term 'chimera' has its origins in ancient Greek mythology. In his encyclopaedia of imaginary beings, Jorge Luis Borges explains that:

> The first mention we have of the Chimera is in Book VI of the *Iliad.* There Homer writes that it came of divine stock and was a lion in its foreparts, a goat in the middle, and a serpent in its hindparts, and that from its mouth it vomited flames… A lion's head, goat's belly, and serpent's tail is the most obvious image conveyed by Homer's words, but Hesiod's *Theogony* describes the Chimera as having three heads, and this is the way it is depicted in the famous

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> Arezzo bronze that dates from the fifth century. Springing from the middle of the animal's back is the head of a goat, while at one end it has a snake's head and at the other a lion's. (Borges, 2002, p. 41).

Modern scientific usage of the term 'chimera' shares some of the characteristics of the term in Greek mythology. Here, too, 'chimeras' refer to a kind of patchwork creature – specifically, an individual composed of cells with different embryonic origins (Lensch et al., 2007).

Chimeras sometimes occur naturally. For example, human-human chimeras sometimes occur when early embryos fuse together in utero, resulting in a child compromised of cells and tissues from two or more different cell lines. Interestingly, human chimerism can result in false negatives in paternity testing and forensic DNA analysis, since the DNA obtained via a mouth swab or blood sample might come from a different cell line than the person's gametes. This possibility has become a key plot point in a range of medical and legal TV dramas (Wolinsky, 2007).

Scientists have also developed a range of techniques to create interspecies chimeras, which are comprised of a mix of cells from entirely different species. Interspecies chimeras can be created by intentionally fusing early embryos of multiple species, or by injecting stem cells from one species into the embryo of another. The former technique was famously used in 1984 to create sheep-goat chimeras – which journalists at the time promptly dubbed "geep" (Time, 1984) – that were comprised of a mixture of sheep and goat cells. Visually, the sheep-goat chimeras resembled a kind of hodgepodge of sheep and goats, with distinct patches of sheep and goat hair (Fehilly et al., 1984). Other interspecies chimeras include quail-duck chimeras ("qucks"), duck-quail chimeras ("duails"), frog-salamander chimeras (which could perhaps be dubbed "fralamanders") and quail-chick chimeras, all of which share some characteristics with both of their constituent species (Trainor, 2003).

One particular technique for creating interspecies chimeras, called interspecies blastocyst complementation, has been the focus of much recent research and debate. Interspecies blastocyst complementation can be used to generate organs belonging to one species inside the body of another. This technique involves: taking a blastocyst (an early stage of embryo) from a host animal species, then using gene editing techniques to disable the development of a particular organ in the host embryo. The blastocyst is then injected with pluripotent stem cells belonging to a different species. If the embryo is allowed to develop, the resulting animal would contain a mix of cells from both the host and the donor species. Most parts of the body would be comprised of a mix of cells from (mostly) the host embryo and (partly) the donor embryo, with one exception: the specifically targeted organ (which the host embryo has been modified to not be able to develop) would be comprised wholly or mostly of the donor animal cells (Rashid et al., 2014; De Los Angeles et al., 2018b).

A landmark 2010 study used interspecies blastocyst complementation to create rat-mouse chimeras whose bodies were comprised primarily of mouse cells, with the exception of a specifically targeted organ. The study used the blastocysts of mice that were unable to generate a pancreas. After injecting the mouse blastocysts with

rat pluripotent stem cells, the rat cells successfully generated a normally functioning rat pancreas inside the rat-mouse chimera's body (Kobayashi et al., 2010). In 2017, this technique was reversed to create mouse-rat chimeras with functional mouse pancreata. These mouse pancreata were then successfully transplanted into non-chimeric mice, where they were functioned normally even in the absence of immunosuppression (Yamaguchi et al., 2017).

These mouse-rat and rat-mouse chimera studies provide proof of concept for interspecies blastocyst complementation, and raise the exciting possibility that it could one day be used to generate functional transplantable human organs inside of human-animal chimera hosts. To generate organs of an appropriate seize, the hosts would need to be significantly larger than mice or rates; candidate animals include pigs and sheep (Rashid et al., 2014). Not only would this technique create a novel means of overcoming the current shortage of transplantable organs, it could theoretically be used to create organs that are immunologically matched to the recipient, avoiding the need immunosuppressive medication (which can be costly and carry their own health risks.) Unfortunately, it has proven more difficult to generate human organs inside of chimeric animals than mouse organs inside of mouse-rat chimeras (and vice versa.)

In 2017, researchers from the Salk Institute for Biological Sciences attempted, and to some extent succeeded, in creating chimeric human-pig fetuses.[1] The study involved injecting early pig embryos with human induced pluripotent stem cells, then implanting the embryo into a sow and allowing it to develop for 28 days. The results were a qualified success; when the pregnancies were terminated and the fetuses examined, human cells could be found throughout multiple tissues of some of the chimeric fetuses. The contribution of humans cells, however, was very low (Wu et al., 2017). As commentators pointed out at the time (e.g., Freedman, 2018), many technical hurdles remain to be overcome before it is possible to generate human organs inside of chimeric animals.

A subsequent study created human-monkey chimeric embryos by injecting human stem cells into monkey embryos, then allowing them to develop *in vitro* up to 20 days' development (Tan et al., 2021). The researchers were not aiming to develop a technique for generating human organs inside of chimeric monkey hosts. Instead, they hoped this study could improve understanding of how human cells contribute to chimeric embryos, and ultimately improve techniques for creating chimeras between humans and more evolutionarily-distant species, such as pigs. Nonetheless, there is at least some broader interest in using human-monkey chimeras to generate human organs and model human diseases (Shaw et al., 2014; De Los Angeles et al., 2018a).

While it is important not to overstate the current state of the science, the prospect of generating human organs inside of chimeric animals no longer seems remote. It might soon be possible to *(inter alia)* create human-pig chimeras that serve as a

[1] The decision to use pigs was a deliberate one; pigs resemble humans relatively closely in terms of anatomy, physiology, organ size, genome, and cell cycle characteristics, which renders them a good candidate for generating human organs (Wu et al., 2016).

source of transplantable kidneys, to test drug toxicity on mice with human livers, or to model psychiatric diseases in human-monkey chimeras with humanised brains. Such breakthroughs could make an important contribution to human health and wellbeing Some of the most exciting potential applications are in the realm of transplant medicine.

Human Organ Donation and Chimeric Transplantation

Donated organs or tissues are transplanted into the body of living persons to replace a failing or failed organ. The aim is to save the patient's life and/or improve its quality. Nonetheless, in many countries the gap between the demand for and availability of human tissues and organs for transplantation continues to widen, for reasons that include advancements and improvements in the availability of post-transplant anti-rejection drugs and a rise in organ failure due to an ageing population (Wilkinson, 2011).

In Australia (where the authors of this paper are based), there have been ongoing academic and political discussion about whether shifting to an 'opt-out' system of donation may see an increase in donation rates (Isdale & Savulescu, 2015; Bhatia & Tibballs, 2017). This type of system of donation 'presumes' that every person has consented to donate their organs after death unless they have declared their objection, while also rendering next-of-kin unable to veto the donation. While there has been increasing social activism towards an 'opt out' system of organ procurement, there has, at least in Australia, been little political appetite. While this remains the case the introduction of an 'opt out' system is unlikely. In any case, an opt-out system is unlikely to be a panacea. The rising demand for transplantable organs may mean that even an ideal system of cadaveric donation, in which all possible organs are utilised, may be unable to meet current and future demand (Levitt, 2015). Chimeric animals may provide an important alternative.

For some, the use of organs from chimeric animals might seem like a mere extension of existing transplant practices, such as the use of heart valves from (non-chimeric) pigs. For others, creating organs inside of part-human animals might seem unnatural, unsettling, or morally problematic. We can see three broad views on how chimeric transplantation might fit into existing systems of organ transplantation:

1. A rejection of chimeric transplantation and a defence of the current system of human organ donation. This might include a greater push for human organ donation awareness and registration, and perhaps other changes to the current system, to help meet the demand.
2. An acceptance of chimeric transplantation, but only as a "last resort" measure in situations where transplantable organs would otherwise be unavailable – with the primary goal remaining on increasing human organ donation rates.

3. A greater push towards using chimeric transplantation wherever possible. As mentioned above, interspecies blastocyst complementation could theoretically be used to create organs that are a perfect immunological match for the patient in question, thereby avoiding the need for immunosuppressive medication. This, in turn, could bring about both health benefits for recipients and potentially create substantial financial savings for patients, insurers, and health systems (Loike & Kadish, 2018), providing reasons to prefer chimeric transplantation over human organ donation. (It may, however, be necessary to maintain existing transplant practices for those who have ethical, religious, or other objections to chimeric transplantation.)

While human-animal chimeras are in some respects an ideal source of transplantable organs, their use raises a range of ethical issues, including some crucial questions about the moral status of these part-human beings. Chimeric transplantation also raises legal questions, especially as this practice would sit at the intersection of human and animal rights. These questions will also need to be addressed if chimeric transplantation is to become a reality. Our focus in this chapter, however, is on the ethics.

Ethical Concerns

The creation of part-human chimeras raises a broad set of ethical issues, not all of which are unique to chimera research. Like other forms of human stem cell research, there are important issues related to the consent of the human tissue donors and, in cases where human embryonic stem cells are used, embryo research more generally (Lo & Parham, 2009). Similarly, because human-animal chimera research necessarily uses animal research subjects, it also raises general issues of animal research ethics (Hyun, 2016). We will leave these issues to one side.

We also leave to one side objections based on the 'unnaturalness' of human-animal chimeras, and worries that their creation involves 'playing God' in some pejorative sense. These concerns have been widely discussed (and usually rejected) in the ethics literature on chimeras (see e.g. Robert & Baylis, 2003; Karpowicz et al., 2005; Koplin & Savulescu, 2019; Streiffer, 2019). While appeals to 'unnaturalness' and 'playing God' do have some defenders,[2] they are deeply controversial in bioethics. One standard response to such arguments holds that objections to 'unnaturalness' and 'playing God' also seem to rule out many once-novel interventions that we now accept and even take for granted, such as the use of vaccines and antibiotics. Concerns about 'unnaturalness' and 'playing God' are also not unique to chimeras; they are also relevant to (and have been discussed extensively in

[2] For a careful analysis of such arguments and a description of where they might have some force, see: (Chadwick, 1989; Sheehan, 2009).

debates regarding) synthetic biology, genetic modification, human enhancement, and elsewhere. We therefore won't discuss them further here.

What we are interested in here are those ethical issues that are unique to human-animal chimeras. The first set of concerns is linked to the way that human-animal chimera research blurs the boundaries between human and nonhuman animals; the second, to what this research might mean for chimeric animals' moral status.

Crossing Species Boundaries

Chimera research has raised general concerns about the commingling of human and animal characteristics. One recent example comes from the US, where the recent human-monkey chimera embryo study described above prompted Republican lawmakers to block research involving the (putatively unethical) 'blending' of human and animal material (Lovelace, 2021). The same study also attracted broader criticism for crossing the boundaries between humans and animals. Writing about the controversy in *The New Atlantis,* Brendan Foht (2021, pp. 24–25) argued as follows:

> [C]himera research aims to blur the boundary not only between animal and human, but also between the body and the person. It disassembles and admixes the living human body, to treat it as an object for exploitation, rather than the physical presence of the person, the seat of the soul.

While human-animal chimera research is new, this unease with crossing species boundaries is not. It is reflected, vividly, in H.G. Wells' *The Island of Dr Moreau* (Wells, 1896), as well as the book's various Hollywood adaptations (Jörg, 2003). The book's plot centres on a mad scientist who has, using the technology of the time, created various "Beast People" – hybridised beings with both human and animal characteristics, including wolf-men, ox-men, and an ape-man who speaks coherent English. In large part a horror story, *The Island of Dr Moreau* continues to be cited in contemporary discussions of human-animal chimera ethics (Clayton, 2007).

The mingling of human and animal characteristics seems to be a common source of unease. But does this unease have any moral import? One of the earliest published bioethics articles on human-animal chimeras tackled this question in detail. After considering – and rejecting – concerns that chimera creation is 'unnatural,' 'repugnant,' or involves 'playing God' in some morally pejorative sense, Jason Scott Robert and Françoise Baylis suggest that much aversion to part-human chimera research is grounded in discomfort with how such research blurs two categories on which current moral thinking relies – i.e., the categories of human and animal. They point out that society currently draws a clear moral demarcation between humans and animals, with the former afforded full moral standing, and the latter very little. There are clear, legally enshrined, widely endorsed moral prohibitions on how we may treat human persons; there are far fewer prohibitions on how we may treat wild animals, livestock, or research animals. Human-animal chimeras

undermine this distinction. Not only do they create a puzzle about our moral obligations to the chimeras themselves (since they straddle the categories of animal and human), their creation will, Robert and Baylis argue, throw our existing moral categories into confusion. It is difficult to maintain a sharp moral line between "humans" and "animals" when beings are created that fit neither category. The question, then, is whether we ought to try to preserve our current social and moral categories by prohibiting the creation of part-human beings (Robert & Baylis, 2003).

Would the creation of human-animal chimeras lead to "inexorable moral confusion" regarding our relationships with nonhuman animals, as Robert and Baylis (2003, p. 9) argue? Not necessarily. One way to shore up the (supposed) moral significance of humanness is to argue that only beings that are *fully* human have full moral status, leaving human-animal chimeras in the same category as nonhuman animals. Some philosophers have taken this approach. For example, Insoo Hyun has argued that humans' moral status is grounded in highly sophisticated cognitive abilities that, Hyun holds, are fleetingly unlikely to be realised in anything other than a fully human brain grown inside of a fully human body (Hyun, 2013, 2016). For those who hold such a view, human-animal chimeras are not, in fact, morally confusing; for better or worse, the moral division between humans and animals holds firm.

Others have argued that it might be possible to adapt our existing legal categories to part-human beings simply by applying these categories somewhat flexibly. We might, for example, ask whether a given human-animal chimera is "substantially human." If it is, we should treat it as human; if not, we may treat it as an animal (Knoppers & Greely, 2019). This kind of flexibility provides another route around the potential problem of moral confusion.

But there is also a deeper question that needs to be asked about Robert and Baylis's argument: would the introduction of 'moral confusion' actually be a bad thing? If current moral thinking on human and nonhuman animals cannot give a satisfactory account of how we ought to treat human-animal chimeras, this might indicate that there is something defective about the ostensible moral boundary that divides human and nonhuman animals. Accordingly, some legal scholars hold that we should welcome the opportunity that chimera creation provides to rethink the moral relevance of species membership (Pietrzykowski, 2018). Some philosophers likewise argue that the correct response to moral confusion is not to attempt to shore up our existing (potentially mistaken) moral categories, but to work through the underlying philosophical questions about what moral status is grounded in. For example, in a commentary published alongside Robert and Baylis's article, Julian Savulescu (2003, p. 25) argued as follows:

> Racists were confused about the moral status of race. The social costs of acceding to irrational confusion are, at least historically, much greater than the costs of clearing it up and reforming society. People are confused about the moral significance of genetics and biology in general. Our job is to clear this up…, not to perpetuate it or allow it to persist or base social policy on it.

None of this is to deny that human-animal chimera research raises difficult serious moral concerns. Robert and Baylis are surely correct that such research raises difficult questions about how we ought to treat these part-human beings. In our view, however, the correct focus for the discussion is on the moral status of the chimeric animals themselves, not the risk that their creation would engender moral confusion.

Moral Status

We treat human persons according to very different standards to nonhuman animals. To list same of the obvious differences: we expect human parents to attend much more closely to the wellbeing of their children than we expect pet owners to attend to the wellbeing of their pets; many people accept the killing and eating of livestock animals, whereas very few would accept the killing and eating of humans; and when we conduct research on human participants we require that the participants give informed consent and that the study not carry substantial risks, whereas when we conduct research on animals we often accept that such research will involve sacrificing animals' most fundamental interests in order to achieve scientific objectives. Moreover, while we do not kill humans in order to provide organ transplants to others – some radical proposals aside[3] – nonhuman animals have long been considered an ideal source of transplantable organs for humans, as the long history of (mostly unsuccessful) attempts at xenotransplantation attests (Deschamps et al., 2005). Inswws, Sir Peter Medawar – a Nobel laureate and one of the pioneers of tissue and organ transplantation – argued in 1968 that an ideal system of organ transplantation would involve grafts "transplanted from lower animals into man" (Medawar, 1968, p. 373). The barriers to xenotransplantation are usually considered *technical,* not *ethical* – or at least, xenotransplantation is not generally thought to raise serious issues of animal ethics, given that we already farm livestock animals for purposes that are much less important than saving human lives (Koplin, 2020).

In other words, we generally treat nonhuman animals as if their moral status is much lower than that of humans.[4] The kinds of purposes for which there is interest in creating human-animal chimeras bearing human organs likewise assume that these chimeric animals would have negligible moral status; they would likely be used as animal research subjects in biomedical research, or farmed and killed as a source of transplantable organs.

Unlike other animals, human-animal chimeras would be partly human. They would, of course, bear an organ that is nearly wholly comprised of human cells. In

[3] Forced organ harvesting has been explored in speculative and dystopian fiction, such as Kazuo Ishiguro's *Never Let Me Go* (2009) and Ninni Holmqvist's *The Unit* (2008). Some philosophers – including John Harris (1975) and Cécile Fabre (2006) – have seriously considered the ethics of state-mandated organ harvesting from living persons, though proposals to harvest organs from living persons have unsurprisingly gained little political traction.

[4] Whether we are right to do so is another question entirely. See: (DeGrazia, 1996; Singer, 2015).

addition, chimeras created via interspecies blastocyst complementation would also contain some human cells throughout the rest of their tissues and organs – potentially including their brains. This raises a crucial question: would it be ethically acceptable to treat these part-human beings in the same way we treat non-chimeric animals? If the moral status of a chimeric mouse, pig or monkey *did* resemble that of a human, then we would act wrongly if we treat it like a regular, non-chimeric animal. To harm or kill such a being would be morally tantamount to harming or killing a normal human adult.

In order to untangle this question of moral status, we first need to consider on what moral status depends. On one view – the 'traditional' view described in the above discussion of moral confusion – moral status depends on species membership. This view has, however, attracted much philosophical criticism, in part because it is unclear why 'humanness,' a biological category, is supposed to carry moral weight. After all, we do not think of other biological categories to which we belong – such as our genus *(Homo)*, family (*Hominidae)*, class *(Mammalia*), or kingdom (vertebrate) – are morally significant. So why should species membership be different (Degrazia, 2007, p. 314)?

Perhaps the most famous criticism of the moral significance of species membership was offered by Peter Singer, who argued that tying moral status directly to species membership is a form of prejudice akin to other prejudices we rightly reject, such as racism and sexism. Singer has famously described this human prejudice in terms of 'speciesism':

> [T]he racist violates the principle of equality by giving greater weight to the interests of members of his own race, when there is a clash between their interests and the interests of those of another race. Similarly, the speciesist allows the interests of his own species to override the greater interests of members of other species. The pattern is the same in each case. (Singer, 2015, p. 107).[5]

The main competitor to the species membership view of moral status is one that grounds moral status in a being's psychological capacities, such as consciousness, sentience, rationality, autonomy, self-consciousness, the ability to engage in moral reasoning, and/or other sophisticated cognitive capacities. Capacity-based views of moral status often hold that moral status can come in degrees, depending on (say) how sophisticated an animal's cognitive capacities are, whether they meet specific criteria for 'personhood' or full moral status, or the nature and strength of their interests (DeGrazia, 1996, 2008; McMahan, 2002; Shepherd, 2018; Kagan, 2019; Jaworska & Tannenbaum, 2021). If a human-animal chimera were to develop new or enhanced cognitive capacities, then, on a capacity-based view of moral status, they might also attain a higher degree of moral status. It is often worried that this might happen if human cells contribute to animal brains, thereby altering or enhancing their cognition. This is arguably *the* central moral concern raised by human-animal chimera research. It is certainly one of the most widely-discussed in both

[5] For a deeper discussion of the problems of the species membership view (and its implications for human-animal chimeras), see: (Piotrowska, 2014).

media coverage of such research (Hagan-Brown et al., 2017) and the bioethics literature (see e.g. Streiffer, 2007; Cabrera Trujillo & Engel-Glatter, 2015; Shaw et al., 2015; Koplin & Savulescu, 2019; Koplin & Wilkinson, 2019; Kwisda et al., 2020; Greely, 2021).[6] It has also been politically influential. Worries about cognitive capacities are the core reason that the US National Institutes of Health (NIH) placed a funding moratorium (which at the time of writing remains in place) on certain forms of human-animal chimera research in 2015 (National Institutes of Health, 2017).[7]

A closely related set of concerns have been expressed not in terms of moral status *per se*, but in terms of human dignity (Karpowicz et al., 2005). The idea here is that certain kinds of beings are endowed with a dignity that renders them worthy of a special kind of respect. This dignity, in turn, is conferred by certain capacities, such as the capacities for autonomy, moral reasoning, or engaging in sophisticated forms of communication. If a chimeric animal were to exhibit such capacities, then it would deserve a kind of respect that ought to rule out its use as an animal research subject or as a mere source of transplantable organs.

Changes to the animal's cognition could theoretically come about in one of two ways. First, they might be an accidental by-product of generating organs other than the brain inside of chimeric animals. Even if the aim is to create (say) a human-pig chimera with a human pancreas, human cells would also contribute, to a smaller degree, to other tissues and organs – potentially including the brain. The effect this might have on the resulting animal's mental life is uncertain. Second, the aim of the research might be to create what Hank Greely (2021) has dubbed a 'human brain surrogate' – in this case, a human-animal chimera with a humanised brain. Such chimeras could be useful for studying human brain development and human neurological diseases. They might also be useful for regenerative medicine – for example, by using chimeras to create human neurons for transplantation into patients with Parkinson's disease (Savulescu, 2016). For the first category of research, it might be possible to circumvent concerns about altering animal cognition by developing techniques to limit the human stem cells' contributions to the animal's brains (Shaw et al., 2015; Bourret et al., 2016). Such solutions, however, would obviously be inapplicable to the second category of research. There is no easy technical way to circumvent moral status concerns when the aim is to create a chimeric animal with a humanised brain.

Is it plausible to think that human cells could affect animal cognition? While the research on interspecies blastocyst complementation is still at an early stage, other techniques have been used to transplant human cells into the brains of animals such as mice and rats. While a recent review of these transplantation studies found little evidence that these chimeric animals possessed 'human-like' cognition or

[6] In addition to the papers already cited in this paper, moral status issues are discussed extensively in: (Degrazia, 2007; Eberl & Ballard, 2009; Capps, 2017; Devolder et al., 2020).

[7] As Monika Piotrowska (2021) points out, some forms of animal-animal research (for example, those involving stem cells sourced from cognitively sophisticated animals) raise similar concerns, and arguably deserve more attention than they have been given to date.

behaviour, very few of the relevant studies directly measured the behaviour of the transplanted animals (Crane et al., 2019). One exception was a study involving chimeric mice with human glial cells (non-neuronal cells in the brain). Strikingly, the chimeric mice outperformed wild-type mice on a range of tasks that measured learning, memory, and fear conditioning (Han et al., 2013).

There are further suggestive findings from the field of animal-animal chimera research. One early brain chimera study involved transplanting regions of the quail brain into the embryos of domestic chickens. The resulting chimeras resembled domestic chickens physically, but their brains were in some respects quail-like, and the animals displayed quail-like behaviours. For example, they made vocal 'crowing sounds' characteristic of quails rather than chickens (Balaban et al., 1988).

While the science is still in its infancy, it is not farfetched to think that the presence of human cells in chimeric animal brains could affect the animal's cognition. If the capacity-based view of moral status is correct, this could, in turn, affect the animal's rights and our moral obligations to it.

Regulatory Possibilities

If a human-animal chimera develops sufficient moral status, it will become unethical to use it in animal research or as a source of transplantable organs. It will, in other words, become unethical to use them for precisely the purposes for which scientists are interested in creating them. How could these moral status concerns be managed?

Koplin and Savulescu (2019) have outlined an array of options. The most restrictive involve prohibiting interspecies blastocyst complementation outright, or else prohibiting the development of human-animal chimeric embryos beyond an early point of development (such as the widely-adopted 14-day limit on human embryonic development.) These approaches avoid moral status concerns, but at a sharp cost: they would prevent potentially life-saving applications of human-animal chimera research. A somewhat less restrictive option would be to allow the creation of live-born human-animal chimeras, but only if human cells do not make a significant contribution to the animal's brain. While this approach would sidestep moral status issues (beyond those affecting animal research more generally), it would, again, prohibit some potentially beneficial forms of research into human neurological disorders.

Perhaps the ideal approach would be to allow the creation of live-born human-animal chimeras, including those with human-like brains, but in cases where there are reasonable worries about chimeric animals developing enhanced cognitive abilities, prohibit experimentation until after their moral status has been assessed. As we describe further below, this is easier said than done; there is ongoing philosophical disagreement about what capacities are relevant to moral status, and considerable challenges in screening for some of the capacities that might be relevant (such as self-consciousness.) In principle, however, this approach would seem to strike the

best balance between protecting chimeric animals' moral status without unduly restricting important research.

The least restrictive approach is to permit human-animal chimera research according to existing guidelines for animal and stem cell research (and without introducing new restrictions to address moral status concerns.) This is the approach favoured by the International Society for Stem Cell Research (ISSCR). In their newly revised *Guidelines for Stem Cell Research and Clinical Translation,* the ISSCR has recommended that the forms of human-animal chimera research we have been considering (including those aimed at producing live chimeric animals with humanised brains) are adequately addressed by existing animal research ethics principles. The Guidelines do recommend tailoring these principles to the context of chimera research. For example, they recommend monitoring certain categories of chimeric animals for behavioural abnormalities, including in cases where there is "significant potential to create some aspect suggestive of human cognition, self-awareness, behavior or behavioural pathology." Such monitoring is aimed, however, at "ensur[ing] the humane protection of animal subjects" (Hyun et al., 2021, p. 1413). The possibility of altered or enhanced cognition is thereby treated as an issue of animal welfare, not an issue of moral status.

On such an approach, the welfare of chimeric animals would still receive *some* protection under existing oversight of animal research. For example, as the ISSCR guidelines point out (Hyun et al., 2021, p. 1412) research involving animals is widely regulated according to the principles of the Three 3Rs (replace, reduce, refine)– which hold, respectively, that animal models should be replaced where possible, the number of animals used per experiment minimised (or reduced), and that the scientific techniques are refined to minimise animal suffering where possible. While the Three Rs help minimise *unnecessary* suffering in scientific research, they nonetheless permit any degree of suffering that is necessary to answer a valid scientific question. The welfare of research animals is not weighed against the important of the research; the value of scientific progress is taken to trump animal welfare considerations (Tannenbaum & Bennett, 2015). Accordingly, animal research principles such as the Three R's would treat human-animal chimeras as if they have a relatively negligible degree of moral status. This treatment is already controversial when it comes to non-chimeric animals, particularly those that – like nonhuman primates – are known to have complex mental lives (Lauwereyns, 2018). If a human-animal chimera were to develop moral status on a par with a normal human, then standard animal research ethics principles are arguably even less appropriate.

The Work Ahead

We have described concerns that chimeric animals bearing human organs might develop higher moral status than their non-chimeric counterparts, and we have described various approaches to managing this concern. In our view, one particularly promising approach would be to screen some categories of live-born chimeric

animals for morally relevant capacities, and prohibit research with chimeric animals that may have developed moral status on a par with humans. This raises two crucial questions. First: what capacities, specifically, would suggest that a chimeric animals' moral status has been enhanced? Second: how should we go about trying to detect these capacities?

As flagged above, there are many different theories of moral status. Within capacity-based accounts of moral status (which has been our focus in this chapter), there is ongoing disagreement about *which* capacities are morally relevant. In order to assess chimeric animals' moral status, we will first need a defensible account of the grounds of moral status.

Much of the ethics literature on human-animal chimeras circumvents the messy philosophical debate on moral status by focusing on the narrower question of whether chimeric animals will develop 'uniquely' or 'distinctly' human capacities (Koplin, 2019). Here, it is uniquely human capacities that are thought to enhance chimeric animals' moral status. However, there are two potential problems for this view. First, it is not clear that all morally relevant capacities *are* uniquely human (perhaps we share some morally relevant capacities with chimpanzees, cetaceans, elephants, and/or other cognitively sophisticated animals). Second, it is not clear that all uniquely human capacities are relevant to moral status (for example, any quirks unique to – say – human visual processing seem irrelevant to moral status.) If we are to assess chimeric animals' moral status fairly there is no avoiding the messier question of what the grounds of moral status are, whether in humans, animals, or combinations of the two.

The second question is *how* we should test for morally relevant capacities. It might be difficult to know what to make of any changes in chimeric animals' behaviour, especially given that some behavioural changes might be the result of biological dysfunction rather than cognitive enhancement (Hyun, 2016). While we do have some tools for testing animals' cognitive abilities – such as the "mirror test," which is used to screen for (a certain kind of) self-consciousness in some species of animals – research into animal cognition has a long history of finding false negatives when testing for cognitive abilities, based on experiments that weren't appropriately tailored to the animals' bodies, forms of perception, or other characteristics (de Waal, 2016). For example, elephants were at one point believed to fail the mirror test (and therefore to lack self-consciousness), but this is only because the mirrors used in initial experiments were too small and positioned too awkwardly for them to see their reflection. Later and better-designed experiments found that elephants do, in fact, recognise their reflection as belonging to themselves (Plotnik et al., 2006).

A related question is how we should resolve uncertainty regarding chimeric animals' moral status. One possibility is to adopt a kind of 'moral status precautionary principle', which would, in effect, give chimeric animals the benefit of the doubt (Savulescu, 2016; Koplin & Wilkinson, 2019). Much work, however, remains to be done in working out whether a precautionary approach is warranted – precautionary principles are, in general, controversial (Sunstein, 2005) – and in and specifying how, precisely, it ought to be implemented (King, 2019; Munthe, 2019; Sandin, 2019).

While it is relatively straightforward to articulate *why* human-animal chimera research raises moral concerns, it is harder to see how, in practice, they should be addressed. But as we move toward generating human organs inside of chimeric animals, it is important that these moral status issues are addressed. What hangs in the balance is (on the one hand) the pursuit of research that could make a meaningful contribution to human wellbeing and (on the other) the rights and interests of beings whose moral status might rival our own.

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Chapter 34
Animal Cloning: Scientific Endeavour, Perception and Ethical Debate

Andrew J. French and Alan Trounson

Abstract In 1996, a single lamb born (Dolly) from an experiment involving 277 embryo reconstructions that developed into 29 early in vitro embryos that were transferred into 13 surrogate females, demonstrated that adult somatic cells can have nuclear developmental equivalence to the germ cell lineage. Dolly was the first mammal produced by the transfer of an adult somatic cell nucleus into an enucleated egg and improved the understanding of cellular reprogramming. Many thousands of cloned offspring demonstrate that animal cloning is consistent and adaptable to a wide variety of species. Pluripotent stem cell technologies have not superseded cloning in any livestock species. The advent of precise gene editing of donor cells used for animal cloning has renewed interest in the epigenetics, mitochondrial heteroplasmy and gene expression changes involved in nuclear reprogramming and normal development of the conceptus. Public perception of animal cloning, while initially negative, is starting to change, when the technology is seen to benefit the animal. Collectively, this implies that animal cloning will continue to offer solutions to a wide range of global challenges surrounding improved quality of food, animal models and pharmaceuticals for medical care and species conservation under a much wider public dialogue and bioethical systems review.

Keywords Animal cloning · Bioethics · Genetic engineering scientific endeavour · Ethical debate

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Introduction

Public attitudes have and will continue to influence research and commercial/industry acceptance of state-of-the-art technologies as well as shape the underlying regulatory framework for their use. Awareness of terms such as genetic modification, cloning and biotechnology have been popularised in many science fiction movies and TV shows and likely help to motivate greater public scrutiny and government regulation. Who doesn't like to be enticed by plots of genetically engineering humans to become superior, or engineering animals to have better or more human traits, and then "unexpectedly" everything goes awry!

In this chapter, we briefly explore the development of animal cloning, its use across a wide range of species, the ongoing refinements and the wider technological application and public awareness. For example, cloning's recent resurgence with emerging precise gene editing technologies such as ZFNs (zinc finger nucleases), TALENS (TAL effector nuclease) and the clustered regularly interspaced short palindromic repeat and associated nuclease Cas9 (CRISPR/Cas9). Animal cloning, also known as reproductive cloning, nuclear cloning and somatic cell nuclear transfer (SCNT) is arguably one of the most powerful experimental systems to study the reprogramming of cell fate determination and differentiation. Simply put, animal cloning enables the de-differentiation (reprogramming) of a terminally differentiated cell into one with a fully totipotent nucleus.

Embryogenesis is governed by an enormously complex set of gene regulatory pathways, and it is remarkable that the donor cell used for animal cloning, can have its differentiated program completely erased and then accurately re-established during the reprogramming process. The ongoing improvements to both *in vitro* culture production systems and embryo micromanipulation techniques, have shown that the technology can be consistently applied to a wide variety of laboratory and livestock species. Interestingly, conservation strategies promoting genetic rescue are also using cloning technology for survival and expansion of critically endangered species (Hildebrandt et al., 2021). While concerns remain about epigenetic errors in cloned embryos, foetuses, and offspring (Campbell, 2018; Martins et al., 2016; Simmet et al., 2021), and particularly in the placentas of cloned foetuses and newborns, that can relate to developmental abnormalities (Palmieri et al., 2008), animal welfare concerns associated the inefficiencies of embryonic development during pregnancy, birth defects, and unpredictable postnatal abnormalities and death, have largely been minimised with refinements of nuclear transfer methodology (La Salle, 2012; Simmet et al., 2021; Watanabe & Nagai, 2008).

New insights into the epigenetic regulatory mechanism during the nuclear reprogramming phase offer novel strategies for improving cloning efficiency. In particular, the epigenetic aberration of the acetylation of histone H3 at lysine9 (H3K9Ac) when comparing parental and nuclear transfer-cloned mammals. Modifiers of histone acetylation have improved the efficiency of development of cloned embryos. H3K9me3 methylation has been reported to be a barrier for successful nuclear reprogramming, and its removal activates the appropriate expression of repressed

genes needed for the developmental competence of cloned embryos by removing previously observed variable gene expression patterns observed in cloned animals (Maalouf et al., 2009). Cloned domestic and laboratory animals coupled with new highly specific gene editing techniques will herald significant commercial opportunities for both agriculture and medicine. The scope of potential applications could impact on the entire spectrum of human life through improved quality of food, medical care and eventually contribute to a cleaner and more sustainable environment.

Institutional animal ethics review boards provide the first checkpoint of justification for any new animal cloning initiatives via biosafety regulations, due diligence and thorough attention to the risks associated with each new application on a case-by-case basis.

Community attitudes are important to any new biotechnology and an informed discussion and debate is needed with the broad community of the benefits and risks of animal cloning to improve public awareness, identify knowledge gaps and track changes in awareness and attitudes over time. It seems that the potential "slippery slope" application of cloning to human reproduction is a primary concern about animal cloning despite a firm international scientific embargo (see: ISSCR Guidelines for Stem Cell Research and Clinical Translation, 2021) and laws preventing this in many countries (Gouveia et al., 2020). Community attitudes are crucial to the development of the biotechnology sector. To understand the public's reaction and fill the void of reasoned debate about the issue, a wide variety of community attitudes need to be canvassed around the concept of biotechnology in order to gauge the state of public awareness, identify knowledge gaps and track changes in awareness and attitudes over time.

Generally, if the public consensus is not in favour of a particular technological application, research and development will be constrained and the potential benefits in fields ranging from medicine to agriculture are likely to be either missed or delayed, resulting in a lost opportunity for individuals, industry and the community as a whole. Bioethicists and policy makers have a role in determining various aspects of the risk, the impact assessment, and management which are important to the comfort and long-term support of animal cloning technologies. An outstanding example for this is the gradual acceptance of mitochondrial replacement technology (using nuclear transfer technology developed for animal cloning) that is presently under clinical study, to prevent the transmission of severe mitochondrial disease from mother to children, in the UK and elsewhere (Greenfield et al., 2017).

Public attitudes help to shape both industry uptake of emerging technologies and the underlying regulatory framework for them. Efficient regulation involving strategies to engage with the community and increase public awareness of these emerging technologies allows ongoing development while addressing the importance of risk assessment, management, and a precautionary approach to environmental impact. Changes to community attitudes and behaviours and its impact on animal cloning will be briefly discussed.

Animal Cloning – The Echinoderms and Amphibian Beginnings

The process of embryogenesis whereby a fertilized egg develops and forms a new individual is both fascinating and essential to life. The determination of cellular fate and differentiation involves a systematic pathway whereby differentiated cells undergo restriction in their capacity to change into other cell types. Animal cloning eliminates the restriction by removing repressive epigenetic modifications at the chromatin structural level. Once removed the nucleus has the potential to re-establish an embryonic genome and direct normal development. The conditions required to permit this phenomenon is the delivery of an intact donor nucleus into the oocyte cytoplasm from which all nuclear genetic material has been removed.

Sea Urchins, Salamanders, Leopard and African Clawed Frogs

The history of the development and application of animal cloning has been well described by others (Campbell, 2002; Di Berardino, 2001; Gurdon & Colman, 1999; Illmensee, 2007; Lewis et al., 2001; McKinnell & Di Berardino, 1999; Niemann & Lucas-Hahn, 2012; Wilmut et al., 2015) and a brief outline is provided of the salient breakthroughs. Early developmental biologists realized that the zygote contained information to develop into a complete individual, however the nature and control of this information was unknown (Di Berardino, 1997b). Using sea-urchin embryos, Weismann (1892) proposed that the control of differentiation at that time was thought to be the sharing of genetic material whereby individual cells received only that information which was required to fulfil their specialised function. Alternatively, Roux (1888) used a hot needle kill a single blastomere of the 2-cell stage sea-urchin embryos and showed development continued in the remaining blastomere to a fully developed half embryo. A further refinement by Driesch (1892) and others separated the blastomeres at the two-cell stage and found normal embryo development continued, albeit at half the normal size (Di Berardino, 1997a). In 1938, Spemann using salamander zygotes and a human baby hair, restricted the nucleus to one half of the cell cytoplasm (Spemann, 1938). The half zygote, or karyoplast, with genetic material continued to divide. After several divisions the constriction caused by the human baby hair was relaxed to allow a nucleus to traverse the cytoplasmic bridge. The cytoplast upon receiving the nucleus (genetic material) resumed cleavage and development resulting in the production of dwarfed but twinned offspring. Based on these results, Spemann proposed that the transfer of nuclei from more advanced developmental stages back to zygotes from which the genetic material had been removed would demonstrate the barriers of progressive differentiation to reinitiate development (Spemann, 1938). In these experiments,

the plan was to investigate the role of the genetic material in cellular differentiation and whether information contained within the genes was lost or inactivated during development and differentiation. This light-bulb moment by Spemann, is recognised as the birth of animal cloning technology.

These early experiments demonstrated that during embryo development each cell retains a complete copy of all nuclear genetic material (Campbell, 2002). It is now well documented that embryo development and cellular differentiation are co-ordinated by highly specific temporal and spatial controls of gene expression. The majority of cells in an adult animal also retain two copies of the genome that are inherited during the process of zygote formation. While Spemann propositioned the transfer of nuclei, in reality, performing these delicate manipulations without damaging the donor nucleus or the host oocyte proved technically challenging. Advancements were not reported until the 1950s when Briggs and King (1952) overcame this challenge by developing micromanipulation techniques that allowed Northern Leopard Frog (*Rana pipiens)* nuclei from the majority of embryonic cells, up to the blastula stage, to direct larval development (swimming tadpoles) when injected into parthogenetically activated oocytes from which the maternal chromosomes had been removed. Further studies by Briggs and King using this approach went on to investigate the developmental potential of nuclei at more advanced stages of development (Briggs & King, 1953). Although all nuclei examined were able to direct blastulae development, the rate of development and the ability of cells of the blastula stage to form larvae appeared to decrease when nuclei from more advanced cell stages were used (Briggs & King, 1952, 1953). This observed difference in developmental capacity between nuclei was conserved with uniformity over many cell divisions, (King & Briggs, 1955) and led to the hypothesis than nuclei, specifically the endoderm lineage, lost nuclear potential by undergoing "irreversible changes" during differentiation (King & Briggs, 1956).

Gurdon and Uehlinger (1966) reported the production of adult *Xenopus* (South African Clawed Frogs) after transferring nuclei from tadpole intestinal epithelial cells (Gurdon & Uehlinger, 1966); however, subsequent experiments using cells taken from adult animals as nuclear donors could not replicate these results and produce adults (Fischberg et al., 1958; Gurdon, 1962, 1974, 1999; Gurdon et al., 1958, 1975).

Hennen (1970) reported a number of technical modifications to the nuclear transfer procedure that were able to remove these irreversible changes from tailbud-stage endoderm cells of *Rana pipiens* embryos. Using spermine, a poly cationic amine to complex chromatin proteins and a decrease in temperature (11 °C) to lengthen the cycle of the oocyte host, Hennen demonstrated a 145% increase (62% treated vs 25% control) in the development of normal larvae from blastula following transfer of tailbud-stage nuclei into enucleated *Rana pipiens* eggs. Hennen (1970) postulated that if the process of normal differentiation involves selective repression of genetic information, this stable repression observed under normal conditions is reversible as far as nuclei from tailbud presumptive midgut are concerned. The work

showed modifications, now consider epigenetic modification, in the nuclear transfer procedure can improve the developmental expression of nuclei from advanced developmental stages.

Reflecting on these amphibian studies at this time, its noted that only a small proportion of larval amphibian nuclei transferred into enucleated eggs resulted in the development of fertile frogs. Fertile adults were derived from larval endoderm (gut) nuclei of newts (*Pleurodeles*, (Aimar & Gallien, 1972)) and from African Clawed Frogs (*Xenopus*) – endoderm (20 frogs (Gurdon, 1962)), intestinal (2 frogs, (Gurdon & Uehlinger, 1966)), and epidermal nuclei (2 frogs, (Brun & Kobel, 1972; Kobel et al., 1973)). However, during the process of isolating these few donor cells it is not known if the totipotency of nuclei being assessed was due to differentiated cells or to stem cells which are also present in the tissue at this time. In contrast, no nuclei transferred from adult tissue were found to be totipotent (reviewed by Di Berardino, 1997b). Numerous nuclear transfer studies involving differentiated larval and adult cells from Leopard and Clawed frogs including melanophores, erythroblasts, skin, and lymphocytes injected into enucleated eggs could direct the development of pre- or post- hatching tadpoles (reviewed by Di Berardino, 1997a, b) and show that the transferred nuclei were multipotent and not totipotent. The most advanced tadpoles were derived from erythrocyte nuclei isolated from juvenile Leopard frogs resulting in the formation of feeding tadpoles (7.8%) that survived for up to a month (Di Berardino et al., 1986).

Studies involving the use of animal erythrocyte (red blood cell) nuclei as donor cells for nuclear transfer are important as they defined the terminally differentiated state of the donor nuclei and introduced two new concepts of cell cycle state involving senescence with absence of transcriptional activity and serial nuclear transfer. This was possible because the mature amphibian red blood cell is nucleated, as compared to the human counterpart, and the colour (red) and shape (oval) makes them easier to distinguish from other cells. This makes it easier to select isolated donor nuclei as opposed to other biological tissues that are composed of both differentiated and stem cell types. Additionally, the mature amphibian red blood cell is associated with the G0 stage (quiescence) of the cell cycle with virtual no transcriptional activity detected. In this experiment, the red blood cell nuclei were first injected into MI eggs and "conditioned" for 24 h while the oocytes matured into MII oocytes (the normal enucleated host). The insertion of a glass needle to parthenogenetically activate the mature MII oocytes and permit resumption of embryo development followed by removal (enucleation) of the maternal (oocyte) nucleus, which left only the red blood cell nucleus in the cytoplasm (Campbell, 2002; Di Berardino, 1997a, b).

Blastulae that developed the next day then became nuclear donors for new enucleated MII oocytes. These serially cloned erythrocyte embryos developed into feeding larvae with hind limb buds. Di Berardino and Hoffner (1983) hypothesised that unknown molecular components of the oocyte cytoplasm prepare oocyte

chromosomes to participate in fertilization and would therefore likewise condition the genetic material of erythrocytes. This was shown when red blood cell nuclei transferred to MII oocytes failed to promote development of the host beyond the early gastrula stage while those nuclei serially exposed first to MI and then MII oocyte cytoplasm directed the hosts to develop into larvae.

Animal Cloning – Leporine, Murine, Ovine and Bovine

In mammals, further technical developments were required due primarily to the differences in oocyte (egg) size (120–150 μm *vs* > 1 mm for amphibians) and delayed the feasible micromanipulation of mammalian eggs for some time. Bromhall (1975) overcame these confines using both direct microinjection and Sendai virus induced fusion to transfer labelled rabbit morula cell nuclei into enucleated rabbit eggs. Embryos resulting from these early nuclear transfers rarely developed beyond the first cleavage divisions (Di Berardino, 1997b) and it was difficult to evaluate whether the donor nucleus participated in development because of the presence of the host nucleus.

A method for transferring a donor nucleus to zygotic cytoplasm successfully was described by llmensee and Hoppe who reported the birth of three live mouse pups after microinjection of ICM-derived donor nuclei into mouse zygotes followed by removal of the male and female pronuclei (Hoppe & Illmensee, 1982; Illmensee & Hoppe, 1981). However, replication of these achievements has raised questions on the initial findings (Marx, 1983a, b; McGrath & Solter, 1983; Robl et al., 1986; Tsunoda et al., 1987; Wakayama et al., 2000). Nevertheless, while this report has initiated many additional studies and further discussion (Illmensee, 1999; Solter, 1999), the transfer of ICM nuclei to enucleated zygotes in mice has yet to be repeated. McGrath and Solter (1983) showed that exchange of pronuclei in zygotes by using microsurgery allowed development to continue.

Subsequently, Willadsen (1986) produced live lambs after transferring nuclei from 8- to 16-cell sheep embryos into enucleated MII oocytes. Following these reports, nuclear transfer offspring were reported from a number of laboratories using 8-cell embryonic nuclei in rabbits (Stice & Robl, 1988), 9- to 16-cell embryonic nuclei in cattle (Prather et al., 1987; Robl et al., 1987) and 16-cell embryonic nuclei in sheep (Smith & Wilmut, 1989). Offspring have also been produced from donor nuclei isolated from ICM cells of blastocysts in sheep (Smith & Wilmut, 1989) and cattle (Collas & Barnes, 1994; Keefer et al., 1994) and from cattle ICM cells after 28 days of in vitro culture (Sims & First, 1994). At this point in time development to term of nuclear transfer embryos was restricted to the use of early cleavage-stage embryos as nuclear donors.

Animal Cloning Breakthrough: Megan, Morag, Cedric, Cecil, Cyril, Tuppence, Taffy, Tweed and Dolly, Polly and Molly

In the mid 1990s, a group of researchers at the Roslin Institute in Edinburgh began a series of experiments that would result in the breakthrough that showed adult terminally differentiated cells could be reprogrammed to produce live offspring, and that a single source of these differentiated cells could produce multiple offspring. Keith Campbell, Jim McWhir, William Ritchie, and Ian Wilmut began their seminal series of experiments by identifying a protein that regulates the cell cycle of an activity modifier called maturation promoting factor (MPF) (Campbell et al., 1996a). The level of MPF determines how a recipient oocyte accepts a donor nucleus. Low levels of MPF in the oocyte meant that the donor nucleus could be transferred without chromosomal damage. Alternatively, oocytes with high MPF levels could only receive a nucleus that had two viable copies of each chromosome or if the nucleus was transferred in a resting state called quiescence (G0). Using different sheep breeds, with the Scottish Blackface sheep providing the oocytes that would show that nuclear transfer offspring produced were not fertilized within the oviduct, they tested the assumption that viable nuclear transfer embryos could only be achieved from totipotent cells (Campbell et al., 1996b). Totipotent cells (TNT4) were derived with the aid of the protein leukemia inhibition factor (LIF) from nine-day-old embryos, which had formed into an embryonic disc. Early passage cells that had not differentiated were induced into a quiescent state by serum starvation. Quiescent donor nuclei were transferred to MII oocytes at the time of activation, prior to activation and following activation to vary MPF levels. They found there was no significant difference between variations in concentrations of MPF proteins among the blastocysts whose donor cells were in the quiescent state. Thirty-four embryos were developed from passages 6–13 of TNT4 nuclei and transferred into ewes. The thirty-four embryos produced eight foetuses and resulted in five live births, all exhibiting characteristics of the same female Welsh Mountain donor. Live lambs (five in total) were obtained from all combinations, but unfortunately two of these died within minutes of birth and a third at 10 days following birth with a range of congenital abnormalities. The remaining two lambs Megan and Morag remained healthy, and both have proved to be fertile (Campbell et al., 1996b). Megan lived to at least age ten in 2005.

In a second set of experiments, they tested the claim that reprogramed differentiated diploid cell nuclei could be totipotent if the cytoplasm from the receiving oocyte (egg) and the donor nucleus were in quiescence (high concentrations of MPF protein). To confirm and extend these studies they subsequently repeated the experiments using a male day 9 embryo-derived cell population, primary foetal fibroblasts from a day 26 foetus and a mammary epithelial cell line isolated from a 6-year-old Finn Dorset ewe. Live offspring were obtained from each of these cell populations, the Day 9 embryo (Cedric, Cecil, Cyril, and Tuppence), the day 26 primary foetal

fibroblast (Taffy and Tweed) and the adult mammary epithelial cell line cell giving rise to the birth of 'Dolly' (Wilmut et al., 1997). Dolly was the result of 277 constructed embryos containing adult cell nuclei that were implanted into 13 surrogate mothers, only one of which became pregnant. This pregnancy was carried to term successfully, a Finn Dorset lamb, born on July 5, 1996.

In 1997, the team generated Polly and Molly, Poll Dorset clones made from nuclear transfer using a foetal fibroblast nucleus genetically engineered to express a human gene known as *FIX* (McCreath et al., 2000). This gene encodes the human factor IX protein, a clotting factor that occurs naturally in most people but is absent in people with haemophilia, who require replacement therapy with a therapeutic form of the protein.

Move forward 25 years and the foundation behind these experiments whereby a diploid nucleus is transferred into an enucleated MII oocytes (unfertilised) has independently and on a worldwide scale shown consistency and adaptability to more than 26 species (see: Fig. 34.1) where conservatively many thousands of cloned individuals have been produced (Heyman, 2005; Lewis et al., 2001; Loi et al., 2021; Niemann & Lucas-Hahn, 2012; Paterson et al., 2003).

Animal Cloning Methodology

Like all Reproductive technologies, animal cloning proceeds in a step-by-step manner, involving timepoints that attempt to keep pace with the natural timing of fertilisation and embryo development. Factors that influence these procedures include oocyte quality, activation procedures, donor nuclei source and their cell-cycle stage, culture system, and the global efficiency derived from all these. Interestingly the methodology appears adaptable across a wide variety of species where the overarching principles remain the same. The current methodology has evolved through many steps with further optimisation likely as research continues and the lessons are learned (Gouveia et al., 2020; Klinger & Schnieke, 2021; Matoba & Zhang, 2018).

Briefly, Animal Cloning steps include:

- Generation of a cytoplast via enucleation/ bisection
- Selection of a diploid donor cell and their cell-cycle stage
- Cell cycle co-ordination in nuclear transfer reconstructed embryos
- Embryo reconstruction – via electrical or viral mediated fusion or direct injection
- Embryo activation – chemical or electrical
- *In vitro* embryo culture (IVC)
- Embryo selection and transfer to synchronised recipient.

A photographic representation of the *In vitro* animal cloning method that's results in live offspring can be seen in Fig. 34.2.

Fig. 34.1 Chronological images of the In vitro method of animal cloning resulting in live offspring. A chronology of cloned offspring derived from the adult somatic cells of different species using somatic cell nuclear transfer. This chronology shows the consistency of the SCNT technique across a diversity of animals as well as the 25-year application timeline to achieve offspring. Unfortunately, the figure does not show, the considerable effort undertaken worldwide by different research groups that have both validated this technology and produced more than 1500 SCNT animal (Heyman, 2005; Lewis et al., 2001; Loi et al., 2021; Paterson et al., 2003)

Fig. 34.1 (continued) Sheep: 1996 – Dolly – Campbell, K. H., McWhir J., Ritchie W. A., & Wilmut, I. (1996). Sheep cloned by nuclear transfer from a cultured cell line. *Nature, 380*(6569), 64–66. https://doi.org/10.1038/380064a0
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Deer: 2003 – Dewey – https://vetmed.tamu.edu/news/press-releases/cvm-researchers-first-to-clone-white-tailed-deer/
Dog: 2005 – Snuppy – Lee, B. C., Kim, M. K., Jang, G., et al. (2005). Dogs cloned from adult somatic cells. *Nature, 436*(7051), 641. https://doi.org/10.1038/436641a
Buffalo: 2005 – Shi, D., Lu, F., Wei, Y., et al. (2007). Buffalos (Bubalus bubalis) cloned by nuclear transfer of somatic cells. *Biology of Reproduction, 77*, 285–291
Murrah Buffalo: 2009 – Samrupa-Selokar, N. L., Saini, M., Palta, P., et al. (2018). Cloning of buffalo, a highly valued livestock species of South and Southeast Asia: Any achievements? *Cellular Reprogramming, 20*(2), 89–98

Generation of A Cytoplast via Enucleation/Bisection

Mature oocytes in MII of the second meiotic division are the cytoplast donor of choice as their use results in the highest developmental potential. A variety of sources dependent upon species are available, including aspiration from ovarian follicles following slaughter or ovariectomy and maturation in vitro. Additionally, immature oocytes may be aspirated directly from the ovary (Choi et al., 2013) and matured or *in vivo* matured and flushed directly from the oviducts of donor animals following superovulation regimes (Campbell, 1999). The quality of *in vivo* derived cytoplasts is higher, but is more expensive and commonly involves superovulation regimes to increase yield. For conservation strategies involving the preservation of endangered species and the inevitable lack of oocytes, interspecies oocytes from closely related species (interspecies NT) can function as suitable cytoplast donors (Galli & Lazzari, 2021; Lanza et al., 2000; Narbonne et al., 2012; Prather et al., 1987; Robl et al., 1987).

The generation of the cytoplast in a process termed enucleation, involves removal of the maternal genetic material from a suitable nuclear recipient oocyte. There are various methods of enucleation (Lewis et al., 2001), the predominant involves microsurgery using a glass micro-pipette that removes the first polar body and a small amount of the cytoplasm that contains the maternal chromosomes. The success of this procedure can be confirmed in the recipient oocytes following exposure to UV light after staining with DNA specific fluorochromes (33342) (Campbell, 1999).

An alternative cloning technique termed Handmade cloning (HMC) does not require the use of micromanipulators and therefore has a lower starting cost.

Fig. 34.1 (continued) Ferrets: 2006 – Libby and Lilly – Li, Z., Sun, X., Chen, J., et al. (2006). Cloned ferrets produced by somatic cell nuclear transfer. *Developmental Biology, 293*(2), 439–448. https://doi.org/10.1016/j.ydbio.2006.02.016

Black-footed ferret: 2021 – Elizabeth Ann – US Fish and Wildlife Service. (2021). https://www.fws.gov/mountain-prairie/pressrel/2021/02182021-USFWS-andPartners-Innovative-Genetic-Cloning-Research-Black-footed-Ferret-Conservation.php

Gray Wolf: 2007 – Snuwolf and Snuwolffy – Kim, M. K., Jang, G., Oh, H. J., et al. (2007). Endangered wolves cloned from adult somatic cells. *Cloning and Stem Cells, 9*(1), 130–137. https://doi.org/10.1089/clo.2006.0034

Camel: 2009 – Injaz – Wani, N. A., Wernery, U., Hassan, F. A., et al. (2010). Production of the first cloned camel by somatic cell nuclear transfer. *Biology of Reproduction, 82*(2), 373–9. https://doi.org/10.1095/biolreprod.109.081083

Coyote: 2011 – Hwang, I., Jeong, Y. W., Kim, J. J., et al. (2013). Successful cloning of coyotes through interspecies somatic cell nuclear transfer using domestic dog oocytes. *Reproduction, Fertility and Development, 25*(8), 1142–1148. https://doi.org/10.1071/RD12256

Monkey – Crab Eating Macaque: 2017 – Zhong Zhong (ZZ) and Hua Hua (HH) – Liu, Z., Caai, Y., Wang, Y., et al. (2018). Cloning of macaque monkeys by somatic cell nuclear transfer. *Cell, 172*(4), 881–887. https://doi.org/10.1016/j.cell.2018.01.020

Note: No image of Ombretta (Mouflon Sheep) 2001 was available as Ombretta did not survive long due to a lung abnormality. Its image is represented by an illustration (https://en.wikipedia.org/wiki/Pyrenean_ibex)

Enucleation of the MII oocytes is achieved by removing the zona pellucida and bisecting the oocyte using a handheld embryo-splitting blade pellucida (Tecirlioglu et al., 2005; Vajta et al., 2003). This process of cutting the oocyte in half generates a cytoplast and a karyoplast. Two cytoplasts are then fused with the donor cell to counteract the loss of cytoplasm during enucleation which improves embryo development (Sayaka et al., 2008). Zona-free embryos require individual culture conditions (well-of-the-well) to prevent embryo amalgamation before they can be transferred to recipients at the blastocyst stage (Vajta et al., 2008). Interestingly, while the overall efficiency of animal cloning is comparable for the standard zona enclosed and HMC techniques, the possibility of mitochondria heteroplasmy derived from three different animals in the case of HMC could induce individual deleterious effects (Bowles et al., 2008; Czernik et al., 2019; Steinborn et al., 2000).

Selection of A Diploid Donor Cell and Their Cell-Cycle Stage

The use of a diploid cell line allows co-ordination of donor and recipient cytoplast cycles. Live offspring can be produced by animal cloning from a wide variety of primary cell cultures derived from expanded *in vitro* cultures of embryonic, foetal and adult cells (Lewis et al., 2001), or even cells extracted from urine (Madheshiya et al., 2015) or other tissues. It has been difficult to identify the most amenable cell types for animal cloning as the cell lines are often not clonally derived and as such comparison between embryonic versus adult do not typically show a different outcome when used in the animal cloning procedure. Interestingly, Wakayama (2008) showed that frozen non-viable diploid cells isolated from mouse bodies that had been frozen at −20 °C for up to 16 years without a cryoprotectant could be used to produce cloned mice via a two-step animal cloning method or serial nuclear transfer. This procedure involved isolation of embryonic nuclei derived from the early brain nuclei SCNT embryo and then using the embryonic nuclei to initiate a second round of reprogramming before embryo transfer. Donor cells frozen without cryoprotectant or requiring expansion *in vitro* culture could now be used to "resurrect" animals or maintain valuable genomic stocks from tissues frozen (Wakayama et al., 2008).

Cell Cycle Co-ordination in Nuclear Transfer Reconstructed Embryos

Successful embryo development following animal cloning requires co-ordination of the nuclear and cytoplasmic cell cycle phases of both the donor (karyoplast) and the recipient (cytoplast) cells (Campbell et al., 1996a). Ideally the process of cell-cycle coordination during animal cloning is designed to: (1) maximises the number of mitotic events which the donor nucleus will pass in the absence of transcription; (2) reduce the changes in the donor cell as a result of transcription and translation; and

Fig. 34.2 Photographic images of the *In vitro* method of animal cloning resulting in live offspring (L-R) 1. Metaphase II (MII) oocyte (*In vivo* or *In vitro* derived) 2. Visualisation of the maternal chromosomes (Oosight (birefringent light) or fluorophore (UV) 3. Enucleation of the maternal chromosomes (micromanipulation or embryo bisection (HMC) 4. Isolation, propagation and selection of a diploid cell (donor DNA). 5. and 6. Selection and transfer of a single diploid cell (micromanipulation or Piezo assisted direct injection) 7. Fusion of the donor cell and enucleated

(3) degrade unnecessary mRNA and chromatin condensation factors that may inhibit the interaction of the donor chromatin with maternal factors in the recipient oocyte cytoplasm.

The onset of mitosis and meiosis is controlled by MPF. MPF increases during the G2 phase of the cell cycle and causes breakdown of the nuclear membrane, chromatin condensation and changes in the cytoskeleton. MPF is maximal at metaphase of the mitotic/meiotic division after which it declines rapidly allowing de-condensation of the chromosomes and reformation of the nuclear membrane. In MII oocytes, MPF activity remains at high levels; when donor nuclei are transferred into this cytoplasmic environment, they respond to the MPF and undergo nuclear envelope breakdown (NEBD) and precocious chromosome condensation (PCC) (Campbell et al., 1996a).

The effects of PCC on the donor nucleus is dependent upon the cell cycle stage at the time of transfer. G1 phase nuclei (prior to the DNA synthetic period or S-phase) or those in G2 phase (post S-phase) form single or double chromatids, respectively, and undergo no apparent DNA damage. Chromatin of nuclei that are undergoing DNA synthesis (S-phase) has a typical 'pulverised' appearance and undergoes large amounts of DNA damage (Campbell et al., 1996a).

In vivo and *in vitro* cell populations enter a non-growing but viable condition with age, termed senescence. Senescent cells complete DNA replication but do not divide, as they arrest in the G2 phase of the cell cycle. Inducing *in vitro* cells to a quiescent (pre-senescent) or G0 state was devised to improve cell -cycle coordination for animal cloning. While the induction of a quiescent state or selection of quiescent cells as the donor nuclei has produced live offspring from both foetal and adult cells, the potential role of quiescence in successful development of nuclear transfer reconstructed embryos using cultured cell populations is presently unclear.

Other factors that influence the coordination of the cycle include nuclear envelope breakdown (NEBD) which occurs due to high levels of MPF which initiates replication of the DNA. Nuclei that are diploid or pre-S-phase at the time of transfer will give rise to daughter cells of the correct ploidy. The cytoskeleton and mitotic spindle can also affect the ploidy of the reconstructed embryo. Formation of an intact spindle resulting in a mitotic or pseudo-mitotic event following transfer of G2 phase nuclei in mice was important in the development of live offspring (Cheong et al., 1993).

Fig. 34.2 (continued) MII Oocyte (electrical and virus mediated) 8. Activation of the fused couplet (calcium ionophore, PLCzeta) followed by (alone or in combination with cycloheximide or cytochalasin), a protein phosphorylation inhibitor that elevates the level of intracellular calcium in the oocyte and inhibits second polar body extrusion. 9. *In vitro* culture of the cloned embryos 9. Morphological selection of embryos for transfer into synchronised recipients. 10. Birth of cloned offspring (Friesian bull clones derived from two Animal Cloning techniques – Embryo Micromanipulation and the HMC technique (see Tecirlioglu et al., 2005; Vajta et al., 2006))

Embryo Reconstruction, Activation and Culture

Following enucleation, the donor cells genetic material (karyoplast) must be introduced into the enucleated recipient cell (cytoplast). To initiate fusion, most animal cloning techniques depend on a DC electric pulse. Piezo- or laser-assisted microinjection are the most common techniques in rodents. Piezo is finding favour in other species with less damage to the cytoplast and as a viable alternative to poor or variable fusion rates following exposure to a DC pulse.

Following fusion, the reconstructed embryo must be induced to exit meiotic arrest and initiate normal embryo development. Chemical (strontium or ionomycin) and electrical activation are used for this and electrical activation remains the most widely used method in livestock (Akagi et al., 2003; Lewis et al., 2001). Individual protocols for activation stimuli, timings, and post-activation treatments have been devised for each species, including the use of HDAC inhibitors to improve donor nuclear reprogramming (Narbonne et al., 2012) and the identification a novel testis-specific PLC, termed PLCzeta (PLCζ), a ~74 kDa protein which was proven to play a key role in oocyte activation (Lewis et al., 2001; Saunders et al., 2002).

In Vitro Embryo Culture

The conditions for *in vitro* embryo culture (IVC) and the developmental stage at which reconstructed cloned embryos are transferred to recipients are species-specific. Assisted reproductive technologies in animals and humans show that *in vitro* manipulation of gametes and embryos, such as embryo culture, can modify the expression of specific imprinted and non-imprinted genes.

The developmental abnormalities resulting from epigenetic defects observed in cloned embryos are similar to those observed during gestation from *in vitro* produced embryos (Ashry & Smith, 2015). Features characterised by overlarge foetuses, placental malformations, reduced pregnancy rates, dystocia, and pulmonary dysfunction (Fleming et al., 2004).

The transfer of reconstructed embryos at an early stage of development to the oviduct of the recipient can reduce or eliminate epigenetic defects associated with many of these abnormalities (Polejaeva et al., 2000; Wakayama et al., 1998). The practicality of this approach in all domestic animals is difficult because of small litter sizes, high costs of surgery, and long gestation intervals which can make the availability of high quality synchronised recipients the limiting factor.

Perturbation to gene expression in both *in vitro* cultured and cloned embryos (albeit at a much higher frequency) have been shown variations in IGF_2 (Young et al., 2001), SNRPN and H19/IGF_2 (Smith et al., 2012, 2015) gene expression. However, it is difficult to discriminate between the effect of *in vitro* culture and dysregulation due to the cloning process (Ashry & Smith, 2015; Wrenzycki et al., 2001). The effects of *in vitro* culture media and associated small reprogramming

(mRNA) errors during early development will likely manifest much larger development abnormalities downstream during organogenesis.

Embryo Selection and Transfer to Synchronised Recipient

The optimal environment for embryonic implantation is the transfer into a synchronous endometrium. Pregnancy rates from embryo transfer (ET) can vary widely. Careful selection of quality embryos based on morphological examination (Lindner & Wright, 1983) and selection and preparation of the recipient have equally important roles in the success of the transfer (Weaver et al., 1986). The transfer of Grade 1 quality embryos into a poorly prepared or selected recipient and vice versa will undoubtedly influence the success of animal cloning and ART technologies. The female reproductive tract is influenced by a range of factors including age at puberty, photoperiod, uterine horn factors, temperament, photoperiod, nutrition and thermal stress. Health and nutritional status of recipients are also recognized as significant factors affecting recipient pregnancy rates. Natural versus induced oestrus on recipient pregnancy rates should also be considered (Weaver et al., 1986).

Applications and Improvements to Animal Cloning

Assisted Reproductive Technologies (ARTs) are comprised of a range of interrelated technologies that include superovulation, artificial insemination, recipient synchronisation, embryo transfer, OPU, i*n vitro* maturation, i*n vitro* fertilisation, semen sexing, i*n vitro* culture and cryopreservation. These technologies are able to manipulate reproductive-related events and/or structures to achieve pregnancy with the final goal of producing healthy offspring (Mapletoft & Hasler, 2005). Animal cloning is another ART that enables the preservation and rederivation of animals with high genetic merit (Galli et al., 2003; Trounson, 2006) and endangered species via interspecies application (Lanza et al., 2000; Sandler et al., 2021). The unmatched potential of animal cloning is the ability to derive embryos from donor diploid cells cultured, expanded, and precisely modified when combined with genetic modification techniques prior to nuclear transfer.

Novel opportunities using this technology are available in both laboratory and livestock species. In laboratory animals it has been used to investigate gene function, gene modification and determining control over the offspring's inherited traits (Colman, 1999). In livestock production, the ability to reproduce genetically identical animals offers prospects for improving genetic gain and increased selection of animals for disease resistance, suitability for climate (heat tolerance), enhanced carcase characteristics, improved fertility as well as consumer preference (Keefer, 2015; Wells, 2005). Animal Cloning also holds great potential for biomedical research (Rogers, 2016).

Genetic Engineering Using Animal Cloning

Humans have been altering the genomes of plants and animals for hundreds of years using traditional breeding techniques. The identification and selection of specific traits results in a variety of different organisms with improved phenotypes. However, the selection of these phenotypes for subsequent generations is limited to naturally occurring variations.

It is of significance to note for the discussion around genetic engineering, that while the human genome contains billions of pieces of information and around 22,000 genes, it is not all from human origins. Eight percent of our DNA consists of remnants of ancient viruses, and another 40% is made up of repetitive strings of genetic letters that is also thought to have a viral origin. These extensive viral regions are not just evolutionary relics, as they impact on with a wide range of diseases including multiple sclerosis, haemophilia, and amyotrophic lateral sclerosis (ALS), and certain types of dementia and cancer (Li et al., 2015).

Advances in the field of genetic engineering have allowed for precise control over the genetic changes introduced into an organism. Today, we can incorporate new genes from one species into a completely unrelated species through genetic engineering. Thus far, animal cloning coupled with modern genome engineering technology has been a valuable alternative strategy for the generation of genetically engineered (GE) livestock. New opportunities have emerged that allow gene function studies and development of animal models for a variety of human conditions and diseases or to improve the health of livestock animals. Remarkable progress has been made over the last two decades in the field of livestock genetic engineering. Initially, knockouts of multiple genes in foetal fibroblasts required in some cases years and were accomplished by sequential targeting and fibroblasts rejuvenation by cloning (Kuroiwa et al., 2004). These animal models have been generated via animal cloning by using genetically modified somatic cells include introduction of human artificial chromosome (HAC) to produce transchromosomic animals for human polyclonal antibody production (Kuroiwa et al., 2002).

Other animal models involving genetic modification include collagen (McCreath et al., 2000), xenotransplantation with knockouts of the alpha 1–3 galactosyl transferase and PrP prion resistant (Cascalho & Platt, 2001), cardiovascular disease (Schneider et al., 2020), diabetes (Renner et al., 2020), cystic fibrosis (Rogers et al., 2008), several types of cancer (Perleberg et al., 2018), Duchenne muscular dystrophy (Klymiuk et al., 2013) and neurodegenerative disorders (Yan et al., 2018) and developing new treatments and diagnostic tools (Moretti et al., 2020; Regensburger et al., 2019; Renner et al., 2020).

Biopharmaceuticals and Nutriceuticals involve the production of human proteins in a range of a range of tissues and bodily fluids including blood, urine and milk. A range of therapeutic proteins are being produced in the milk of transgenic animals and include modifications to enhance nutritional value and the removal of allergenic proteins (Kues & Niemann, 2004).

Animal cloning and its application to GE livestock offers a wide variety of opportunities for improving important agricultural production traits, enhancing

disease resistance, animal welfare and health (Carlson et al., 2016; Walters et al., 2017). In the biomedical field, the development of refined animal models of human disease helps to understand the disease aetiology and develop innovative therapeutic procedures (Polejaeva, 2021). Advancements in precision, efficiency and scope of genetic engineering technologies will continue to accelerate GE livestock production and broaden its applications.

Technology Renaissance – Animal Cloning and Genome Editing With Designer Nucleases

The development of genome editors (programmable nucleases) including ZFN (zinc finger nucleases) and TALENS (TAL effector nuclease) and CRISPR/Cas 9, (Clustered Regularly Interspaced Short Palindromic Repeats (Doudna & Charpentier, 2014)) that enable a high efficacy for gene editing somatic cells have integrated effectively with animal cloning as the development of major pathways to produce genome-edited livestock for research, agriculture and biomedical fields (Perisse et al., 2021).

The IVC of primary cells lines has a finite lifespan and population doublings before undergoing senescence. Despite this limitation, it is possible to target specific multiple loci in the donor cell at the same time both for inserting (KI, knock-in) or deleting fragments of genes (KO, knock-out) or to induce homology-directed repair (HDR) with relatively high efficiency compared to random integration or classical homologous recombination.

While the direct injection of CRISPR/Cas9 into zygotes represents a major technological advantage over SCNT for the generation of gene-targeted animals. Embryo mosaicism, and low and variable germ-line transmission, present challenges with this approach, particularly when multiplexed gene editing is required (Le et al., 2021; Tanihara et al., 2016). It is also possible that microinjection may become less critical as methods for delivering one or multiple ribonucleoprotein complexes by electroporation are becoming more efficient in livestock (Hirata et al., 2020; Tanihara et al., 2016).

The renaissance of animal cloning efforts with gene editing techniques has seen single genes modified in the donor cell before SCNT to enhance agricultural systems including mastitis resistance, double muscling, hornless (polled), β-lactoglobulin (see review, Bishop & Eenennaam, 2020) and hypoallergenic milk (Sun et al., 2018). Biomedical applications include cattle KO for galactose-α1,3-galactose and N-glycolylneuraminic acid antigens (Perota et al., 2019).

Disruptive Technologies That Impede Animal Cloning Developments

Realising the potential of animal cloning and its ongoing development has been impeded by two disruptive technologies. Up until their discovery, animal cloning was the main technology for reprograming somatic cells across multiple species.

The consequence of inconsistency in the regulation and use of animal cloning in some countries and the diversion of global funding to stem cell research, has hindered the ability to undertake studies to improve the overall efficiency, safety and applications of animal cloning.

Embryonic Stem Cell (ESC) Technologies

The targeted (and non-random) genetic modification of animals has its beginnings in utilisation of mouse embryonic stem cells (ESC) and the generation of chimeric founders that are bred to homozygosity (Doetschman et al., 1987; Thomas & Capecchi, 1987). The short inter-generational interval and embryonic stem cell technologies in mice have been available since 1981 (Evans & Kaufman, 1981). Despite considerable effort, adapting this technology to livestock and other species and demonstrating germline competent ESC has not been forthcoming.

Recently, reports have derived novel porcine and human embryonic stem cells (ESCs) from preimplantation embryos that can robustly generate primordial germ cells (PGC's) *in vitro* and can contribute to chimeric foetuses (Gao et al., 2019; Yu et al., 2021). Undoubtedly this technology could be adapted to other livestock species, to allow prospects for genetic modification. In a recent study in cattle, ESC lines were established following inhibition of the Wnt-pathway (Bogliotti et al., 2018). However, efficient germline contribution in chimeric offspring is still required. The long inter-generational interval to breed for homozygosity needs to be considered before a broad use of livestock stem cells before genetic modifications can be realised.

Induced Pluripotent Stem Cells (Ipscs)

Many believed that the milestone discovery which showed a terminally differentiated cells could be reprogrammed to an embryonic state by using four specific factors, Oct4, Sox2, Klf4, and c-myc (Takahashi & Yamanaka, 2006), would replace the need for animal cloning as generation of iPSCs cells is ethically less controversial. Many of the safety concerns of iPSCs around the use of viral vectors to deliver the reprogramming factors have been addressed to allow the safe delivery of reprogramming factors (Woolwine, 2013). However, iPSCs cells remain elusive in livestock (Scarfone et al., 2020; Soto & Ross, 2016). Despite global investment, iPSC research over the last 20 years and the goal of a cell-based therapy has not been achieved (Yamanaka, 2020).

The use of ntESCs (stem cells derived from Cloned embryos) offers an alternative route to reprogram cells to pluripotency once conditions to maintain pluripotency have been established (Hildebrandt et al., 2018; Lazzari et al., 2006; Navarro et al., 2020; Tachibana et al., 2013). Artificial gametes have been generated from ntESCs (Hayashi, 2019) and could be used in ARTs for both livestock and

endangered species. Deriving gametes for breeding purposes are based on male (only) germ line PGC culture with or without genetic engineering and transplantation (Zhang et al., 2020) and repopulation of the testis with spermatogonial stem cells to produce fertile spermatozoa (Ciccarelli et al., 2020). Zygote microinjection has also been re-examined (Lee et al., 2020; Menchaca et al., 2020).

Restoring the Epigenetic Landscape Following SCNT

During fertilisation, comprehensive chromatin remodelling occurs in both sperm and the oocyte, this dynamic union results in the development of a healthy new individual. Extensive epigenetic reprogramming occurs without changes to the DNA sequence and is supported by transcriptional profile modifications. To avoid the persistence of alterations in epigenetic marks, the epigenetic information contained in each gamete is reset during early embryogenesis. Covalent modification of DNA by methylation, as well as post-translational modifications of histone proteins and non-coding RNAs, appear to be the main epigenetic mechanisms to control gene expression. These differences allow differentiated cells in an organism to express different transcription profiles, despite each cell containing the same DNA sequence (Canovas & Ross, 2016).

The main epigenetic marks in mammals are covalent modifications (methylation) of the DNA and post-translational modifications of histone proteins (histone code) which reinforce cell-fate decisions and establish barriers against reversion to the preceding cellular state. Uniquely, fertilization in the pre-implantation embryo and during primordial germ cell specification shows this epigenetic information is erased to a basal state in a process referred to as epigenetic reprogramming.

Solving the SCNT problems associated with pregnancy losses and early mortality, involves in part unravelling the mechanisms of cell reprogramming and will permit the wider adoption and uptake of animal cloning technologies. Modifying chromatin to increase accessibility to transcription factors using factors that influence DNA methylation, histone acetylation and histone methylation could improve reprogramming in the donor cell by opening up chromatin structures so the oocyte molecular machinery can exert a stronger reprogramming effect on the donor genome.

Histone Acetylation

Treatment of the donor cell or reconstructed SNCT embryos with a potent histone deacetylase inhibitor, was initially demonstrated in mice using Trichostatin A (TSA) and improved nuclear reprogramming as shown by a dramatic increase in live offspring (Kishigami et al., 2006; Kohda et al., 2012; Rybouchkin et al., 2006; Yokota et al., 2004). Other researchers have utilised more efficient HDAC inhibitors including Scriptaid, suberoylanilide hydroxamic acid, oxamflatin, m-carboxycinnamic

acid bishydroxamide, and PXD101 (see review Ogura et al., 2013; Ogura et al., 2021; Ono et al., 2010). However, the identification of efficient HDAC inhibitors for SCNT experiments for enhancing the development of SCNT embryos is still ongoing.

Another typical epigenetic abnormality present in SCNT embryos is histone H3 lysine 9 trimethylation (H3K9me3) (Matoba et al., 2014). In differentiated cells, H3K9me3 is generally associated with constitutive heterochromatin and this condensed chromatin prevents transcription of genes. Matoba et al. (2014) showed that donor cell-derived H3K9me3 prevents zygotic genome activation (ZGA) from the injected donor somatic cell nucleus following NT, thereby blocking the normal development of SCNT embryos (Matoba et al., 2014). The H3K9me3 in the reprogramming resistant regions' (RRRs) in the somatic cells is likely to be held in constitutive heterochromatin.

These restrictions could be removed by overexpressing the H3K9me3-specific histone demethylase Kdm4d which allowed the SCNT embryos to activate their own genome. A combination of H3K9me3 removal by Kdm4d with correction of Xist gene expression in SCNT embryos has further increased the cloning efficiency (Matoba et al., 2018).

However, the application of maternal Xist knockout in donor cells and/or Kdm4d mRNA injection in other species for reconstructed embryos does not necessarily confer positive effects to the term development of cloned embryos. In a bovine study, inhibition of the epigenetic writer EHMT1/2 catalytic activity, markedly reduced H3K9me2 and H3K9me3 levels in cloned blastocysts but did not improve preimplantation development (Sampaio et al., 2020). Alternatively, other Kdm4 family genes, such as Kdm4a (Chung et al., 2015) or Kdm4b (Liu et al., 2016) can boost the efficiency of SCNT. The enhancement in cloning efficiency is also effective in other mammals including sheep (Zhang et al., 2018), cattle (Liu et al., 2018a), monkeys (Liu et al., 2018b) and in the human (Chung et al., 2015) for producing pluripotent stem cells.

DNA Methylation

Treatment with DNA methylation inhibitors (e.g. 5-aza2′-deoxycytidine), has had only minor effects on improvements in SCNT efficacy in animals (Akagi et al., 2014; Whitworth & Prather, 2010).

Genomic Imprinting

Parental-specific gene expression is maintained by genomic imprinting, a form of epigenetic regulation that has evolved uniquely in eutherian mammals. Functional differences between paternal and maternal alleles have different imprinted gene expression profiles.

Imprinting control regions (ICRs) regulate the specific expression of single or multiple, in the same cluster, imprinted genes. One ICR specifically controls the imprinting of a single gene or multiple genes within the same cluster. ICRs impose epigenetic memories (imprints) during germline (oogenesis or spermatogenesis) development. Differentially methylated regions (DMRs) occur due to ICRs and canonical imprinting. During fertilization and implantation, germ-line derived DMRs are resistant to the broad genome-wide waves of genomic reprogramming. DMRs are thereby maintained through that germline to embryos and neonates. Given this persistent nature of DMRs, genomic imprinting can be maintained normally in SCNT embryos and their placentas (Inoue et al., 2002).

A recently discovered non-canonical form of genomic imprinting that depends on regulation by histone methylation (H3K27me3) is placenta-specific and is largely eliminated in the embryonic lineage (i.e. in somatic cells). Unique non-canonical imprinting is important in the imprinting disorders associated with SCNT. Non-canonical (H3K27me3-dependent) imprinting is associated with defective placental development in SCNT embryos (Lin et al., 2011). In a recent paper by Wang et al., 2020, deletion of the maternal allele from four genes (Gab1, Sfmbt2, Jade1/Phf17, and Smoc1) resulted in placental morphologies that were similar to normal, and the birth rate of clones was increased to about 14% (Wang et al., 2020). This demonstrated the involvement of non-canonical imprinted genes in SCNT-specific placental anomalies and associated poor embryo development rates to term.

Recent studies, involving the targeting of maternal alleles with an epigenome editing technology involving the dCas9-fusion system (Brocken et al., 2018) suggests that maternal H3K27me3 could be introduced into donor somatic cells or reconstructed SCNT embryos, which may contribute to improved SCNT efficiency.

Non-canonical imprinted genes largely disturb the development of mouse SCNT embryos in two ways: abnormal placental development by biallelic expressions of placenta-specific genes including Sfmbt2 miRNAs; and massive repression of X-linked genes in SCNT embryos by ectopic maternal expression of Xist.

The search for the totipotent genome signature and selection of reconstructed cloned embryos that have totipotent somatic cell genomes with equivalent ability to the normally fertilized oocyte genome is still ongoing. Yet perhaps the overall goal should be to identify those embryos that result in viable offspring. The presence of many thousands of cloned offspring attest, albeit at a low percentage, that totipotent reprogramming of the somatic donor cell does occur when using animal cloning technologies.

Paternal and Maternal-Specific Nuclear Reprogramming Strategies

The foundation of these types of approaches is to mimic the process of fertilisation. While the oocyte contains abundant genome organisation and molecular machinery it is unable to process nucelosomally genomes found in the terminally differentiated cell. However, the sperm protaminised nucleus is easily processed by the oocyte.

Modifying the genome in the somatic cell to a protamine-to-nucleosome ratio similar to that typically found in the spermatozoa of the studied species (Yoshida et al., 2018) could have significant consequences for animal cloning.

The sperm (paternal) approach is derived from the progressive expression of testis-specific proteins to drive male gametogenesis. Identification of nucleomorphogenesis pathways in sperm (Martínez-Soler et al., 2007) led to expression of protamine 1 in sheep fibroblasts that resulted in the appearance of interphase nuclei similar in shape to spermatid nuclei (Palazzese et al., 2018). This genome protaminisation was fully reversible after SCNT and IVC blastocysts rates was double that of the control SCNT groups. The production of cloned offspring is still required to validate this protaminisation approach (Czernik et al., 2016).

Maternal specific nuclear reprogramming involves reorganising the somatic donor cell genome to chromosomes-like structures found in the oocyte. While this approach is in its infancy, mature oocytes have highly accessible chromatin (Gu et al., 2019; Lu et al., 2016) that is enriched by specialized histones that have accumulated at universally high levels in the oocyte (McGraw et al., 2006; Zhang et al., 2018) Using insights from a *Xenopus* study, the accumulation of histones in mice oocytes at specific developmental stages to directly benefit reprogramming (Gao et al., 2004; Shinagawa et al., 2014; Wen et al., 2014), has shown remodelling of mouse somatic cell nuclei when transplanted into the germinal vesicle (GV) stage oocyte produced extensive transcriptional reprogramming resembling an oocyte-like state within 48 h (Miyamoto et al., 2018). Using an alternative approach involving selectively enucleated GV (SEGV) oocytes demonstrated that transferred somatic nuclei undergo a similar nuclear remodelling event, gaining a morphology and size similar to that of control GV-stage oocytes (Fulka et al., 2019).

Collectively these studies, offer new insights into improving universal nuclear reprogramming strategies that are required to re-establish post-nuclear transfer events following nuclear reprogramming.

Ethical Considerations and Rationale for Animal Cloning

Animal cloning, and the birth of cloned animals that look for all purposes like normal newborns have always captured the public attention. Despite 25 years of scientific research in this field, there has been little public discussion on the ethical and animal welfare issues raised by animal cloning. Scientific innovations have in the past proceeded faster than the bioethical dialogue. Early survey data suggests that the public is decidedly against the cloning of animals (Fiester, 2005; Saad, 2004) although there has been little evidence that the food value and acceptability of cloned offspring is any different to animals produced by natural breeding or other artificial reproductive techniques (see: European Food Safety Authority, 2012; Van Der Berg et al., 2020). Nevertheless, Animal Cloning studies have continued against the backdrop of relatively little public discussion of the science (Fiester, 2005) and in an environment with inconsistent regulations or governmental control

(Sinha et al., 2019). There is good reason to apply systems bioethics and developmental biology to the discussions of animal cloning in the same way as recommended for discussion and decisions for stem cell biology (Robert, 2006). This requires that sound science, ethics and policy evolve from a firm understanding of the cloning process and how it can be utilised to the benefit of animal welfare, environmental stability, maintenance of animal biodiversity and human well-being. This may be advanced if these fields of interest collaborate in the dialogue and open debates of the subject of nuclear transfer, gene editing and animal cloning.

With improved education and public discourse, perhaps including the broad umbrella of climate change and sustainability, around animal cloning and the development of specific applications of gene editing for human medical applications (see: Alberio & Wolf, 2021; Polejaeva, 2021) will further enhance the range of transgenic animals for medical application including: a goat model of the TGFβ1 gene, that is heart-specific and overexpressing, for studies on human atrial fibrillation; a CF transmembrane conductance regulator (CFTR) homozygous and heterozygous gene knock-out sheep models for cystic fibrosis research; the establishment of transchromosomic goats where a human artificial chromosome has been inserted in their genome, that comprises the whole human immunoglobulin gene (Ig) which expresses human Ig and the goats are responsive to immunization that enables production of human antibody products; sterile goats with the NANOS2 gene knock-out as a model for exogenous spermatogonial stem cell transplantation; an f508del cystic fibrosis sheep model to study the most common mutation in patients with this disease; pigs with a gene knock-out of α-1,3-galactosyltransferase and expressing human complement regulatory protein CD46 and human thrombomodulin, for organ transplantation to terminally ill patients. Hearts from these animals survived for more than 900 days when heterotopically transplanted to the abdomen of baboons, for up to 195 days as functional orthotopic transplants. Kidney transplants from these animals survived for 136 days in baboons. All these models have been achieved using animal cloning techniques.

Furthermore, attitudes to advances in improved animal welfare or the rescue of endangered species, appears to be changing to more positive view (McConnachie et al., 2019; Sandler et al., 2021). This also includes a willingness to consume products from these animals (McConnachie et al., 2019). For example, animal cloning when coupled to gene editing technologies has enabled spread of the naturally occurring POLLED gene with the resulting genetically hornless animals then not subject to the painful procedures used to remove the horns or horn buds (McConnachie et al., 2019). The rescue of the endangered black footed ferret to help extinction of this species (Sandler et al., 2021) and the potential to gene edit to reduce methane production in cattle suggest a wider public support may evolve for animal cloning and gene modification technologies when there are perceived benefits to both animals and the environment involved. The loss of animal populations due to the increasing occurrence and severity of bush fires, and other catastrophes, can be partly offset by cloning valuable livestock from recently deceased tissues to regain the herds or flocks for farmers that have spent decades or longer in their development. In many developed countries, tissue banks are maintained to

ensure genetic diversity is not lost due to concentrated genetic selection breeding methods or by accident, and cloning from such tissues enables the re-establishment of these livestock when needed or desired. Tissues recovered from wild and native animals from such disaster areas may also be banked and used to repopulate the recovering habitats to prevent biodiversity extinctions.

To advance discussion on the use of animal cloning technologies for livestock production and conservation strategies, requires a framework for evaluating animal cloning and gene editing technologies that provides clarity and reassurance for realising the potential of these technologies. The cooperative involvement from researchers, industry and public should include justification for the project, determination of the need to use the technology and considerations of the social ramifications of the project so that it is completed responsibly (See: Table 34.1, adapted from Sandler et al. (2021)). The goal is to provide an informed debate and decision-making process that should enable valuable, logical and sustainable applications of these new technologies (Cormick, 2019; Greenfield, 2021; Prakash et al., 2011).

Food and Safety – Debbie, Denise, Dianna and Daisy

Animal cloning procedures have raised ethical and biological concerns relating to the overall efficiency of SCNT, in utero and perinatal losses, shortened biological age, longevity and health of cloned offspring. These concerns threatened the viability of the animal cloning procedures and associated genetic modification technologies.

In utero losses, developmental abnormalities and neonatal morbidity were attributable, at least in part, to the culture of gametes and embryos, which contribute independently to epigenetic dysregulation at both imprinted and non-imprinted loci (Chen et al., 2017; Young et al., 2001).

Other health questions were raised relating to Dolly, when she was diagnosed with osteoarthritis and when terminal fragment restriction analyses of her genomic DNA appeared to support the concept of telomere shortening and premature ageing (Shiels et al., 1999). Additional animal cloning studies found telomeres to have rejuvenated during nuclear reprogramming (Marión & Blasco, 2010).

Retrospective radiographic assessments of the skeletons of Dolly, Megan and Morag reported a prevalence and severity of osteoarthritis no different to that of naturally conceived sheep of comparable age (Corr et al., 2017). However, a more recent long-term study involving four sheep using the cell line that gave rise to Dolly - Debbie, Denise, Dianna and Daisy assessed the long-term health outcomes of animal cloning in large animals. In the 13 sheep study, animal cloning has no obvious detrimental long-term health effects when compared to aged match groups of normally breed sheep (Sinclair et al., 2016).

Indeed, several studies over the years have concluded that cloned offspring which survive beyond the neonatal period are healthy, age normally, produce viable offspring and animal products safe for human consumption (Heyman et al., 2007; Sinclair et al., 2016; Watanabe, 2013; Yang et al., 2007).

Table 34.1 Animal cloning project assessment – rubric for conduct of ethical research

Type of Assessment	Analyses	Applicability
Goal Assessment		
Justification	Feasibility	Project Goals – Successful and Feasible Criteria
	Environmental Value	Economic/Environmental Impacts Protected and Promoted Benefits
	Social Value	Enhanced or safeguarded moral principles defined by society dynamics, institutions, | traditions and cultural beliefs
	Scientific Value	Excellence, Passionate, Integrity, Collaborative, Progressive and Respect
Level of Assessment	**Analyses**	**Appropriateness**
Means Assessment		
Responsibility	Opportunity Cost	Efficient and Effective Use of Resources Alternate use of Resources Sustainable use of Resources—less inputs, efficient, low-carbon economy.
	Competing/ Comparable Alternatives	I/P Freedom or Confidentiality More effective, immediate, lower cost, great chance of success.
	Animal Welfare	Direct and Unintended effects on animals Involvement and Impacted by.
	Ethical Research	Sensitive to Social and Cultural Values Avoid Bias and Conflicts of Interest
	Oversight	Accountability—Local, State and Global
Desirability Assessment		
Appropriateness	Public Support	Community Support Scientific Peer and Kinship Support Engaged with those affected by species, population and functional systems.
	Contextual Biases	Intersection with alternative attitudes or theories Challenge or Synergistic approach Objectivity vs Extraneous influences
	Project Management and Support	Collaborative/Collegiate Broad Support Organisational commitment and necessary resource allocation.

Adapted from Sandler et al. (2021)

In 2008, the US Food and Drug Administration (FDA) issued a formal risk assessment (RA) declaring food products from cloned cattle, pigs and goats safe for human consumption. Foods from animal cloning technologies are “no different” from foods from non-cloned animals and there is “no material difference” between cloned or other comparable organisms. Within the UK and EU, animal cloning for agricultural use in the EU and UK is in a limbo (European Food Safety Authority, 2012). No agreement between the EU Commission, who is in favour of approval,

and the EU parliament, who instead voted to ban cloning (European Food Safety Authority, 2012; Food & Drug Administration, 2008; Fox, 2008; Tanne, 2008).

Public perceptions and risks regarding Animal Cloning and GM foods have included unknown long-term or unintended effects on consumer health, animal welfare, and the environment. However recent research suggests that public perceptions are changing in relation to both the application of gene modification (heat stress and genetically modified polled cattle) that have the potential to improve animal welfare (McConnachie et al., 2019) and a willingness to consume products from these animals.

Today, animal cloning is very much in play in the commercial sector. Multiplication of livestock with particular genetic characteristics, production of cloned dogs and cats, post-mortem rescue, reproduction of castrated animals, and production of animal models for human pathologies. High genetic value cattle and pigs are reproduced *via* animal cloning on a commercial scale. Unlike other horse breeds, such as the English thoroughbred, reproductive technologies, including cloning, are allowed in polo horses. In South America, several commercial companies have produced in excess of 200 cloned horses. Dogs and cats and their importance as both companion and working animals has fuelled the emergence of cloning companies (Kim et al., 2018), that offer animal cloning in the cases of terminally ill or even deceased animals.

Conclusion: Animal Cloning, Gene Editing and Genetic Modification

The pursuit of scientific knowledge is valued because its application provides many basic human needs and economic improvements to living standards, but also because it is continually challenged from a rich diversity that empowers and drives our understanding of new science, innovation and opportunity. The arrival of "Dolly" the sheep, the first mammal produced by the transfer of a terminally differentiated cell nucleus into an enucleated egg heralded a new era, improving our understanding of cellular reprogramming as well as offering innovative reproductive opportunities for improved livestock breeding, regenerative medicine developments and endangered/extinct species conservation.

Dolly demonstrated nuclear equivalence amongst somatic cells and voided the previously held 1889 doctrine that cells of a developing organism lose developmental plasticity during differentiation. The methodology has proved consistent and adaptable to a wide variety of species. Many thousands of clones have been produced, predominantly from domesticated and laboratory animals. Conservation biologists are increasingly looking to this technology to address conservation challenges. The arrival of new technologies involving pluripotent stem cells from domestic animals, suggested that the animal cloning would be superseded. However, while these new technologies continue to be explored, they are yet to prove they are viable alternatives to animal cloning. Recently the entrance of precise gene editing

technology has seen a renaissance and refocus of animal cloning technologies. Specifically, new efforts have focused on improving epigenetic reprogramming events and incorporating the gene editing platform. Failing to address public sentiment on animal cloning might be expected to have serious implications for commercialisation and the acceptance of animal cloning products from agriculture to the medical and pharmaceutical industries.

The public's negative view and objections to animal cloning and genetic engineering can be comprehended on either consequentialist or deontological grounds (Rollin, 1981; Singer, 1975). The zoologist John R. Baker in 1945 proposed "the advancement of knowledge by scientific research has a value as an end in itself" also known as the "free-science" approach. His plea for the preservation of freedom of inquiry, for valid argument and insistence on the cultural value of science is pertinent. Cooperative involvement from researchers, industry and public suggests a framework for evaluating animal cloning and gene editing technologies would provide clarity and reassurance for realising the potential of these technologies.

Animal cloning has continued to evolve and develop since those pioneering experiments some 25 years ago. Recent gene editing developments suggest it will likely remain a valuable technology for years to come. Improved knowledge of the molecular mechanisms of cellular reprogramming and more efficient techniques of nuclear transfer will continue to keep the technology at the forefront. Coupled with other modern gene manipulation technologies will see solutions to urgent biomedical needs (animal models of disease, production of nutraceuticals), improvements to sustainable animal production (genetic selection and animal welfare) and preservation of critically endangered species for conservation (Hildebrandt et al., 2021). The debate around the transformative potentials of animal cloning for medicine, biodiversity and sustainable agriculture centres is underpinned by the safe and ethical use of advanced reproductive technologies in human medicine (e.g. mitochondrial transfer technologies for inherited genetic disease) and livestock production.

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Part VI
Animals, Food and Environment: *Decision Making and Alternatives to Animal Use in Research*

Chapter 35
Replacement, Reduction and Refinement: Ethical Considerations in the Current Applications of the 3Rs

Tamara Tadich and Ariel Marcel Tarazona

Abstract Scientific integrity is a modern paradigm of science and marks some regulatory principles of how to do research in the contemporary world. Among the relevant aspects of integrity is the proper use of animals, of all kinds, in research. Issues such as sentience and animal welfare have gained ground in public consciousness, which is increasingly demanding better quality in our relationships with other animals, in addition to putting pressure on the creation of public policies and regulations. To avoid pain and suffering that can be avoided, mitigate it when impossible to avoid, and minimize the number of animals used, the principle of the 3Rs (reduction, replacement and refinement) is applied. The application of this principle also seeks to obtain scientific results that are reliable. It is impossible to separate the task of science from ethical considerations; therefore, in this chapter some ethical considerations to contemplate when applying the principle of the 3Rs in relation to the use of animals in research are presented. The 3Rs continues to be a valuable principle that adapts to changes in the morality of humanity and whose application requires ethical considerations that include particularities of the historical moment, such as morality, culture, legislation, and scientific progress.

Keywords Reduction · Replacement · Refinement · Animal welfare · Ethics

Introduction

How human beings relate to other animals, the ethics behind these relationships, and their consequences now and in the future are aspects of growing societal interest, which shows an evident concern about the way we use animals in all areas:

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food, clothing, pets, entertainment and of course in research (Tarazona et al., 2020). One goal of modern science is its scientific integrity, which can be defined as the professional standards, values, and practices of the scientific community to ensure quality (academic objectivity, clarity, reproducibility, and usefulness), while preventing bias, fabrication, falsification, plagiarism, external interference, censorship and ensuring the ethical handling of information (Kretser et al., 2019). The ethically acceptable use of animals in research and their moral status has been discussed for decades. To date, no consensus has been reached regarding the moral duties of human beings toward animals (Miziara et al., 2012). Some authors consider that the use of animals in research that causes any kind of harm to them is immoral and therefore should be abolished (Regan, 2004), while others argue that if animals have certain basic moral rights, we should extend the regulatory principles from research with humans to other animals (Martin, 2022). Despite all efforts, using animals in research remains essential to test foods, drugs, and devices before being used in humans since security protocols require it, and even the most advanced systems fail to imitate the complex cellular interaction of living beings (Dahiya & Ogden, 2010).

The aim of this chapter is to address general ethical aspects of the application of the 3Rs that, with more than 60 years, are still valid and in constant evolution following the changes in paradigms of humanity.

The Value of the Individual and Its Ethical Implications

Each animal used in research is an individual. The probability of the existence of each animal whose reproduction is sexual, including the human being, is very low; this implies that we have greater ethical considerations and respect for other forms of life as unlikely as ours (Tarazona et al., 2020). The last is a good argument for minimizing the use of animal subjects in research, avoiding painful or aversive procedures, and mitigating pain if it is unavoidable. There is sufficient evidence to recognize that vertebrate animals and some invertebrates, (including cephalopods, decapods, and others), have neuroanatomical and biochemical mechanisms that allow them to feel, in addition to expressing voluntary behaviors (Broom, 2020). The 2012 Cambridge declaration of consciousness explicitly states: "The absence of a neocortex does not appear to preclude an organism from experiencing affective states. Convergent evidence indicates that nonhuman animals have the neuroanatomical, neurochemical, and neurophysiological substrates of conscious states along with the capacity to exhibit intentional behaviors. Consequently, the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Nonhuman animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates." (Low et al., 2012). New evidence is added every day beyond the declaration of consciousness. It is possible that the sentience to other taxonomic groups, including several species of invertebrates, will be recognized (Chapouthier, 2020; Villamor Iglesias, 2021). Additionally, discussions have already been made

regarding moral duties and animal welfare in invertebrates (Broom, 2013; Carere & Mather, 2019).

On the other hand, some groups of animals used in research have drawn the attention of scientists and public concern, such as dogs (Simmonds, 2018) and nonhuman primates (Arnason, 2020), possibly due to the empathy that we have with them. Curiously the UK, reported an increase in the number of dogs and nonhuman primates (NHP) of 22% and 17% from 2017 to 2018, respectively, even though the general use of animals decreased for the same period by 7% (Robinson et al., 2019). Intense discussions have been made regarding the ethical considerations of continuing its use in research (Beauchamp et al., 2014; Andersen & Winter, 2019).

The principle of ensuring animal welfare does not make research ethical if it does not have sufficient scientific value (Strech & Dirnagl, 2019). In addition, ethical considerations regarding the death of animals are essential when it becomes necessary at the end of the investigation or as an endpoint during its development; this is particularly important because death ends all possibility for the individual, and, therefore, the value of his existence ends. Although there is no evidence of death awareness in animals, it can be assumed that life has inherent value for them, and that survival and self-preservation are innate motivations. Therefore, the need to sacrifice animals in research should have ethical considerations (Dahiya & Ogden, 2010; Martin, 2022).

Thus, in this context, we can affirm that the moral obligation to use animals in research is expanding, and new aspects must be considered to meet public demands.

Where Are We Going?

The use of animals in research is a topic of public interest due to the change in the perception of humanity regarding our responsibility and moral duties toward other animals with whom we interact. However, the general idea of the public regarding animal research is usually negative; this has led to social pressure that has promoted regulations and public policies that seek to reduce the use of animals and improve the living conditions of those still used for this purpose. For example, the directive, 2010/63/EU of the European Parliament, which in article 1 states: "the replacement and reduction of the use of animals in procedures and the refinement of the breeding, accommodation, care and use of animals in procedures" that shows an intention over time to reduce the number of animals and replace them with other methods.

However, despite global concern about the decrease in the use of animals in research, the exact number of animals used annually in research worldwide is unknown. This is mainly because not all countries have official reports of the data, a recently published study calculates that approximately 192 million animals are used worldwide, a number higher than in 2005 (115 million). Even though enormous efforts to replace and reduce the number of animals in research, the data show an increase. The countries that use animals the most are China, Japan, and the USA (Taylor & Alvarez, 2019). It is expected that the construction of policies around the

use of animals in research will be expanded and include both scientists, public opinion, and ethicists (Hvitved, 2021).

Brief History of the 3Rs

For over a century it has been recognized that the way in which we treat animals in research can affect the experimental results, with correct handling considering animal welfare and ethical principles being a prerequisite for successful animal experiments. During the early 1950s Dr. William Russell was appointed by the Universities Federation for Animal Welfare (UFAW) to carry out a laboratory animal survey, with the aim to discuss the techniques used, attitudes to modifications and possibilities of animal replacement techniques (Balls, 2009).

As Rex Burch recalls, he contacted the Founder and Secretary General of UFAW, Major Charles Hume, and was also appointed to this project without knowing that this would be the start of the Three Rs framework (Burch, 1995). Their work culminated in the publication of the book "The principles of humane experimental technique" in 1959 (Russell & Burch, 1959), but the Three Rs had already been mentioned publicly by William Russell at the "UFAW Symposium on Humane Technique in the Laboratory", held in 1957 (Russell, 1957).

They were defined by Russell and Burch (1959) as:

- Replacement: The substitution of conscious living higher animals by insentient material;
- Reduction: Reduction in the number of animals used to obtain information of given amount and precision;
- Refinement: Any decrease in the severity of inhumane procedures applied to those animals, which still have to be used.

The Three Rs are internationally recognized as an ethical framework under which researchers should conduct experiments and are described in the order that they should be addressed (Hubrecht & Carter, 2019). In this chapter we will address them in this same order and highlight how each has evolved since the late 50s and the challenges researchers may face when applying them.

Application of the 3Rs and Their Ethical Implications

It is expected that in the future, the maximum reduction in the number of animals used in research will be achieved, and even some groups in society hope for its total abolition. However, while the use of animals in research is still necessary, the acceptance of a minimum of discomfort or pain to achieve maximum benefits (for humans, other animals and the environment), is conditioned to the standards acceptable by the law (especially regarding animal care, human safety, industrial research,

wildlife protection, environmental protection and transportation) and society (MacArthur Clark, 2018; Dahiya & Ogden, 2010). The 3Rs of replacement, reduction, and refinement have a sufficient rationale for their application to publicly justify animal use in research. The following guiding principles are fundamental when making ethical considerations in animal research and could well be implemented when considering the application of the 3Rs. The principle of no alternative method; the principle of expected net benefit; the principle of sufficient value to justify harm; the principle of no unnecessary harm; the principle of basic needs; and the principle of an upper limit to harm (Beauchamp & DeGrazia, 2020; DeGrazia & Beauchamp, 2021). The use of animals is acceptable when there is a lack of scientifically proven, recognized, and accepted method (including normatively) to carry out the required tests prior to use in humans; however, it is unacceptable that experiments continue to be carried out in the animal model in cases in which such alternative methods already exist and are tested and recognized (Rusche, 2003).

Replacement

The term "replacement technique" was first used for any scientific method employing non-sentient material which may in the history of experimentation replace methods which use conscious living vertebrates (Russell & Burch, 1959). The National Centre for the Replacement, Refinement and Reduction (NC3Rs) has updated this definition considering the available technology and capacities for experimentation nowadays to: "Accelerating the development and use of predictive and robust models and tools, based on the latest science and technologies, to address important scientific questions without the use of animals."

The former definition of replacement proposed mainly the substitution of vertebrates and proposed for example the use of octopus as a suitable replacement for an albino rat model for studies on visual discrimination according to studies from Sutherland (1958 and 1959). Today, cephalopods and some decapods have been recognized as sentient animals, and they would not be suitable as a replacement technique in many types of studies. On the other hand, the updated definition seeks that animals are not used at all.

Replacement can be applied as a "full replacement" when the use of animals is avoided. In this case human volunteers, tissue and cells, *in silico* models or established cell lines are used and they are collectively known as non-animal technologies (NATs). When these technologies are used for assessing chemical or drug toxicity, they are sometimes called new approach methodologies (NAMs) (NC3Rs, 2022). When full replacement is not possible, "partial replacement" can be applied by including animals that according to the current scientific knowledge are not sentient (capable of experiencing suffering). This includes the use of some invertebrate species such as Drosophila and *Caenorhabditis elegans*, and some immature forms of vertebrates (*Danio rerio*) (Doke & Dhawale, 2015; NCR3s, 2022).

During the twentieth century animals were used in many different research areas, however the advances in new technologies together with an increase in societal concern about the welfare of animals has led to the possibility of full replacement in many cases (Celentano, 2017). A database containing information for over 1000 modern NATs from diverse areas of biomedicine and life sciences can be found at www.nat-database.org. There are many examples of how animals have been replaced by *in silico* and *in vitro* techniques successfully. A good example of how advances in science have allow for full replacement is the obtainment, and later purity verification, of insulin. Until de 1980s, insulin was extracted from the pancreas of pigs and cattle and nowadays can be obtained from bacterial cultures to then check its purity, efficacy and dosage calculation by chromatography, steps that were also done with animals in the past (Doke & Dhawale, 2015). According to the World Health Organization (WHO, 2021) report on universal insulin access, worldwide there are 420 million people living with diabetes, from which an estimated nine million with type 1 diabetes and 63 million with type 2 diabetes rely on insulin as part of their treatments. This provides an idea of the relevance of having an alternative method for insulin production. Biomedical research, and in particular toxicological research in the pharmaceutical industry, has been showing positive advances that allow replacement of animals by the incorporation of alternative techniques (Törnqvist et al., 2014; Eskes, 2019). Nevertheless, there are other research areas where replacement is not possible, since the aim of the studies is to better understand the biology, behavior or ecology of particular species (Tadich et al., 2020). In these cases, special importance should be given to reduction and refinement techniques.

Reduction

The progress of replacement is gradual or may not apply to all experimental biology, therefore reduction also needs to be considered. Reduction was first defined as minimizing the number of animals used consistent with scientific aims (Russell & Burch, 1959). This definition has also been updated by the NC3Rs (2022) as "appropriately designed and analyzed animal experiments that are robust and reproducible, and truly add to the knowledge base". Reduction requires of different strategies to be achieved, among which an appropriate study design, use of adequate statistical methods in order to avoid loss of statistical significance, control of variability and over all a rigorous hypothesis are needed (Tadich et al., 2020). Törnqvist et al. (2014) showed that reduction within pharmaceutical toxicity testing could be achieved through three different strategies: improved study design, method development and coordination. Improved study designed was achieved by changing study designs based on experience, historical data or increased knowledge which resulted in optimized study designs and reduction of animal use. Method development was a result of more sensitive techniques optimizing the delivery of test parameters from the same animal instead of using different animals for each

parameter or the use of *in vitro* assays before testing *in vivo*. Coordination allowed a reduction in animal use through increased collaboration and communication between departments in the same institution. This enabled the possibility of sharing control animals and combining aims in a same group of animals when possible (Törnqvist et al., 2014).

Collaboration among scientists is a critical component of research worldwide, in particular when addressing complex problems in a context of rapidly changing technology, exponential growth of knowledge and highly specialized expertise (Hara et al., 2003). Animals used in research would benefit from multidisciplinary collaboration, which could avoid duplication of experiments and significantly reduce the number of animals used each year for scientific purposes.

Refinement

When for a particular study replacement is not possible and the number of animals used has been minimized, then refinement starts (Russell & Burch, 1959). Refinement consists in reducing to an absolute minimum the amount of distress imposed to the animals that will be involved in the experimental design (Russell & Burch, 1959). This definition has been updated to "advancing research animal welfare by exploiting the latest *in vivo* technologies and by improving understanding of welfare on scientific outcomes" (NC3Rs, 2022). Morton (1998) includes in the definition of refinement the use of methods that enhance animal wellbeing, emphasizing the need to not only avoid suffering, but to provide conditions that improve the quality of animals involved in research. This R is the most important aspect to consider in terms of the welfare of the individual animals. Animal welfare refers to the physical and mental state of an animal in relation to the conditions in which they live and die (WOAH, 2022), conditions that differ according to the experimental conditions, meaning that refinement needs to be adjusted for each specific situation. During an experiment the welfare of the animals could be affected by the housing conditions or by the experimental procedures being carried out, which could cause suffering.

Suffering consists in a wide range of unpleasant emotional states such as fear, boredom, exhaustion, pain, thirst, among others, that interrupt the quality of life of the individual experiencing them (Gregory, 2004). During research suffering can be "avoidable" when the experimenter applies appropriate will and competence, or "unavoidable" when suffering appears to be necessary to carry out the procedure, also described as "the minimum suffering necessary to achieve the scientific objective" (Morton, 1995). To avoid or mitigate suffering it is a prerequisite for researchers to understand the biological and behavioral needs of the species that they work with. One framework that can be considered for this is the five animal welfare domains proposed by Mellor et al. (2020) which includes consideration of the environmental, nutritional, health, behavioral and emotional needs of animals; the actions that should be taken in order to satisfy these needs and also the

physiological, behavioral and emotional consequences of not doing so on animal suffering. It can be difficult to meet all needs in the context of animal experimentation, but researchers should apply the most updated technologies and knowledge in order to minimize situations that could cause suffering. In order to promote animal welfare, researchers should not only consider the reduction of events that can induce poor animal welfare states but should also incorporate strategies that elicit good animal welfare or the promotion of a life worth living through positive affective states (Jirkof et al., 2019).

There are several environmental variables that are known to affect the quality of experimental results and thus research validity. Among these factors are those associated to the microenvironment or primary enclosure, which is the physical environment immediately surrounding it such as the cage, pen, or stall. The microenvironment contains all the resources with which the animals come directly in contact and is characterized by many factors, including illumination, noise, vibration, temperature, humidity, among others; and to the macro environment or secondary enclosure (room, barn, outdoor habitat) (Rowan, 1990; NRC, 2011). Environmental enrichment programs should be implemented in the microenvironment of the animal whenever possible. Environmental enrichment (EE) is defined as "how the environments of captive animals can be changed for the benefit of the inhabitants" (Shepherdson, 1994). EE programs are dynamic processes in which modifications of structures or husbandry practices are made with the aim of increasing the opportunity of animals to engage in appropriate behaviors, which are species specific, or to reduce the development of negative behaviors that can affect their welfare. Conventional cages for housing laboratory animals typically only contain food, water and a flooring substrate, these housing conditions can induce physiological and behavioral changes associated to poor welfare in the animals and thus result in failure of the experiments (Cait et al., 2022). On the other hand, enriched cages that include structures and materials that animals can manipulate allow them to perform some highly motivated behaviors, if we take rodents as an example, they are willing to pay a cost in order to have the opportunity to exercise, burrow and build nests, all behaviors that are highly rewarding (Bradshaw & Poling, 1991; Makowska & Weary, 2016; Sherwin et al., 2004).

Adequate handling or gentling from a young age can have a significant impact on data, however the way in which experimental animals need to be handled will vary according to the species. During experimental procedures animal handling is almost always unavoidable, resulting in a stress response which can act as a confounding factor in research, but may also affect animal welfare (Gouveia & Hurst, 2019). Refinement of handling techniques can mitigate these negative effects, for example Hurst and West (2010) showed that picking up mice by the tail induced aversion and anxiety, while the use of tunnels or open hand reduced these negative responses. Similarly, the 3D-handling technique for mice has also shown positive results with habituation to handling facilitating routine handling, improving animal wellbeing and decreasing data variability (Marcotte et al., 2021). In the case of rats, a handling technique that has shown to reduce stress responses is the implementation of

"tickling" by caretakers, which mimics the rat's rough and tumble play (Cloutier et al., 2018). Tickling not only elicits positive affective states in the rats, but also has positive implications for the caretakers (LaFollette et al., 2020).

When research is conducted with wild animals it is impossible to incorporate handling from a young age and habituation techniques since most times animals are captured, sampled and released. Any interventions done to these animals will have a direct or indirect impact on their welfare, thus researchers need to minimize these impacts (Soulsbury et al., 2020). Special consideration should be given to the capture technique, these should be adequate for the species that is being studied, reduce by-catch, be placed in appropriate areas and reduce the risk of injuries and mortality. Some risks associated to the technique, weather and species sex, age and size can be identified before the implementation of the capture technique, and researchers should consider them in their study design (Soulsbury et al., 2020). Once animals have been captured the total handling time required for physical sampling should be minimized and the use of anesthesia should be considered if it improves the safety of the animals and researchers. Other important refinement considerations are those associated to marking or tagging of the animals, housing conditions when required, transport and finally the release of animals when appropriate. For further recommendations on research ethics on wild animals please see ARRP policies and guidelines (2019), Lindsjö et al. (2016), the Code of Ethics from the Society for Conservation Biology (2019) and the Guidelines of the American Society of Mammalogists for the use of wild mammals in research and education (Sikes, 2016).

Within refinement the definition and effective implementation of endpoints is critical, the "experimental endpoint" corresponds to a point in time in which the aims of the experiment have been achieved and the study is concluded (NRC, 2011). On some occasions it may be necessary to end the experiment early due to animals experiencing unnecessary pain, distress or other forms of suffering, in this case a "humane endpoint" or "ethical endpoint" needs to be considered by the researchers in which the animal is removed from the experimental design either to be treated or if necessary, apply euthanasia. Morton (2000) describes a systematic approach for establishing a criterion for this type of ethical endpoint which requires researchers to design a score sheet system for supervision of signs of suffering. This score sheets include a list of observable and measurable signs that can be identified and scored by the caretakers, when one or a combination of signs are observed the decision to remove the animal from the experiment and apply adequate suffering mitigation strategies should be implemented. A useful resource for identifying and implementing endpoints is the "Humane endpoints in laboratory animal experimentation" website (www.humane-endpoints.info/en) developed by the 3Rs-Centre, Utrecht Life Sciences. To determine which are the best euthanasia protocols according to species the latest edition of the "AVMA Guidelines for the Euthanasia of Animals" (AVMA, 2020) provides a complete description of the acceptable methods according to species and environment.

Challenges Associated to the Use of Animals in Research

There are many factors that can influence scientists work with animals in research, including social, economic, legal and institutional aspects (Hobson-West, 2012). All these factors can end having an effect on the welfare of animals, and thus should be considered. Social acceptability of research with animals has changed over the last decades and requires a social contract between scientists and researchers funded on mutual trust (Davies et al., 2016). Although the regulation of animal research has increased worldwide, there are still differences among countries regarding legal minimum standards. Nevertheless, there are common guiding principles recognized internationally, including the application of the 3Rs approach (Fontana et al., 2021). In Fig. 35.1 you can find some guiding questions that facilitate the applications of the 3Rs when planning research that involves the use of animals.

There is a widespread concern about the lack of reproducibility of animal research and science in general, the relevance of results and the failure in translating them from animals to humans (van der Worp et al., 2010; Olsson & Franco, 2015; Fanelli, 2018). A proper implementation of the 3Rs is essential to increase reproducibility by a thorough planning of the experiments involving animals. The Planning Research and Experimental Procedures on Animals: Recommendations for Excellence (PREPARE) guidelines allow researchers to increase their attention to details before the start of their experiments. The PREPARE guidelines aims to incorporate the needs of all stakeholders involved in the study design, such as animals, technicians, veterinarians, caretakers, among others, by covering 15 topics that cover from legal aspects and costs up to the consideration of appropriate euthanasia methods (Smith et al., 2018). In a similar way, the Animal Research:

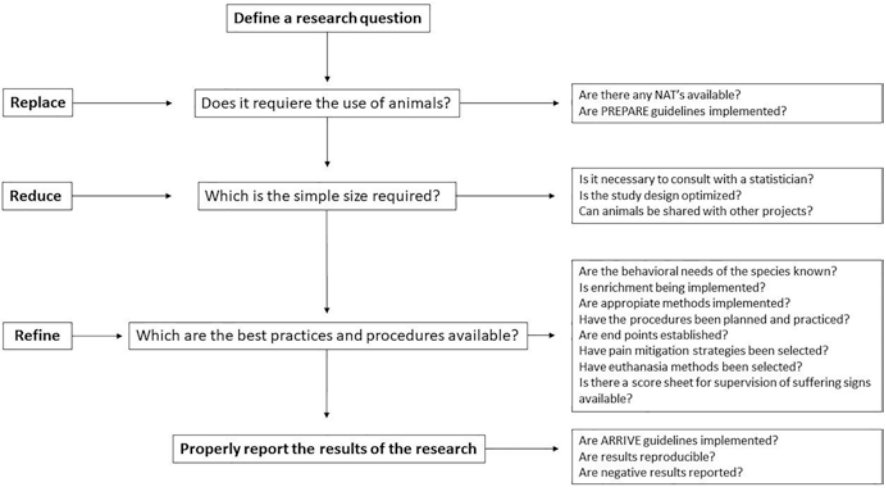

Fig. 35.1 Decision tree with guiding questions to be considered by researchers when designing a study with animals

Reporting In Vivo Experiments (ARRIVE) guidelines were developed to improve reproducibility of research involving animals through transparent and accurate reporting since many publications fail to include key information (Kilkenny et al., 2010; Percie du Sert et al., 2020). The ARRIVE guidelines contain 10 essential minimum reporting requirements associated to: study design, sample size, inclusion and exclusion criteria, randomization, blinding, outcome measures, statistical methods, experimental animals, experimental procedures, and results. All of this allow reviewers to better scrutinize the studies and to understand how the 3Rs have been considered and applied by scientists. Over 1000 scientific journals have adhered to these guidelines and recommend authors to follow them in order to improve the quality and transparency of research (Tadich et al., 2020).

Scientists' attitudes towards animal welfare and ethics are crucial for a correct implementation of the 3Rs. In many cases training in aspects of ethics, animal welfare, skills and competency for conducting animal research is mandatory, but should always be promoted. Franco and Olsson (2014) reported that 58% of participants in laboratory animal science courses were unaware of the 3Rs principle, while one year after taking the training course 96% of participants were able to correctly name them. Another interesting finding was that the majority of participants reported that the course made them more aware of animal welfare and that it allowed them to integrate the 3Rs into their own experiments (Franco & Olsson, 2014). Implementing training courses can be a challenge in institutions that do not have a well implemented Institutional Animal Care and Use Committee (IACUC) or where no legal requirements exist.

Although scientists are free to generate scientific questions, this must be done with responsibility, in particular when the methods to address those questions involve animals. It is clear that there is a close relationship between scientific quality and ethics in animal research (Brill et al., 2019). Societal concern about the way in which we treat animals is increasing and as scientists we have a duty to adhere to the highest ethical standards. The 3Rs principle established by Russell and Burch (1959) represents minimum standards and the fourth R for Responsibility proposed by Banks (1995) should always be present in order to advance in knowledge and improve the welfare of animals involved in research.

The New Rs and the Future of Animal Research

Reduce, replace, and refine directly address the ethical principle of animal welfare by reducing the number of animals and avoiding unnecessary discomfort and suffering; however, it does not encompass the ethical principle of the scientific value of research. Given this, Strech and Dirnagl (2019) proposes expanding the reference framework towards 6Rs, including Robustness, Registration, and Reporting as operating principles that guide to ensure ethics in animal research. Other proposals have been made to include principles such as Responsibility, Reproducibility, or Rigour. However, these broad principles are included in the definition of scientific integrity

and do not make a direct and specific contribution to ethical aspects of animal research.

Other aspects to consider, are to include the guidelines for research with human beings to research with animals and take into account aspects of acceptability such as social value; scientific validity; independent review; fair subject selection; favorable risk-benefit ratio; informed consent; and respect for research subjects (Martin, 2022). For example, because animals cannot express their opinion, it would seem that informed consent would not fit. However, there are human groups that cannot express their consent (infants, people with mental problems, or people in a coma), and this does not exclude them from investigations that potentially bring benefits; therefore, investigations of minimal risk that do not represent damage or affectation are allowed. Although not yet widely accepted for animal research, such considerations are likely to be included in future guidelines or regulations.

Therefore, it is suggested that they be taken into account in ethical discussions of the use of animals in research.

Final Remarks

Considerations on aspects in the use of animals in research cannot be separated from the direct consequences on individuals, the consequences on the quality of the results and the perception of the general public. It has to be considered that minimum legal requirements for the use of animals in research do not necessarily meet minimum ethical standards, thus the responsibility of thoughtfully designing experiments largely falls on researchers. This requires a deep knowledge of the behavioral needs of the animal species being used, and of ethical principles. Some proposals for ethical considerations and guiding questions are made before making decisions regarding the use of animals in research and the application of the 3Rs.

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Chapter 36
Integrating Human and Nonhuman Research Ethics

Jeff Sebo

Abstract I argue for developing a unified moral framework for assessing human and nonhuman subjects research. At present, our standards for human subjects research involve treating humans with respect, compassion, and justice, whereas our ethical standards for nonhuman subjects research merely involve (half-heartedly) aspiring to replace, reduce, and confine our use of nonhuman animals. This creates an unacceptable double standard and leads to pseudo-problems, for example regarding how to treat human-nonhuman chimeras. I discuss general features that a more integrated moral framework might have, assess the pros and cons of this kind of this framework, and suggest that the pros decisively outweigh the cons.

Keywords Research ethics · Nonhuman animals · Moral frameworks · Human and nonhuman subjects research · Three Rs.

Introduction

At present, we accept radically different moral frameworks for assessing human and nonhuman subjects research. On one hand, we accept a very high standard for morally permissible human subjects research, according to which we are morally required to treat humans with respect, compassion, and justice. On the other hand, we accept a very low standard for morally permissible nonhuman subjects research, according to which we are merely required to replace, reduce, and refine our use of nonhuman animals to the extent that doing so is compatible with achieving our scientific goals. The result is that we categorically forbid a wide range of harmful, lethal, nontherapeutic, nonconsensual research on human subjects while generally permitting such research on nonhuman subjects.

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We treat human and nonhuman subjects differently not only because we accept different moral frameworks for human and nonhuman subjects research, but also because our assessment of this research takes place in a cultural and institutional context that heavily favors humans over nonhumans. When all decision-makers are human, we can expect human bias to affect our application of moral principles. And when educational opportunities, occupational opportunities, and research teams, facilities, and technologies center on a particular kind of research – in this case, nonhuman subjects research – we can expect these factors to affect our application of moral principles too. As a result, not only do we accept lower standards for our treatment of nonhuman subjects, but we also take less care in our application of these standards.

These different approaches to human and nonhuman subjects research constitute an unacceptable double standard, and they also create pseudo-problems in research ethics. In particular, these different approaches lead us to treat humans and nonhumans differently in ways that cannot plausibly be justified on the basis of species difference alone. As a result, they also lead us to ask ethical questions that we might otherwise be able to avoid. For example, many people wonder how we should treat human-nonhuman chimeras. Should we apply "human" standards to them and treat them very well, should we apply "nonhuman" standards to them and treat them very poorly, or should we strike a balance between these extremes? Yet this question would be nonsensical with a more principled, integrated approach to research ethics.

In this chapter, I discuss our current, highly fragmented moral frameworks for assessing human and nonhuman subjects research and make the case for a more integrated approach. I suggest that a more integrated approach would require us to treat all sentient beings with respect, compassion, and justice, but would also allow us to treat different animals differently on the grounds that, for instance, different animals have different interests, needs, and other morally relevant features. This more integrated approach has benefits and risks; for instance, it makes our approach to research ethics more consistent and principled, but it also risks obscuring important differences across species and compromising scientific and medical progress. But I suggest that the benefits decisively outweigh the risks, particularly if we mitigate the risks.

Before I begin, I should make a couple of caveats about my approach to this chapter. First, I will assume in this chapter that all sentient animals – that is, all animals who are capable of consciously experiencing positive and negative states like pleasure and pain – have moral standing – that is, morally matter for their own sakes, and so we morally ought to consider their interests and needs when deciding how to treat them.[1] I will also assume that, even if all sentient animals have moral standing in this sense, we can still be justified in treating different animals differently if they have different interests, needs, or other morally relevant features.[2]

[1] For a classic consequentialist argument for this idea, see Singer, 1975, and for a classic nonconsequentialist argument for this idea, see Regan, 1983.

[2] For an argument that we should treat different animals differently in light of their capacities, see Kagan, 2019. For an argument that we should treat them differently in light of our relationships with them, see Palmer, 2010.

Of course, not everyone will agree with these assumptions. But ethicists have spent decades defending them, and my aim here is to build on that work rather than replicate it.

Second, I will not assume a particular moral theory – such as utilitarianism, rights theory, virtue theory, or care theory – in this chapter, nor will I attempt to flesh out the details of a more integrated approach to human and nonhuman subjects research ethics. Instead, I will discuss the general features that I expect a more integrated approach to have, focusing on features that can serve as the basis for "overlapping consensus" among different moral theories.[3] And I will assess the general benefits and risks of a more integrated approach in these terms. I will also discuss further questions that we need to answer as we flesh out the details, for instance concerning how to assess the nature and strength of nonhuman interests and rights. But I will not attempt to answer these further questions here.

The Human Paradigm

In general, the human subjects research paradigm assumes a rights-based moral framework. We assume that treating humans well involves more than simply increasing human happiness and decreasing human suffering in the aggregate. It also means treating humans with respect, compassion, and justice along the way, by respecting human autonomy and balancing the benefits and burdens that we impose on individuals and groups. As a result, this rights-based moral framework tends to prohibit research that would impose excessive burdens on vulnerable individuals or populations – particularly when they are not capable of providing informed consent and when we are not capable of providing them with compensatory benefits – even when this research has the potential to produce valuable knowledge.[4]

Consider each of these points in turn. First, human subjects research tends to place a high premium on *respect* for research subjects. In particular, we aspire to respect the autonomy of research subjects as much as possible. When humans are capable of providing informed consent, we require that researchers secure informed consent. Otherwise we proceed by seeking informed consent from relevant third parties, as well as by seeking assent or dissent – that is, an expression of approval or disapproval with respect to particular interactions – from the research subjects. And in the case of particularly harmful or risky research, we simply decide not to proceed at all. We also set a high bar for consent, for example by treating humans as incapable of consent in cases where they face strong economic pressure to say "yes."

Second, and relatedly, human subjects research tends to place a high premium on *compassion* for human research subjects. We generally limit how many harms and risks we can impose on human research subjects, even when they provide informed

[3] For discussion of the idea of overlapping consensus, see Rawls, 1987 and Fleischacker, 2011.

[4] For general discussion of the ethics of human subjects research, see Resnik, 2018.

consent, and even when this harmful or risky approach is necessary for the science. We also generally allow research subjects to stop participating in research at any point, without retribution, and we allow flexibility in the timing or location of office visits, medicine administration, and other activities so that research participation can fit into a full life. While these accommodations might make research less efficient, they are necessary as a matter of both respect and compassion, since they allow for sustained consent from, and care for, research subjects.

Third, and also relatedly, human subjects research tends to place a high premium on *justice* for human research subjects. As noted above, we attempt to avoid conducting excessively harmful research on vulnerable humans, particularly when they lack the ability to provide informed consent and when they lack access to meaningful alternatives (Grady, 2005). And when we do conduct harmful research on vulnerable humans, we attempt to compensate not only the research subjects but also their communities, for instance by making sure that resulting benefits are accessible to community members (Bracken-Roche et al., 2017). Otherwise we risk a situation where the burdens of research flow disproportionately to the worst-off among us and the benefits of research flow disproportionately to the best-off among us.

In light of these considerations, we generally set a high bar for morally permissible human subjects research. In particular, we generally hold that this research is morally permissible only when it respects human autonomy, limits harm to individuals and communities, and provides compensatory benefits to individuals and communities. As a result, we prohibit many studies that might produce valuable knowledge on the grounds that they fail to satisfy one or more of these criteria. In short, when it would be impossible to (a) secure informed consent from potential research subjects or guardians such as parents, (b) limit the harms that we impose on individuals or communities, or (c) compensate individuals or communities for the harms that we impose on them, we generally decide not to proceed.

Indeed, one might even argue that the bar for morally permissible human subjects research is sometimes *too* high. For example, during the COVID-19 pandemic, many bioethicists called for human challenge trials that would expose consenting adults to a controlled dose of COVID-19 in a controlled setting rather than wait for them to catch any amount out in the world.[5] But even though many humans volunteered to participate, and even though the expected benefits of this approach clearly outweighed the expected harms, our leaders generally decided not to pursue human challenge trials because they felt that the risks were too high.[6] Many other cases have similar features, raising the question whether we sometimes forbid human subjects research that we should have permitted instead.

[5] For an open letter signed by many bioethicists, including me, see here: https://www.1daysooner.org/us-open-letter

[6] The UK permitted small COVID-19 challenge trials to proceed in October 2020, but even this approval occurred nearly a year after vaccines were ready for testing (Callaway, 2020).

The Nonhuman Paradigm

In contrast, the nonhuman subjects research paradigm assumes a welfare-based moral framework. We assume that nonhuman animals have welfare but not rights, and we also assume that human interests generally trump nonhuman interests. As a result, we do not aspire to treat nonhumans with respect, compassion, and justice in the same ways that we do with humans, particularly vulnerable humans. Instead, we aspire to follow the "three Rs." That is, we aspire to replace, reduce, and refine our use of nonhumans where possible, while allowing ourselves to perform harmful, lethal, nonconsensual, nontherapeutic research on nonhumans where "necessary." And we define 'necessity' simply in terms of what means are necessary to achieve a particular scientific or medical aim.[7]

Consider each of these points in turn. We do not aspire to treat nonhumans with respect, compassion, or justice in the same ways that we do with humans, particularly vulnerable humans. First, we do not seek informed consent from guardians or assent or dissent from research subjects nearly as much as we do with humans. Second, we do not aim to limit the harm that we cause nonhumans nearly as much as we do with humans, nor do we aim to compensate them for harm caused nearly as much as we do with humans. Third, we do not aim to distribute the benefits and burdens of research equitably across human and nonhuman populations. And insofar as we consider human and nonhuman welfare in harm-benefit analyses, we tend to prioritize human welfare over nonhuman welfare.

Instead, we aspire to follow the three Rs in nonhuman subjects research. According to this method, when we evaluate proposed nonhuman subjects research, we start by asking: Can we achieve the same goals without using animals at all? If so, we should. If not, then we ask: Can we achieve the same goals while using fewer animals? If so, we should. Either way, we then ask: Can we achieve the same goals while harming each animal less? If so, then we should. If not, then we generally permit the harm. In theory, this method allows us to harm animals insofar as, and only insofar as, we need to do so in order to achieve our scientific or medical aims. In practice, this method allows us to conduct harmful and lethal research on an estimated 100+ million nonhumans per year (Taylor & Alvarez, 2020).

As this description makes clear, the nonhuman subjects research paradigm thus defines 'necessity' in terms of what means are necessary to achieve a particular scientific or medical end. As we have seen, in the human case we generally allow ethics to trump science, prohibiting harmful, lethal, nonconsensual, and nontherapeutic studies *whether or not* we see them as necessary for achieving particular scientific or medical ends. In contrast, in the nonhuman case we generally allow science to trump ethics, permitting such studies when we see them as necessary for achieving particular scientific or medical ends. Put differently, in the human case we

[7] For general discussion of the three Rs, see Russell et al., 1959.

remember that instrumental rationality requires *either* taking the means *or* giving up the end, but in the nonhuman case we tend to forget that we have the second option.[8]

In light of these considerations, we generally set a low bar for morally permissible nonhuman subjects research. We proceed on the assumption that a wide range of harmful, lethal, nonconsensual, nontherapeutic, animal studies are morally permissible on the grounds that they have the potential to produce "knowledge worth having," and that no alternative methods currently available to us have the same potential.[9] The result is that we currently breed, raise, harm, and kill millions of nonhuman animals per year in order to produce epistemic and social benefits for humans. And while we do provide (varying levels of) care to these animals, we still treat them in ways that we would never treat humans – particularly humans who are incapable of providing informed consent – in modern science and medicine.

While we can debate whether or not the bar for morally permissible human subjects research is sometimes too high, there is no debating that the bar for morally permissible nonhuman subjects research is, in the vast majority of cases, far too low. We should treat humans and nonhumans alike with respect, compassion, and justice, taking into account both the similarities and differences across species. And if this is right, then we should discount nonhuman welfare much less than we do, harm nonhuman animals much less than we do, and benefit nonhuman animals much more than we do. In short, the only possible justification for the status quo is the view that nonhuman interests carry either no weight at all or vanishingly little weight, and this view is simply not morally acceptable.

The Cultural and Institutional Context

Unfortunately, the ethical gap between human and nonhuman subjects research oversight is even greater in practice than in theory, since our application of the principles of human subjects research ethics is much more rigorous than our application of the principles of nonhuman subjects research ethics, due to the cultural and institutional context of each kind of research. In particular, when everyone involved in the decision-making process is human, it can be easy to let that affect our decisions. And when our research infrastructure is built to support particular kinds of research, it can be easy to let that affect our decisions as well. The result is that we achieve respect, compassion, and justice for humans much more than we achieve replacement, reduction, and refinement for nonhumans.

For instance, consider how we use harm-benefit analysis in nonhuman subjects research. We think: On one hand, this study will harm many animals. On the other hand, this study has the potential to contribute to scientific progress, and if it does,

[8] For discussion of the idea of 'necessity' in nonhuman subjects research, see Ferrari, 2019.

[9] For discussion of the idea of knowledge worth having, see Eggel et al., 2020 and Sebo & DeGrazia, 2020.

then it has the potential to benefit *very* many humans. In other words, we reason that the expected benefits outweigh the expected harms, since even though the probability of benefit is very low, the level of benefit is high enough to compensate for that. And given the nature of science, it can be hard to predict which studies will contribute to scientific progress, and which contributions to scientific progress will, in turn, produce social benefits. As a result, this reasoning can seem persuasive with respect to a wide range of harmful, lethal studies (Sebo & DeGrazia, 2020).

But notice how this application of harm-benefit analysis stacks the deck in favor of harming animals. We consider long-term benefits for humans via scientific progress, but not long-term risks for humans via false positives or negatives in toxicity or efficacy, long-term risks for nonhumans via normalization of exploitation and extermination, or opportunity costs for humans and nonhumans via neglect of animal-free alternatives. We also credit scientific progress to animal research without considering the counterfactuals, that is, without considering whether we might have produced the same benefits via animal-free alternatives, without producing the same costs. And we merely aim to do more good than harm rather than aiming to do as much good and, perhaps more importantly, as little harm as possible (Bass, 2012).

Our application of the Three Rs is similar. When evaluating harmful, lethal nonhuman subjects research, we tend to decide that replacing the use of animals is impossible when we are unaware of, or unprepared for, animal-free alternatives. We also tend to set limits on how much we can reduce and refine our use of animals, since, for instance, we might need to use a particular number of animals for our findings to be valid, and we might need to forego many methods of reducing harm to animals or increasing support for animals because we think that these methods will undermine the science or because we see them as too expensive. For instance, we kill instead of retire the vast majority of lab animals partly to collect further data and partly because there are simply too many for us to affordably retire.

That we assess nonhuman subjects research in these ways is predictable given the cultural context of this work. Everyone involved in the decision-making process, from the researchers proposing the research to the committees evaluating the research to the policy-makers supporting this activity to the community members electing the policy-makers, is human. We all have human interests and perspectives, and we are all vulnerable to self-interest, speciesism, status quo bias (that is, a bias in favor of the status quo), scope insensitivity (that is, insensitivity to the significance of numbers), and other human biases. We also make these decisions in a cultural context that assumes human exceptionalism and the moral permissibility of nonhuman exploitation and extermination for human purposes.

That we assess nonhuman subjects research in these ways is also predictable given the institutional context of this work. In some jurisdictions, people see animal research as part of the best, if not the only, possible route to approval for new foods or drugs.[10] Additionally, many research teams and facilities are built for

[10] For example, see this page from the United States Food and Drug Administration website: https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-information

animal research. These factors make people more likely to believe that animal research is ethically, legally, or, at least, practically necessary. The result is a kind of institutional path dependence, where everyone assumes that animal research is necessary, and senior scholars create educational and occupational opportunities for junior scholars accordingly. The "need" for animal research then becomes a self-fulfilling prophecy, made apparently true by our failure to invest in animal-free alternatives.

Double Standards and Pseudo-Problems

As a result of these different moral frameworks, as well as these different cultural and institutional contexts, we currently have an unacceptable double standard in human and nonhuman subjects research ethics. We treat humans much better than we treat nonhumans, to a degree that cannot plausibly be justified by species differences alone. This double standard reveals inconsistency and creates pseudo-problems. For instance, many people wonder how we should treat human-nonhuman chimeras: Should we treat them well, like we treat humans, or should we treat them badly, like we treat nonhumans? But many of these questions arise only because our approach to research ethics is so unprincipled and inconsistent. They would disappear entirely with a more principled and consistent approach.

To be clear, my claim here is not that we should treat humans and nonhumans the same way. As Peter Singer famously argued, equal consideration is compatible with differential treatment (Singer, 1975). For instance, to the degree that humans and nonhumans have different interests and needs, we might have different moral duties to them accordingly. To the degree that some animals have stronger interests and needs than others, we might have stronger moral duties to the former animals accordingly. And depending on which moral theory we accept, we might also think that we have different, or stronger, duties to some animals than to others in light of our relationships other features of our context; for instance, we might think that we owe more to animals we have harmed than to animals we have not (Palmer, 2010).

So when I say that we currently have an unacceptable double standard in human and nonhuman research ethics, I am not merely saying that we treat humans and nonhumans differently. I am saying that these differences cannot plausibly be justified by differences in interests, needs, histories, relationships, or other morally relevant features. For instance, even if we accept that we should generally prioritize humans on the grounds that humans generally have stronger interests and needs and we generally have stronger histories and relationships with them, that would still not justify a status quo that, on one hand, mostly forbids consensual and only moderately risky human challenge trials and, on the other hand, mostly permits harmful, lethal, nonconsensual, nontherapeutic nonhuman subjects research.

This double standard reveals inconsistency. Either we are forbidding too much human subjects research, we are permitting too much nonhuman subjects research, or we are doing some combination of the two. Of course, there is a danger in making

such a point. The danger is that we might decide to resolve this inconsistency not by treating nonhumans much better but rather by treating humans much worse. I will consider that possibility below. But for now, it is enough to state that this inconsistency exists, that we need to resolve it, and that we should resolve it (at least in part) by treating nonhumans much better, not by treating humans much worse. The only question is how to flesh out the details, both in our development of new ethical standards for nonhuman subjects research and in our application of these standards.

This double standard also creates pseudo-problems. For instance, many people are currently developing human-nonhuman chimeras for research and transplantation. The basic idea is that we want animals who are human-like enough for research to be human-relevant and for transplantations to be human-compatible, yet who are nonhuman-like enough that we can permissibly harm and kill them in ways that we could never permissibly do with humans. Many people are also concerned about new moral questions that these animals raise, such as: Which moral framework should we apply to human-nonhuman chimeras? Should we apply human standards to them and treat them very well? Should we apply nonhuman standards to them and treat them badly? Or should we strike a balance between these extremes?[11]

However, this entire line of reasoning presupposes our current, unacceptable double standard between human and nonhuman research. After all, if we eliminated this double standard, then we would eliminate the rationale for most (in vivo) chimera use, since we would accept a presumption against harmful, lethal, nonconsensual, nontherapeutic research for humans and nonhumans alike, rather than accepting this presumption much more for humans than for nonhumans. We would also eliminate the new questions that human-nonhuman chimera use raises, since our aspirations for human-nonhuman chimeras would match our aspirations for all animals: to treat them with respect, compassion, and justice, and to replace, reduce, and refine our use of them as much as possible with those principles in mind.

Toward an Integrated Moral Framework

It would take much more space than I have in this chapter to develop and defend an integrated moral framework for human and nonhuman subjects research. So I will not attempt to do that here. Instead, I will attempt to lay the groundwork for this project, by describing and motivating some general features that I expert this moral framework to have, as well as some hard questions that we will need to answer as we develop it. In particular, I expect that this framework will combine the human and nonhuman paradigms by requiring us to treat all sentient animals with respect, compassion, and justice while replacing, reducing, and refining our use of them where possible. I also expect that this framework will allow us to treat humans and nonhumans differently insofar as their individual circumstances warrant that.

[11] For discussion of these issues, see Hyun, 2016.

First, I expect that an integrated framework will require us to treat all sentient animals with respect. To the degree that animals are capable of consent (which, at present, might apply only within humanity), that means allowing them to provide informed consent to harmful or risky research. To the degree that they are not, that means (a) adopting a presumption against harming or killing them for non-therapeutic reasons, (b) appointing a representative to make decisions on their behalf with their interests and needs in mind, and (c) allowing them to assent or dissent to particular interactions to the degree that they are able. This is how we treat humans, including humans who are capable of consent and humans who are not. If we value both respect and consistency, then we should treat nonhumans similarly.

Second, I expect that an integrated framework will require us to treat all sentient animals with compassion. That means considering animal welfare in harm-benefit analyses, as I will discuss in a moment, and it also means reducing harms and increasing benefits for nonhuman research subjects. As with humans, we should set a limit on how much we harm nonhuman research subjects, even if they assent to the harmful activity, and even if the harmful activity is necessary for the science. We should also create the conditions necessary for nonhuman research subjects to live full, happy, and healthy lives, both during research, via species-appropriate enrichment, and after research, via species-appropriate retirement. And we should allow enough flexibility in research practices that participation can fit into a full nonhuman life.

Third, I expect that an integrated framework will require us to treat all sentient animals with justice. In general, we should aspire to distribute the benefits and burdens of research equitably within and across species. That means, first, that we should compensate nonhuman animals for participation in research by benefiting them at least as much as (if not much more than) we harm them. It also means that we should generally avoid distributing the burdens of this research disproportionately to nonhumans and the benefits of research disproportionately to humans. These principles imply that we should avoid harming nonhumans more than we can benefit them in research, which, in turn, implies that we should harm them *much* less and benefit them *much* more than we currently are, as a matter of respect, compassion, and justice.

Fourth, and relatedly, I expect that an integrated framework will require us to *improve* our use of harm-benefit analyses. In general, we should consider all relevant expected impacts, taking into account both the probability and level of benefit and harm for everyone involved. We should also take into account all relevant counterfactuals and aim to do as much good and as little harm as ethically possible rather than merely more good than harm. While the results will naturally vary from case to case, the general result is likely to be that we will permit fewer harmful nonhuman studies, since we will discover that these studies produce fewer expected benefits (once we consider counterfactual impacts) and more expected harms (once we consider long-term risks), and we will likely also set a higher bar for acceptable harm.

Fifth, and also relatedly, I expect that an integrated framework will require us to *supplement* our use of harm-benefit analysis. After all, even if we accept a welfarist moral theory such as utilitarianism, we might still think that rules, rights, virtues, relationships, and other such factors have an important role to play in promoting human and nonhuman welfare. For instance, when we implement systems of rules and rights, we increase the chance that humans will treat nonhuman populations well rather than use biased harm-benefit analyses to rationalize harming nonhumans to benefit humans. And when we cultivate antispeciesist beliefs, values, and habits and build antispeciesist social and professional environments, we create the conditions necessary for people to be motivated to follow these rules and respect these rights (John & Sebo, 2020).

Sixth, I expect that an integrated framework will still include the Three Rs, but with much more emphasis on all three, particularly replacement. If we aspire to treat humans and nonhumans with respect, compassion, and justice, and if we aspire to both improve and supplement our use of harm-benefit analysis accordingly, then it follows that we should aspire to replace, reduce, and refine harmful human and nonhuman subjects research as much as possible. In particular, there is simply no way that we can follow the above principles while maintaining anything like current levels of harmful nonhuman subjects research. Instead, the only way that we can follow these principles is by developing animal-free alternatives as much as possible, and changing our cultural and institutional structures to accommodate them (Herrmann et al., 2019).

Seventh, I expect that an integrated framework will still allow for different standards of treatment for humans and nonhumans, but much less than the status quo does. For instance, we might think that we can permissibly prioritize an individual human over an individual mouse, on the grounds that the human has more and stronger interests than the mouse. But even if we accept that, note two caveats. First, we might not always be permitted to prioritize humans for such reasons, since humans might not always have more, or stronger, interests than nonhumans, either individually or, especially, collectively (given how many nonhumans there are). Second, even when we *are* permitted to prioritize humans for these reasons, we might still be required to prioritize nonhumans much more than we do, both individually and, especially, collectively.

Eighth, I expect that an integrated framework will require us to invest in the structural conditions necessary for effective implementation. As noted a moment ago, improving our treatment of animals requires more than simply aspiring to do so. It also requires creating the cultural and institutional environments that allow us to live up to that aspiration. That means improving our education system to include less content on animal research and training with animal models and more content on animal-free alternatives and training with animal-free models – as well as more content on animal health, welfare, and rights in general. It also means creating more

employment opportunities in animal-free alternatives, and creating the facilities, equipment, and technologies necessary for that to happen.[12]

Of course, fleshing out the details requires answering many extra difficult questions. First, we need to answer difficult questions about welfare. For instance, how can we estimate how much welfare different animals can have at a time and over time? Some people are exploring the idea of treating neuron counts as a proxy for welfare at a time and lifespans as a proxy for welfare over time. In that case, we might estimate that a typical human life contains about 50,000 times more welfare than a typical mouse life, and so we might assign a typical human life about 50,000 times more weight than a typical mouse life in harm-benefit analyses.[13] But of course, it is far from clear that these are the correct proxies for welfare at a time or over time (my own view is that they are not), and a lot depends on which proxies we select and why.[14]

We also need to answer difficult questions about rights. For example, should we treat rights as *constraints*, such that we should avoid infringing them no matter what? Or should we instead treat rights as *presumptions*, such that we should avoid infringing them ordinarily but can permissibly infringe them when the stakes are sufficiently high? Either way, we would need to forbid many nonhuman studies that we currently permit. But we might need to forbid a wider range of studies if we treat rights as constraints than if we treat them as presumptions. This is especially true if we think that the strength of these presumptions depends on the strength of our interests, since, in that case, the bar for infringing the rights of some animals could be much higher than the bar for infringing the rights of others (Kagan, 2019; Sebo, 2022).

We need to answer difficult questions about many other issues as well. For example, some people think that we can permissibly prioritize human interests because we have special duties of assistance to fellow humans, given the special relationships that we have with members of our own species (Brody, 2012). But even if this is true, there might be a limit to how much we can permissibly prioritize human welfare, and there might also be a limit to what we can permissibly do to nonhumans in order to promote human welfare. We should also keep in mind that the reverse might sometimes be true as well; that is, we might sometimes have special duties of assistance to nonhuman animals as well, given how much we harm them, how much we benefit from them, and how much better off many of us are than many of them.[15]

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[12] For more on alternatives to animal use in education, see Van Der Valk et al., 1999.

[13] This back-of-the-envelope estimate is based on the assumptions that a typical human has about 86 billion neurons and can live for about 79 years, whereas a typical mouse has about 70 million neurons and can live for about 2 years. But these assumptions should be questioned as well, particularly questions about nonhuman lifespans.

[14] For more on cross-species welfare comparisons, see Budolfson & Spears, 2020, Schukraft, 2020, and Višak, 2017.

[15] For general discussion of these principles, see Shue, 1999. For arguments that humans and nonhumans can and do have morally relevant relationships, see Gruen, 2005, Palmer, 2010, and Sebo, 2022.

Assessing This Integrated Moral Framework

While it would be difficult to assess this integrated moral framework for human and nonhuman subjects research without fleshing out the details, we can make some general observations about the benefits and risks of this approach. On one hand, this approach would allow us to treat everyone as they deserve while still accommodating morally relevant differences across species. It would also allow us to improve our assessments of research, and to avoid double standards and pseudo-problems. On the other hand, there is a risk that this approach would be simplistic and reductive, and that it would compromise scientific and medical progress. I think that the benefits of a more integrated framework clearly outweigh the risks, particularly if we mitigate the risks, but we will need to consider them all carefully.

Consider first the benefits of an integrated moral framework. First, this approach would allow us to treat everyone as they deserve. In particular, it would require us to treat each and every research subject as an individual with rights, welfare, and morally significant relationships. Thus, it would require us to extend respect, compassion, and justice to humans and nonhumans alike, and to replace, reduce, and refine our use of them as much as possible, as a means to this end. Granted, we might still think that harming research subjects can be permissible in some cases, depending on the details of the situation and the details of our moral framework. But we would at the very least think that we should harm many fewer nonhuman animals, harm them much less, and help them much more than we currently do.

Second, this approach would still accommodate morally relevant differences across species. As I have emphasized, we can fully consider the interests and rights of, say, humans and mice while still thinking that the content and strength of our interests and rights differ dramatically – particularly if we think that rights are presumptions, that the strength of our rights depends on the strength of our interests, and that some animals can have stronger interests than others. Thus, even if we accept a unified moral framework for our interactions with, say, humans and mice in principle, we can still accept different moral frameworks for our interactions with them in practice (as we do with, say, human adults and children), provided that these different moral frameworks follow from our unified moral framework together with the facts.

Third, this approach would allow us to avoid double standards and pseudo-problems. When we think about human and nonhuman subjects research holistically, assessing each in light of the other, we are more likely to achieve consistency, since we are more likely to identify our rationalizations of nonhuman subjects research *as* rationalizations. As a result, we will not need to ask whether to apply heavily restrictive "human" standards or heavily permissive "nonhuman" standards to our interactions with human-nonhuman chimeras, since we will instead simply apply the same standards to them as to everyone: treat them with respect, compassion, and justice, and, so, replace, reduce, and refine our use of them where possible – which, in this case, means stopping this research before we start (Sebo & Parent, forthcoming).

Now consider some risks of an integrated moral framework. First, there is a risk that this approach would lead us to dehumanize humans. We already have a general tendency to dehumanize humans by treating them badly, and then rationalizing this behavior by comparing them with nonhuman animals (where the idea is that we can permissibly treat nonhumans badly, and so we can permissibly treat humans who resemble nonhumans badly as well). Humans use this rationalization to support racism, sexism, ableism, classism, and other human oppressions. In light of this tendency, we might wonder if creating a more integrated moral framework for human and nonhuman research will erode our current, fragile sense of human dignity and create a permission structure for treating humans "like animals."[16]

Second, and relatedly, there is a risk that this approach would lead us to "humanize" nonhumans. We already have a general tendency to anthropomorphize nonhumans by attributing human characteristics to them whether or not they have those characteristics. We appear to develop this tendency at an early age, and we apply it to a variety of nonhumans, including not only animals but AI systems. In light of this tendency, we might wonder if creating an integrated moral framework for human and nonhuman subjects research will erode our current appreciation of the many morally relevant differences across species, with the result that we attribute human interests to nonhuman research subjects much more than we should, and attribute (distinctively) nonhuman interests to them much less than we should.[17]

Third, there is a risk that this approach would compromise scientific and medical progress. Our current systems of science and medicine are based on massive amounts of harmful, lethal, nonconsensual, nontherapeutic nonhuman subjects research. As noted above, we currently see nonhuman subjects research as part of the best, if not the only, path to approval for many foods and drugs, and while animal-free alternatives are available in some cases, they might not be available in all cases. Thus, if we hold all research to high ethical standards, then we might slow scientific and medical progress (under current regulations) or compromise the safety and efficacy of new products (under new regulations). Either way we would be replacing one set of risks and harms with another, likely burdening nonhumans less and humans more.

My own view is that the benefits of an integrated moral framework decisively outweigh the risks. The benefits of an integrated moral framework are difficult to overstate. The current research ethics paradigm is neither scientifically nor ethically optimal, given how different humans and nonhumans are and how much nonhumans suffer in research. Yet we continue with it anyway because of cultural and institutional bias, ignorance, and path dependence. If we improve and integrate oversight of human and nonhuman subjects research in the ways that we have discussed here, then we can still make progress in science and medicine while reducing harm to nonhumans via research, reducing risks for humans via false positives and negatives, and reducing risks for nonhumans via reinforced speciesism.

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[16] For more on dehumanization, see Smith, 2020. For more on dehumanization and speciesism as they relate to racism, sexism, and ableism, see, respectively, Ko & Ko, 2017, Adams, 1990, and Taylor, 2017.

[17] For general discussion of anthropomorphism, see should Daston & Mitman, 2005.

Meanwhile, we can mitigate the risks. Consider each in turn. First, we can mitigate the risk that an integrated moral framework will lead us to dehumanize humans. As we have seen, we can accept a unified framework for humans and nonhumans in principle while still accepting different frameworks for them in practice, since we might think that our rights can vary with our interests and relationships. And if we emphasize that our goal is to extend dignity to nonhumans rather than restrict it from humans, then we can mitigate the risk that this extension will erode our sense of human dignity. Granted, it might erode our sense of human *supremacy*, but that would be appropriate. When the status quo involves massive and unnecessary exploitation and extermination of vulnerable others, the status quo needs to change.

Second, and relatedly, we can mitigate the risk that an integrated moral framework will lead us to "humanize" nonhumans. Again, we can accept a unified framework for humans and nonhumans in principle while still accepting different frameworks for them in practice. And if we make sure to do this work together with research in cognitive ethology and comparative psychology, taking care to note the similarities as well as the differences across species, then we can mitigate the risk that we will treat nonhumans as more human-like than they are. Granted, we might treat nonhumans as more human-like than we currently do, but, again, that would be appropriate. When the status quo involves excessive *anthropodenial*, at least some additional anthropomorphism might be necessary to establish an equilibrium.

Third, we can mitigate the risk that an integrated moral framework will compromise scientific and medical progress. We already have alternatives to many current research methods, and we will likely be able to develop more with time (Herrmann et al., 2019). Of course, there might be trade-offs between ethics and science during the transition, and we should take these trade-offs seriously. But while taking these trade-offs seriously might require harming nonhumans for the greater good in some cases (particularly if we treat rights as presumptions rather than constraints), it might also require not doing so in other cases. And if we are prepared to delay some scientific and medical advances for the sake of human rights, welfare, and justice, then we should be prepared to do the same for the sake of nonhuman rights, welfare, and justice.

In short, if we build an integrated moral framework for human and nonhuman subjects research with the general principles that I have described here in mind, then we can strike a much better balance between integration and fragmentation in research ethics. Our treatment of humans and nonhumans can be integrated in that they can flow from a unified set of considerations regarding respect, compassion, justice, replacement, reduction, and refinement. And they can be fragmented in that they can still have different implications for different individuals, depending on, for instance, the nature of their interests, rights, and relationships. The upshot might be priority for humans in some respects, but not nearly as much as we currently enjoy. This is a change that we should welcome rather than continue to resist.[18]

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Chapter 37
Regulation of Animal Research

Emilio A. Herrera

Abstract The use of animals in several areas dates back to recorded and written history. Much of our knowledge in science, medicine, and our understanding of the environment had depended in part on specific research using animal models. However, the regulation of its use, considering the welfare and ethical aspects, is very recent. Indeed, in the last decades, the regulations for protecting animals and their welfare have increased worldwide. This chapter exposes and analyses general and comparative aspects of the regulation of animal research, based on different directives, recommendations, and reports on animal experimentation welfare, derived mainly from the World organization for animal health (OIE), the European Union (EU), the United States of America (USA) and the United Kingdom (UK). In addition, some regulations from other countries are mentioned to highlight the advances in preserving animal welfare. At the same time, the most accepted and implemented international guidelines, oriented to the correct use and care of laboratory animals according to international standards, are mentioned. In summary, the most critical aspects (but not the only ones) that must be known when using animals for research are highlighted, considering their legal and moral obligation. A general idea is offered on the legislation that affects animal experimentation, which essentially seeks to optimize animal welfare through responsible maintenance of them, considering the care and procedures, as well as the facilities where they are kept. In addition, many regulations (several of them emerging) consider the degree of sentience of each animal species. Accordingly, the regulation of animal use is constantly changing, adapting to the development of our knowledge of the sentience capacity of each species, the rights of animals, and the ethical-cultural aspects in each country or society. For this reason, this chapter only guides the reader regarding the regulation of the use of animals and in no case replaces the local laws or indications that must be complied with to carry out experimentation with animals in a responsible manner.

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Introduction

In principle, any animal species can be used in research or teaching procedures, since the concept of "experimental animal" or "laboratory animal" is not a concept linked to the species of these animals, but to the use that is made of them (Kehinde, 2013).

However, it is recommended that some animal species be bred specifically for this purpose, due to their characteristics and frequency of use, so that their biological, genetic, and behavioral background can be known in detail. In this way, the variability between animals is reduced, determining fewer animals necessary to achieve reliable scientific results. For this reason, in many countries, there is legislation that makes particular reference to the care and rights of non-human animals such as endangered species, wild animals, primates, and highly sentient species. Regarding research on these species, a clear justification must include that the objectives of the study cannot be met using other species.

Objectives of the Regulation of Animal Research

Currently, the scientific community considers the proper care of animals used in research as a priority because the validity of their outcomes depends on animal welfare (Kehinde, 2013; Landi et al., 2021; Percie du Sert et al., 2020). In addition, welfare of animal has become an interest of people in most parts of the world (Wilkins et al., 2005). Considering the impact of animal care in research, as well as pressure from animal protection groups and society, most countries have established (or are in the process of generating) laws to regulate the care and use of animal experimentation, some of them focused on animal protection (animal rights) and others on animal welfare assurance. Depending on the country and awareness of the society, there are currently various levels of oversight of animal research worldwide. However, most of the regulations consider avoiding unnecessary suffering of animals. In addition, the 3R principles (Replace, Reduce, Refine, reviewed elsewhere in this book) developed by R. Russell and R.L. Burch over 60 years ago (Russell & Burch, 1959) have provided a framework for performing more humane animal research. Hence, the 3R principle has been included in several guidelines and laws worldwide. The ultimate aim of the regulation on the use of animals in research is to ensure that animals receive a correct care and are not exposed to unnecessary pain and distress. In addition, the regulation allows the implementation of animal protection measures to optimize their welfare and reduce the number of

individuals used (3Rs). The regulations on animal experimentation also help to make transparent the number of animals used and the objective of the research, and provide clear information to recognize the contribution of the study. Several guides and directives come from scientific, non-scientific, and animal protection associations. These documents are inputs for generating regulations and laws in many countries that have promoted legislative changes to assure animal welfare.

Relevant Guidelines and Declarations

World Organisation for Animal Health (OIE)

The leading worldwide organization aiming to improve animal care, health, and welfare is the World Organisation for Animal Health or OIE (Brown et al., 2018). It was created in 1924 as the Office International des Epizooties to fight animal diseases. In 2003, it became the World Organisation for Animal Health, and currently, it has 182 member countries. OIE offered scientific-based solid recommendations to improve animal welfare and provided codes and manuals with guiding principles on animal health and welfare (Petrini & Wilson, 2005; Bucher et al., 2020). These principles also support the incorporation of the 3Rs and state "that the use of animals carries with it an ethical responsibility to ensure their welfare to the greatest extent practicable" (OIE, 2022).

Cioms, Iclas and Iaclam

The Council for International Organization of Medical Sciences (CIOMS) is an international scientific association for the advance of public health through guidance on health research ethics. In addition, the International Council for Laboratory Animal Science (ICLAS) is another scientific organization dedicated to advancing human and animal health by promoting the ethical care and use of laboratory animals. Together, both organizations offer the International guiding principles for biomedical research involving animals (CIOMS & ICLAS, 2012). This guide was first published in 1985. Since then, it has been updated and expanded to address issues when using animals for research, offering a comprehensive framework for developing laws, policies, and guidelines for animal research worldwide. The CIOMS-ICLAS partnership offers ten guiding principles useful for the scientific community of countries that are still developing regulatory mechanisms for animal research as well as countries with well-developed research regulations and programs for the use of animals in research and teaching. The principles are directed to guide the responsible use of vertebrates in research, assuring the health and welfare at any stage of life of the animals used for research (CIOMS-ICLAS, 2012).

In addition to the guiding principles, CIOMS and ICLAS offer publications, training, and education programs for people associated with research activities, including scholarships in Laboratory Animal Science and Medicine (ICLAS, 2022).

In addition, the International Association of Colleges of Laboratory Animal Medicine (IACLAM), together with ICLAS support communities of laboratory animal science professionals as well as the development of local associations and professional colleges promoting the training and education of research facility personnel and veterinary specialists (Turner et al., 2015).

Farm Animal Welfare Council (FAWC)

In 1979, the "Farm Animal Welfare Council" was established in the United Kingdom to configure a basic regulation on animal treatment, which concluded with the proposal of five basic principles, known worldwide as the five freedoms (FAWC, 2009). Although the council was created to maintain under review the welfare of farm animals, the five freedoms have been transversally adopted for all kinds of animals, including research animals. These five freedoms represent minimum standards of protection that must be respected under any circumstance.

The five freedoms are:

1. Freedom from hunger or thirst.
2. Freedom from discomfort.
3. Freedom from pain, injury, or disease.
4. Freedom to express normal behavior.
5. Freedom from fear and distress.

The Council pointed out these five principles as bases for legislation, not issuing any regulations of legal value in this regard. However, both British and other countries' legislation have gradually implemented its criteria and parameters. The FAWC was renamed to Animal Welfare Committee (AWC) on 2019 (AWC, 2022).

The Cambridge Declaration on Consciousness

The Cambridge Declaration on Consciousness was written during a series of conferences regarding consciousness in human and non-human animals, held in July 2012 at the University of Cambridge (UK). The conference attendees signed the declaration and concluded that non-human animals have consciousness, including mammals, birds, fish, and cephalopods. In their statement, neuroscientists affirm that non-human animals have the neuroanatomical, neurochemical, and neurophysiological characteristics of conscious states and the capacity to exhibit intentional

behaviors, indicating consciousness (Low et al., 2012). Since its publication, this declaration has made an important impact in the public awareness of animal consciousness and sentience, and in the advances of regulations aimed to ensure their well-being and avoid negative sensations.

Relevant Regulations

European Regulations

Animal research regulations in Europe have been promoted and developed mainly by the Council of Europe and the European Union.

The Council of Europe has contributed to the creation of a common European legal space through different regulatory instruments, mainly Conventions, Agreements, Recommendations, and Resolutions. In many cases, these instruments have served as a reference throughout the continent and constituted the basis for the modification and harmonization of the legislation of the different countries that make it up; in particular, the EU takes them as a working base document to elaborate regulations in this stuff.

Regarding the protection of experimental animals, there is Treaty No. 123 (European Treaty Series 123, in force since 1991), which establishes aspects of:

> (1) staff training, (2) facilities, (3) animal care, (4) procurement, and (5) transportation (Council of Europe, 1991).

This Convention is primarily designed to reduce both the number of experiments and the number of animals used for experimental and scientific purposes. It encourages not to experiment on animals except when there is no other alternative. In addition, it establishes that the selection of animals for research purposes should be on the basis of clearly established quantitative criteria and must be well cared and avoid suffering.

This agreement was modified and improved in its technical aspects according to Treaty No. 170 (in force since 2005) (Council of Europe, 2005). This text helps to update the terms of the Convention, to take into account the development of scientific understanding and practice. Also, it refers to the standards for the care and housing of laboratory animals, as well as the presentation of statistical data on animal experimentation.

The European Union published in 1986 the Council Directive 86/609/EEC, about the laws, regulations, and administrative provisions of the Member States regarding the protection of animals used for experimentation and other scientific purposes, with aspects like Treaty No. 123 (EUR Lex, 1986; Council of Europe, 1991).

This directive aimed to eliminate disparities in the laws for the protection of laboratory animals among member nations, outlining the principles and guidelines for the proper care and use of animals, avoiding unnecessary pain and the duplication of experiments. The directive also states that each member nation must submit a report on the number of animals used in research (EUR Lex, 2013).

In July 2007, Recommendation 2007/526/CE was published on the guidelines regarding the housing and care of animals used for experimentation and other scientific purposes, in line with the modifications of Treaties No. 123 and 170.

Later, in 2010, Directive 2010/63/EU of the European Parliament and the Council was published (EUR-Lex, 2010) on the protection of animals used for scientific purposes, which involved essential changes to the previous directive. It structured a much more detailed regulatory framework and covered aspects that had not been regulated until then, incorporating new species of animals, stages of development, and updating procedures, among others.

This directive establishes measures for protecting animals used for scientific or educational purposes, regulating their replacement, reduction, and refinement (3Rs), in non-human vertebrate animals and live cephalopods. The directive consists of 6 chapters and 66 articles aimed at defining provisions for the use of animals in experimental procedures, the types and severity of the procedures, the authorization of the breeding and use of animals, avoiding repetitions, and transparency of the use of animals. Compliance with this directive and an optimal implementation of the 3Rs helps to increase the scientific quality and reliability of the results, which ultimately leads to a refinement in procedures and reduction in the number of animals used. Furthermore, for animal welfare and conservation reasons, the use of wild-caught animals should be limited to cases where the objective of the study cannot be achieved with animals bred specifically for that purpose.

This directive has been slightly modified over time (EUR-Lex, 2019a). Since 2019, it is declared that Member States shall collect and make publicly available, the statistical information on the use of animals in procedures, including information on the current severity of the procedures and on the origin and species used in procedures (EUR-Lex, 2019b).

The Directorate-General for Environment (European Commission) created a working group of experts (GTE) to develop guidelines on inspections and enforcement in order to meet the requirements outlined in articles 34 and 60 of the Directive 2010/63/EU on the protection of animals used for scientific purposes. In 2019, guidance and good practice principles were published concerning the inspection and enforcement requirements of the Directive (Directorate-General for Environment, 2019).

The regulations cover a variety of aspects that some of them have been considered to require greater detail in their development. Thus, the European Commission has convened different ad hoc groups to prepare help documents on these specific issues. These documents serve to facilitate the homogeneous interpretation of the requirements of the directive and favor compliance of member states. In 2021, the European Commission published an evaluation and suggestions about the European Union Strategy for the Protection and Welfare of Animals (2012–2015).

This evaluation does not cover the EU animal welfare legislation; however, its findings are to be considered for future actions in the animal welfare area to be taken in line with the "One Health" approach (EUR-Lex, 2021).

United States of America

Animal Welfare Act

The first federal law regulating animal research in the US was the Laboratory Animal Welfare Act, passed in 1966 (U.S.Law, 1966). This is the main federal law in the United States that regulates the treatment of animals in research. This law contained aspects related to the transport, sale, and handling of animals. In addition, it granted licenses to animal dealers to prevent the theft of pets and their sale to research centers. The original law covered dogs, cats, non-human primates, guinea pigs, hamsters, and rabbits. However, the Act excluded birds, rats, mice, farm animals, and all cold-blooded animals (U.S.Law, 1966).

The Act is also known as the Animal Welfare Act (AWA), and it has been updated four times between 1970 and 1991, aiming to elevate the standard of animal care. In 1985, it was amended with two very significant outcomes (NRC, 2004). The first one was the creation of an Animal Welfare Information Center (AWIC) at the US Department of agriculture (USDA, 2022), established to provide a database to improve care and use of animals in research, testing, and teaching in the USA. The second one was to establish an Institutional Animal Care and Use Committee (IACUC) to review all experimental protocols involving live, warm-blooded animals in each institution that utilize animals in their research activities.

Surprisingly, the AWA does not cover the most common species of laboratory animals, such as rats, mice, and birds. However, another piece of legislation, the Health Research Extension Act, covers all vertebrates used in research, testing, and education when funded by the Public Health Service.

The Public Health Service (PHS) Policy

Another federal regulation that guides the care and use of laboratory animals is the Public Health Service Policy on the Humane Care and Use of Laboratory Animals (PHS Policy) (PHS, 2015). The PHS policy was established in 1985 and applies to any research center receiving PHS funding, including most universities conducting animal research in the USA. This policy states that researchers must comply with the guidelines established in the Guide for the Care and Use of Laboratory Animals (also known as the Guide, among researchers who use animals). Although the PHS Policy only applies to PHS-funded research, it is broader than the AWA as all vertebrate animals are covered.

United Kingdom

The legislation that regulates the use of animals in research in the United Kingdom (UK) was created in 1986 and is known as the Animals (Scientific Procedures) Act 1986 or ASPA (UK Public General Acts, 1986). This Act was created to protect animals used for experimental or other scientific purposes and provides the licensing (personal and projects) to perform procedures on cephalopods and any living vertebrate other than humans. This Act aims to ensure compliance with the 3Rs principles, covering all scientific procedures on any vertebrate animal, including blood sampling, surgical procedures, and euthanasia, among others. While this Act was passed in 1986, it has been amended according to updated views and knowledge regarding animal welfare. Initially, ASPA refers to all living vertebrates other than humans, but, in 1993 (UK Statutory Instruments, 1993), an amendment added the "octopus" as a protected animal, modified as "any living cephalopod" in 2013 (UK Public General Acts, 2013). In addition, in 1998, it was amended regarding the Council Directive 86/609/EEC suggestions (UK Public General Acts, 2022). As several other regulations along the world, it also establishes a committee to provide advice to the Secretary of State and the Animal Welfare and Ethical Review Bodies, relating acquisition, breeding, accommodation, care, and use of animals, known as the Committee for the Protection of Animals Used for Scientific Purposes in the UK. Any suggestion, decision, or outcome of the committee must consider both the legitimate requirements of science and industry and the protection of animals from avoidable suffering and unnecessary use in scientific procedures. The licenses given under ASPA are reviewed and renewed every 5 years. The Animals Inspectorate is responsible for assessing applications for licenses and inspecting work in progress to ensure compliance with ASPA. Each project must undergo an in-house ethical review process that usually involves a bioethical committee equivalent to an IACUC.

Other Relevant Regulations Worldwide

Currently, the countries that have specific laws for research on animals are based on the 3Rs principles as core (Guillen, 2014). However, several countries still do not have specific legislation to regulate the research on animals. Despite this, several countries recognize sentiency in non-human animals in their legislation. Interestingly, the recognition of animal sentiency has markedly increased in the last decade in states legislations around the world (Blattner, 2019; Zapata et al., 2018). To depict the current situation, some brief examples are given.

Argentina published in 1954 Law 14.346, about Animal protection from abuse and acts of cruelty. Like other countries, this law establishes penalties for people who mistreat animals (Honorable congreso de la nación Argentina, 1954). However, the law is broad, and there are no further animal research and experimentation regulations.

Australia is a federal country, and therefore animal welfare is the responsibility of each State. Interestingly, The National Health and Medical Research Council (NHMRC) of Australia published the Australian code for the care and use of animals for scientific purposes (NHMRC, 2013), which regulates the use of all live non-human vertebrates and cephalopods in research and teaching. Similar to the Guide for Care and Use of Laboratory Animals (the Guide), it aims to promote the ethical, humane and responsible care and use of animals used for scientific purposes. This book introduces principles aligned with international standards protecting animal welfare, including the 3Rs. In addition, it comprehensibly describes the responsibilities of institutions, researchers, and animal carers, to effectively promote and safeguard animal welfare in research activities. The Code also details the duties of animal ethics committees (AECs) regarding ethical review, approval, and monitoring of animal care and use. Currently, the Code has been updated in 2021.

Brazil is a country with norms and legislation focused on animal welfare, acknowledging the suffering capacity of animals and the need to avoid it. In 2008, Law 11.794 (Presidencia da Republica, 2008) was published, which regulates procedures performed with animals in research and teaching-related activities. It also established a National Council for Animal Research control (CONCEA), responsible for establishing and ensuring the accomplishment of norms relevant to animal welfare in research. This law also establishes the creation of the Ethics Committee for the use of animals (CEUAs) for the accreditation of institutions with teaching or research activities with animals. CEUA is equivalent to IACUC, an essential entity to evaluate, approve, and monitor animal care and use in the institution (Presidencia da Republica, 2008).

Chile published its first law about Animal protection (20.380) in 2009 (Biblioteca del Congreso Nacional de Chile, 2018). This law is broad and includes all animals. In addition, it defines experimentation in animals and the required conditions that must be accomplished to perform research in animals. It also establishes the creation of an Animal Bioethics Committee, in charge of defining guidelines under which experiments on animals can be performed. In addition, the national research agency developed its guidelines based on international norms, providing a clear guide for institutions, their bioethical committees, and researchers (Agencia Nacional de Investigación y Desarrollo, 2022).

Mexican legislation includes the Federal Animal Health Act (2007) and the Official Mexican Standards at the Federal level, and general animal welfare legislation at the State level. The Federal Act establishes the Five Freedoms to be respected for all animals, which apply to the whole country. In addition, the official Mexican norm NOM-062-ZOO-1999 published in 1999 (Diario Oficial, 2001), establishes a specific regulation for laboratory animal housing, breeding, care and use. Specifically, the norm includes rodents, lagomorphs, carnivores, primates, and swine. The Agriculture, Livestock, Rural Development, Fisheries and Food Secretary in Mexico is responsible for the proper production, care and use of laboratory animals. This authority applies techniques designed to ensure animal welfare in research. However, the regulatory compliance depends on regional governments, several of them with laws mandating animal care and welfare protection (Animal Protection Index, 2020).

New Zealand (1999) defines animals as "any live member of the animal kingdom that is a mammal, or a bird, or a reptile, or a amphibian, or a fish (bony or cartilaginous), or any octopus, squid, crab, lobster, or crayfish (including freshwater crayfish).", in the Animal Welfare Act (New Zealand Legislation, 2021). In this Act, it is clearly established the responsible care of animals and the ethical conduct towards them.

Other Agencies and Associations Guidelines

American Association for Laboratory Animal Science (AALAS)

The AALAS, established in 1950, is an association of laboratory animal science professionals dedicated to animal humane care and treatment (AALAS, 2022). It offers a learning library and training courses for laboratory animal care and use (AALAS Leaning library, 2022) and has been dedicated to institutional accrediting programs that meet the minimum standards to ensure and guarantee animal welfare.

Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)

The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) is a private, nonprofit organization founded in 1965, aiming to promote standards of animal care in U.S. laboratories. It promotes humane and ethical treatment of laboratory animals through voluntary program assessment, accreditation, and education. AAALAC International monitors animal care and accredits research institutions by evaluating laboratories to ensure scientists comply with the guidelines outlined in the Guide (AAALAC, 2022).

Federación de Sociedades Sudamericana de Ciencia en Animales de Laboratorio (FESSACAL)

La Federación de Sociedades Sudamericana de Ciencia en Animales de Laboratorio (FESSACAL) is an international scientific society that represents the common interests of the south American associations related to laboratory animal science. It was founded in 1999, and it promotes training and education through events and scientific meetings (FESSACAL, 2022). Currently, there are seven countries in the Region with strong alliances (Argentina, Brazil, Chile, Colombia, Uruguay, Peru, and Venezuela).

The Federation of European Laboratory Animal Science Associations (FELASA)

The Federation of European Laboratory Animal Science Associations (FELASA) was established in 1978 and publishes guideline, recommendation, and policy documents on topics about laboratory animal science and care (FELASA, 2022). It represents common interests in maintaining all aspects of laboratory animal science, focusing on the 3Rs principles, and promoting responsible scientific conduct with animals to ensure animal welfare.

FELASA maintains relations with national, international, and governmental bodies concerned with laboratory animal science in Europe, such as the Council of Europe, the European Commission, and European Parliament, and continuously seeks collaborations with laboratory animal science associations outside Europe (FELASA, 2022).

American Veterinary Medical Association (AVMA)

The AVMA was established in 1898 to improve the practice of veterinary medicine. Nowadays is a reference for the profession, raising educational standards and advancing the science and practice of veterinary medicine to improve animal health (AVMA, 2022a).

The responsible use of animals for human purposes, such as research conducted for the benefit of both humans and animals, is consistent with the Veterinarian's Oath and, therefore, their guidelines. AVMA promotes animal welfare by offering education policies and free-of-charge guidelines (AVMA, 2022b). One well-known document provided by this association is the AVMA Guidelines for the Euthanasia of Animals (AVMA, 2020), where the acceptable and unacceptable methods and agents used for euthanasia are established, depending on the species and life stages. These guidelines also recognize the importance of appropriate pre-euthanasia and animal handling. The guidelines have been firmly implemented in several worldwide norms and regulations to achieve a respectful and humane termination of an animal's life when needed.

The Guide for the Care and Use of Laboratory Animals (The Guide)

The Guide, published by the National Research Council and the Institute for Laboratory Animal Research, is not only the basis for AAALAC International accreditation (mentioned previously) but is also a central part of Public Health Service Policy on the humane care and use of laboratory animals, and it has been the

core of several regulations along the world. Published in 1963, under the title Guide for Laboratory Animal Facilities and Care, the Guide has been updated, and it is currently on its eighth version. The Guide aims to assist institutions and researchers in using animals in scientifically, technically, and humanely appropriate ways. This book is divided into five chapters: 1. Key Concepts, 2. Animal Care and Use Program, 3. Environment, Housing, and Management, 4. Veterinary Care and 5. Physical Plant. The Guide was created to encourage the scientific rigor and integrity of biomedical research when using laboratory animals, while establishing the minimum ethical, practice, and care standards for researchers and their institutions (NRC, 2011). As well, the Guide provides information to support animal care and use committees (IACUCs) in the implementation of effective and appropriate animal care and use programs.

Institutional Animal Care and Use Committee (IACUC) and Equivalent Committees

The institutional animal care and use committees (IACUC) have a vital role in enforcing animal research laws in the United States and other parts of the world. These committees are also known as Comité Institucional de Cuidado y Uso de Animales (CICUA or CICUAL in South America), Ethics Committee for the Use of Animals (CEUA or ECUA in Brazil) or Animal (Bio)Ethics Committee (AEC or CBA), among other given names. Any institution that uses animals for research, testing, or education must create this type of committee to oversee the animal program and assure animal welfare (Brown et al., 2018; Prentice et al., 2018). IACUCs are composed of scientists, veterinarians, and at least one general public member who is not affiliated with the institution. These committees are mentioned as a vital step in regulating animal welfare in international guidelines, including the Guide and the Code (NRC, 2011; NHMRC, 2013). The indications established in these guidelines led to the creation and publication of several laws that oblige the establishment of an institutional animal care and use committee to protect animal welfare in research institutions. These committees are established to review all proposed procedures involving animals in teaching and research. The committees must review each animal research protocol considering: (1) a justification for using animals, the number of animals to be used, and the species chosen, (2) the procedures or drugs to be used to eliminate or minimize pain and discomfort, (3) a description of the methods and sources used to search for alternatives to painful procedures, (4) a description of the search used to ensure that the experiment does not unnecessarily duplicate previous research (5) a detailed description of any procedure performed in animals (e.g. Housing, feeding, surgical procedure and euthanasia) and the qualification and training of the personnel conducting procedures. In addition, protocols shall include funding information to assure financial support.

In the review process, the IACUC must ensure that the proposed work falls within the current accepted guidelines and laws and that all procedures with animals avoid or minimize discomfort, distress, and pain in animals. Moreover, medical care for animals must be available and provided as necessary by a qualified veterinarian or equivalent professional.

An IACUC also evaluates and approves (certifies) all the diverse types and sizes of facilities that house animals used for research, including breeding, maintenance and procedure sites (Leszczynski et al., 2018). All certifications must be followed by reports, meetings, supervisions or inspections aimed to ensure compliance with local regulatory policy.

In addition to the certifications issued by the IACUC, an essential role of these committees is the promotion of animal welfare through recommendations and training on animal handling and care. In turn, the committees must generate strategies to ensure compliance with the bioethical aspects, regulations, and the institutional Program. Moreover, depending on the faculties granted to the Committee, they may receive and review complaints related to the care and use of animals in the institution (Hansen et al., 2017).

In addition, many of these committees have become the institutional spokesperson on issues related to animal welfare. Finally, the Committee informs on its work, activities, and institutional animal uses through reports to the institutional authority.

An IACUC typically has at least five members, one of whom must be a veterinarian responsible for animal care at the institution. The committee must also include at least one scientist experienced in animal research, a professional whose primary concerns are not scientific (e.g. an ethicist or lawyer) and a citizen who is not affiliated with the institution to represent the community's interests at large (NRC, 2011).

In several countries, local governments or research agencies publish guidelines to help institutions organize and support IACUCs, to provide effective oversight of the welfare of animals used in research. Only in the USA, there are approximately 1400 IACUCs associated with research, testing, and educational laboratories (AVMA, 2022c).

These Committees can also influence the culture of care and help ensure animal welfare, sound science, implementation of the 3Rs, and regulatory compliance (Brown et al., 2018). As such, this committee should be strongly supported by the institution.

Animal Care and Use Program

The Animal Care and Use Program is an institutional guide that considers all the activities conducted at an institution that directly impacts the well-being of animals. The Program includes animal and veterinary care, policies and procedures, personnel management and oversight, occupational health and safety, IACUC functions, and animal facility design and management (NRC, 2011; Bloomsmith et al., 2018).

A solid program of animal care and use is vital for the institution for several reasons: regulatory compliance, quality of scientific outcomes, addressing public and institutional sensitivities, and ethical behaviour. The accomplishment of the Program will permit a proper implementation of the regulations on animal use and care at the institution.

Conclusions

The use of animals in research remains controversial. There have been significant advances in the regulation of animal use for scientific purposes, pushed by the scientific and non-scientific community awareness of animal sentience. Curretntly, there are enforced standards to ensure adequate care, health and safety of animals used in research.

The researcher and the institution must accomplish several steps to achieve the regulatory and ethical standards. In addition, the committees for the care and use of animals provide advice on research proposals and procedures and oversee animal experimentation and welfare.

Effective supervision is a critical component of the legislation. It ensures that all parties involved or interested in the care and use of animals in scientific procedures comply with regulatory requirements. In addition, a well-planned and executed inspection program has many other benefits for all parties involved in the process, including the animals and the research community.

In each country or locality, in addition to the specific legislation related to the use of animals for research, it will be necessary to consider legislation that addresses animal protection, transport, conservation, euthanasia, among other aspects. Therefore, it is strongly encouraged to review source documents for local regulations and guidelines.

The approval to perform experiments involving animals is dependent on several factors, including adherence to the 3Rs, justification of cost and benefit, characteristics of the experimental procedures, animal welfare supervision, appropriate implementation of measures to mitigate discomfort and distress on animals, and training and experience of the personnel involved. The aims of animal regulation in research are to accomplish animal welfare, avoid unnecessary distress, develop highly valid and reproducible data and facilitate the advances of high standard science. Although some countries still lack specific legislation on animal research, the advances have been enormous in the last decades.

Regulations in animal research are dynamic and in constant evolution. They depend on the scientific advances and their benefits (for human and non-human animals), the community's interest in the quality of life of animals, the knowledge we have acquired of their level of sentience, and the dialogue between affected parties. Keeping animal welfare is essential for the quality of the research and therefore must be a priority to the researcher, the research institution, and the funding agency. Being aware of the responsibility when using animals in research and respecting the associated regulations is a duty of every researcher to attain professional, scientific, and ethical integrity.

In conclusion, regulatory mechanisms of animal research are frequently evaluated and amended considering the updated scientific, social, and environmental developments and views on animal protection and welfare.

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Part VII
Animals, Food and Environment: *GMOs for Global Challenges*

Chapter 38
Ethical Issues in Genetically Modified Foods: From Transgenesis to CRISPR-Cas9 Genome Editing Technology

Erick Valdés and Juan Alberto Lecaros

Abstract Traditional ethical quandaries related to GM foods have been addressed profusely throughout the years. Still, some concerns remain regarding potential impacts on human health, natural environment and society. Moreover, the emergence of new genome editing technologies, such as CRISPR-Cas9, has implied relevant breakthroughs for plant and animal breeding. However, this enormous milestone in biotechnology has also raised new and unprecedented quandaries involving ethical, regulatory, policy and global governance dimensions. In this chapter, we analyze some of the ethical concerns that the production of GM foods involves, by addressing and discussing "traditional" issues as well as those emerging from new genome editing techniques.

Keywords Ethical issues · Genetically modified foods · Transgenesis · CRISPR-Cas9 genome editing technology · Biotechnology

Introduction

The debate on potential impacts of GM foods on human, environmental and social life is rather spent in its traditional facet. Indeed, there is evidence enough about the actual consequences these organisms can produce. Ethical quandaries related to them, being empirical and normative, have been addressed profusely throughout the years. Still, some concerns remain and will be analyzed here accordingly.

Furthermore, the emergence of new genome editing technologies, such as CRISPR-Cas9, has implied relevant breakthroughs for plant and animal breeding. However, this enormous milestone in biotechnology has also raised new and unprecedented

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quandaries involving ethical, regulatory, policy and global governance dimensions. As genome editing advances can have significant applications in dealing with climate change, sustainability and global food security, no analysis of their implications, limits and scopes can be carried out without paying attention to potential risks associated to them. The uptake of these new technologies is not a quick process and encompasses an epistemological and practical reception that often causes reluctance and uncertainty. In the meanwhile, compelling and accurate governance of CRISPR/Cas9 genome editing may entail expecting great innovative potential for society's welfare. Efficient action is needed to catch up with rapid biotechnological empowerment, epitomized, now more than ever, by newly developed genome editing techniques, with the ability to speed up breeding and enhance plant production at every stage of development.

Consequently, in this chapter, we analyze some of the ethical concerns that the production of GM foods involves, by addressing and discussing "traditional" issues as well as those evolving from new genome editing techniques.

Ethical Issues in GM Foods

Transgenic foods have been criticized as they would imply manipulation of life, hidden risks and threats, violations of animals rights and, eventually, humans', as well as environmental hazards (Lawson & Charnley, 2016). These criticisms lie on objections involving ethical dilemmas. Such objections are displayed upon two sorts of statements: (i) empirical ones about how the world is, based on best scientific observations available, or on scientific principles or theories that lead to reject GMOs; (ii) normative statements about how the world should be, based on the best existing moral judgments, or moral principles or theories demonstrating the world should not be a place where those GMOs flourish.

Objections to the use of genetic technology to modify organisms are mainly of two kinds: extrinsic and intrinsic (Watson & Preedy, 2016). 1) *Extrinsic objections:* based on potential damages that the production of GMOs and transgenic foods could imply. It is supposed that such production might have disastrous effects on the ecosystem, animals and humans. Possible harms to humans would be, perpetuation of social inequities (access to goods); food insecurity (health) in underdeveloped and developing countries, by broadening the gap between first world economies and the rest of the planet; risks for future generations; and the promotion of a reductionist, commodified and exploitative science, among others. Potential damage to the ecosystem would be environmental catastrophe; decrease of genetic diversity; deterioration of phytosanitary conditions of soils, as well as degradation of air and water. Potential damage to animals would involve unjustified pain and suffering infringed on them when used for research and production of GMOs and GM foods.

Extrinsic objections do not work so well to justify a ban on producing transgenic organisms and food. Indeed, as the potential nature of alleged GMO's threats tolerates at the same time the possibility of marginal damages, or that benefits eventually outweigh risks, designing and implementing policies and institutional frameworks

to ensure GM foods' safety as well as an efficient control of scientific research structures should be a regulatory platform enough to allow GMOs' production.

2) *Intrinsic objections* state that GMOs production is obnoxious *per se.* These kinds of objections come from a diffuse premise: *It is unnatural to genetically modify humans, plants, animals and food.* If this statement is right, we should not be involved in the production of GMOs or in non-therapeutic genetic modification of any organism. This, even though the resulting consequences signify a great loss for industry. If the statement is wrong, we should discard it immediately.

Another argument against GMOs production is based on the precautionary principle (Engelhardt, 2008). There are several reasons to be careful with what we eat. Yet, the mere fact of knowing that there are dangerous, harmful or poisonous foods out there does not necessarily imply that a real danger is lurking binding is time to harm us. Likewise, human natural tendency to be vigilant about what is eaten suggests that, in many cases, a single person with a negative opinion about GM foods could be more influential than many people with a positive idea of them.

Consequently, addressing the issue from an intrinsic perspective encompasses a likely intractable logical crossroad: if we agree GM Foods are risky, then their production should be prohibited right away. However, having no scientific certainty and consensus about that, if a society's s subsistence would depend on GM Foods' consumption, according to the precautionary principle (the same that leads to reject GM Food's production), their production should not be only allowed but effusively advocated. Therefore, intrinsic objections lead to affirm that, (1) GM Foods should not be produced, and, (2) GM Foods should be produced. Certainly, policy, governance and oversight of GM Foods cannot be based upon such inconsistent points of view (Valdés, 2021: 191).

Other concerns about GM foods production involve human health, natural environment, and societal settings. We will address them briefly in turn.

Human Health

There is plenty of scientific studies suggesting that GMO foods have no demonstrable or measurable effects on human health (Newton, 2021; Pinholster, 2012; Ronald, 2011). Still, some criticisms remain simply overlooking such an evidence. One of them states that testing GM food raises some uncertainties, as food feeding studies for GMO safety assessment are tricky since plant varieties have diverse chemical composition and the effect of the introduced genes or changes caused by them are very tough to puzzle out (Kuzma & Haase, 2012).

Other worries emerge from three potential hazards that GM foods may involve: (i) they can be toxic to humans and other animals; (ii) they are risky to the nutritional needs of humans and other animals; and (iii) they are allergenic to an important fraction of the human population (Newton, 2021: 103–106). As many studies have been conducted on very specific effects of GM foods on experimental animals, such as rats and mice, some researchers claim that such organisms may be

catastrophic to health, by referring to the pernicious effects of Bt corn on rats' liver and other organs, as well as the impacts of transgenic soybeans on the reproductive system of female rats, and the function of their adrenal glands, among others (Sarich, 2015; Séralini et al., 2012)). However, as these conditions have not been presented in humans, such concern encompasses a slippery slope argument.

In addition, some plants can produce toxic materials whether or not they have been genetically modified, and it is very hard to find out if some GMO technique has produced such toxic substances (Newton, 2021: 103).

Questions have also been raised about the potential allergic effects of GMO foods. The banner of this concern is an old episode occurred when a Brazil nut protein was introduced into soybeans to improve the nutritional value of that crop. During the testing of the GMO crop, researchers found that some consumers of the 106 GM Food modified soybean had an allergic reaction to the product. Upon the finding, further research on the GMO soybean was discontinued, and it was never made commercially available (Newton, 2021: 106). However, evidence showing that GM food are allergenic has not been found. In fact, empirical studies to systematically obtaining such evidence have been quite unsuccessful (Dunn et al., 2017; Porterfield, 2019). Consequently, there is no reason to say that GM foods may produce allergic reactions that other natural products cannot.

Natural Environment

Opponents of GM foods also state these products can be harmful for the natural environment. First, they affirm that horizontal gene transfer facilitated by wind or insects' pollination engenders a non-virtuous interaction between GMO and non-GMO plants. The travel of modified genes into non-modified ones may cause an undesirable colonization of natural organisms and alter their traditional reproduction.

However, systematic research about this topic has demonstrated that such concern is rather mythical as potential risks for the natural environment associated with pollination in the case of GM foods are quite insignificant (Keese, 2008; Price & Cotter, 2014; Tsatsakis et al., 2017). In fact, such potential issue could be addressed through the construction of a buffer zone around areas where GMO crops are planted. It is true that one problem of buffer zones is that they should be considerably large to work properly, but once this "problem" is solved, buffer zones are effective to prevent the growing of GMO crops in areas where they should not (Kruse-Plass et al., 2017).

Another worry is related to the insertion of a foreign gene into a plant, as this process may have unexpected and undetermined impacts on the genetic composition of that plant. As accurate information on possible plant mutations is not available, it would be risky to carry out such experiments without counting on sound information about the possible effects that change might produce (Banks, 2012).

Nevertheless, there are very few scientific evidence of unintended adverse effects on non-targeted species (Romeis et al., 2019; Cremer, 2019). As a matter of fact,

even if inserting genes into a plant may have extensive effects on a plant's genome, such a change has been going on for so long, ever since humans began crossbreeding plants (Newton, 2021: 109).

There also concerns about the possibility that genes injected into a crop plant might accidentally activate sleeper genes, which are inactive in a plant but able to be turned out by the introduction of an abnormal substance or event into the plant's environment. Not being so popular and having received some attention from the Food and Agriculture Organization of the United Nations, Newton (2021: 109–110) clarifies that there is no much scientific evidence on the nature of sleeper genes, their functioning, and whether or not they may be affected by the genetic modification of a plant genome.

Probably, the hardest question posed by opponents of GM foods is what the potential consequences of horizontal gene flow from cultivated transgenic plants into the wild may be. Some researchers have asserted that the growth of new GMO plants in the wild produced this way could cause loss of native, non-GMO plant species. Such a loss could derive in a less diverse and more lethargic biological system than existed before the gene transfer (Lu, 2008).

Still, some queries remain, such as whether those transfers can actually happen, when, how, under what conditions, and whether or not such events are likely to negatively impact the diversity of a biological population.

Society

Being GM foods' possible hazards for human health and environment rather unclear, the potential risks that GM foods and biotechnology in general may imply for society have not been deeply analyzed, and arguments for and against are hardly found in academic literature.

First of all, GM foods can create monopolistic practices that raise problems at a global scale. Such a monopoly can boost control over agriculture and food, by endangering food sovereignty of individuals and countries.

Second, it may be naive to think that more expensive seeds, engendering greater dependence on farmers for a few multinationals, can solve the problem of global hunger. Maybe, the actual problem is not food shortages but the lack of political will to ensure equitable food distribution among the entire world population.

Another problem is that transgenic seeds are patented and their use requires payment of intellectual property rights. Then, the local farmer who decides to adopt transgenic seeds is subjected to the company's conditions and eventually trapped in the system.

Autonomy issues are also important. Labelling systems are not sophisticated. In many countries the term "genetically modified" only appears in foods containing more than 0.9% of transgenic ingredients. This means that there are GMOs in many everyday consumers' products, without people being informed of that, or having a way of getting to know it.

Proper policy, regulation and governance are needed. Thus far, institutional and epistemological tools to ameliorate possible biotechnology's impacts on society have not proliferated. Yet, one of the them is the Precautionary Principle, which is an international biolaw instrument, conceived in 2005, by the World Commission on the Ethics of Scientific Knowledge and Techonology, UNESCO. Overall, the instrument defines actions on issues related to the application of knowledge through new technologies' practices performed under uncertainty and that as such offer poor predictive ability to foresee actual or potential aftermaths for people and the environment. In other words, when lacking reliable information to assess risks and benefits associated with a potentially dangerous practice, and not having enough evidence to determine its likely consequences, the precautionary principle orders to refrain from acting.

The instrument explores some concepts and definitions of the precautionary principle. These include London Declaration (1987), Rio Declaration (1992), and EU's Communication on the Precautionary Principle (2000). Even though such documents show some discrepancies, they also display significant coincidences, such as:

(i) The precautionary principle applies when there is considerable scientific uncertainty about the causality, magnitude, probability and nature of the damage.
(ii) Some forms of scientific analysis are mandatory. This means that mere fantasy or speculation is not enough to activate the precautionary principle device.
(iii) Because the precautionary principle operates in risk contexts with little known outcomes and probabilities, the only possibility of risk, even if unquantifiable, is sufficient to consider the application of the principle.
(iv) The application of the precautionary principle is restricted to those dangers that are unacceptable, such as possible threats to the lives of future generations or more vulnerable human groups in the global context.
(v) Intervention of the precautionary principle should be required before possible damage occurs, not once it has occurred.
(vi) The intensity of application of the precautionary principle should be proportionate to the magnitude of the potential damage. Therefore, and although in many cases the only answer to a possible negative impact of technologies is total prohibition, it should be considered that, for example, an absolute moratorium may not always be the best response to a latent risk.

Therefore, if assessing possible threating consequences of technological actions is not compelling, as well as not conclusive regarding such concerns, modelling must be made, not only on the basis of available empirical data, but also on a rational ponderation aimed at determining how to minimize those risks. Assessment's fallibility obliges and, at the same time, encourages preventing disaster from happening by taking certain measures to dwindle hazards' odds that new technologies encompass.

Being the principle ambiguous and not epistemologically dense, it requires morally sensitive axiological judgments when applied. Indeed, there exists a wide

diversity of ethical approaches that the principle seems to tolerate. This miscellaneous trait is often contradictory especially when claiming universality for ethics. Hence, the precautionary principle is a supplement, but in no case, it is lexically preeminent regarding other crisis management strategies that can face large scale uncertainty and scientific ignorance more efficiently.[1]

CRISPR-Cas9 and GM Foods

CRISPR-Cas9 is a brand-new genome editing technique with enormous innovative potential, especially in early stages of plant and insects breeding (Pirscher & Theesfeld, 2018: 419–423; Gjerris et al., 2018: 424–429; Röcklinsberg & Gjerris, 2018: 430–435; Hundleby & Harwood, 2019). Through modification of genes either adding, cutting out or suppressing specific gene sequences of the DNA, this groundbreaking practice allows not only speeding up breeding and increasing yields, but also creating the so called cisgenic plants, even in very unfavorable conditions, in a more precise, faster and cheaper way than former genetic modification devices (Baker, 2014).

When comparing this new application of CRISPR-Cas9 to traditional breeding methods, differences are substantial. While cross breeding is intended to improve traits through crossing an elite recipient line with a donor line and selecting a better progeny with specific desired traits, mutations breeding takes one step further by enhancing a trait using mutagens and engender mutants through random mutagenesis. Transgenic breeding goes even beyond that. It improves traits by transferring exogenous genes into elite types, by augmenting accuracy in achieving the expected target. Yet, genome editing reaches a level of precision unseen until now. It precisely modifies the target genes in elite varieties, by displaying a huge constellation of possibilities in early stages of the food change (Chen et al., 2019).

Thus, the emergence of CRISPR-Cas9 and its launch into the universe of living organisms to edit their genome seems to announce a promised dawn for those who see biotechnology not only as an end but as a strong means to fight food scarcity, global warming, and decrease of arable land and water, as this technique permits diminishing the use of pesticides, herbicides and fertilizers proven to be one of the most infamous causes of environmental degradation (Bomgardner, 2017).

In addition, the use of insects in food and feed production is quickly increasing as it is a more efficient and more sustainable source of protein in comparison to conventional protein supplies such as cow and pig's meat, chicken's eggs, or soy to feed animals (Van Huis, 2017; Van Huis et al., 2013). Using new breeding technologies, such as CRISPR-Cas 9, in intensive insect-production is probably intended to impulse a future transition into a more insect-based diet (Gjerris et al., 2016), and

[1] See, for example: Bostrom & Cirkovic, 2008; Bostrom, 2011, 2013; MacAskill et al., 2020; Ord, 2020.

seeing a company introducing into the market a genetically edited cricket to be used as a crispy snack (Gjerris et al., 2018: 425) does not seem like an extravagant idea whatsoever.

In Sweden, in the framework of the MISTRA Biotech research programme, CRISPR-Cas9 has started to be used to enhance the quality of starch in potatoes in order to boost their levels of amylose. This endeavor is meant to favor consumers' health and impulse research on replacing fossil-based oxygen barriers in food packages, by dwindling the climate impact (Röcklinsberg & Gjerris, 2018: 430–435). Thus, by combining potato starch with plant protein, a composite material similar to plastic is created to be used as an oxygen barrier in packages. Then, researchers design potatoes with longer storing capacities as they have a different starch composition (Andersson et al., 2017).

Thus, some of the goods expected by applying this technique are developing crops that are safer, healthier and more nutritious, to face disease and starvation; enhancing genome editing technologies in advanced breeding lines in crops; reaching environmental sustainability in addressing global food security issues (Valdés & Rendtorff, 2022); and likely, delivering gene-edited plants variety to developing countries.

All these enterprises, being laudable, are ethically controversial as they have an argument behind, that is, they represent a strategy of using biotechnology to achieve new kinds of goals never sought before in our species' history. Thereby, evaluating genetically modified organisms (GMOs) and gene edited organisms (GEOs) emerging from the use of CRISPR-Cas9 not only entails "socio-economic concerns" (Gregorowius et al., 2012) but also impacts ethical atmospheres (Röcklinsberg & Gjerris, 2018: 430), by deploying a cast of new moral quandaries, whose resolution is key to advance in designing and implementing policy and governance.

As CRISPR-Cas9 remains within species barriers and can iterate nature, by producing identical results, its applications on food and feed make difficult determine if a GMO is defined by the product or process (Pirscher & Theesfeld, 2018: 420). This may have implications for building compelling local and inter-jurisdictional regulation. In fact, understanding a GMO as a product (Huang et al., 2016) leads to laxer regulations and oversight, as defining new plant breeding techniques only considering the new traits it is possible to obtain, would forcely imply a more permissive policy and governance approach.

By taking into consideration that human intrusion into the plant encompasses a risk in itself as impacts for such organism are still unknown, it would be recommendable to go forward in designing strong categorization for CRISPR-Cas9 modified products, by taking some elements from the precautionary principle (Pirscher & Theesfeld, 2018: 421). Yet, rejecting this technique brandishing only a concept of naturalness as an overriding moral criterion to guide the construction of policy and governance, sounds like insufficient. Indeed, such a concept seems to be anachronistic and even *démodé*, as the old paradigm dictating that nature is an unchanging entity has already been shot down by genetics (Valdés, 2021).

Other controversial focus regarding the ethical status of CRISPR-Cas9 applied on agriculture is whether genome editing should be regulated like genetic modification or rather like conventional breeding (Gjerris et al., 2018: 425) or like something

in between (The Norwegian Biotechnology Advisory Board, 2017). As in conventional animal breeding for producing food the genetic change is reached by selecting existing natural mutants and selective cross-breeding, such process is quite different from that of genetic modification, where the genetic change may entail a transgene transfer. However, in genome editing, the change of the original genotype needs no transgenesis (though it may eventually involve it), therefore, such a process is above any form of genetic editing applied thus far (Gjerris et al., 2018: 426).

In addition, CRISPR-Cas9 genome editing technology has some specific ethical, legal and social implications (Šutković et al., 2020). First and foremost, interfering with natural processes may have potential undesirable impacts both for humans and the environment. A possible aftermath might be to disturb natural homeostasis through editing plant genes, specifically regarding how it has been working for thousands of years (Worall, 2011). Homeostasis is key for a new life to survive, as temperature, acidity, and oxygen concentration have to be controlled with absolute precision and be maintained under precise conditions in each of the cells that compose us. Therefore, although not completely proven, possible consequences of modifying natural dynamics of homeostasis could be disastrous.

Second, GM foods are becoming an increasing public health risk due to microbial and chemical contamination, food adulteration, additives, mislabeling, and food allergens, among others (Gizaw, 2019; Branum & Lukacs, 2009). Besides, as antibiotic resistance genes are commonly used in most genetic engineering experiments as selection method, antibiotic resistance of bacteria also implies an increasing threat. There are also economical concerns since new GMO technologies are expensive and as such only large companies can afford and developed them in detriment of local farmers (Šutković et al., 2020: 2122).

The emergence of an agriculture monopoly is another important apprehension. Indeed, GMO production, potentiated by new genome editing techniques is favoring the creation of bigger and better BIOTECH companies, which are gradually engendering such hegemony. A recent research showed that the ten most developed GMO companies hold more than two-thirds of the global proprietary seed market (Mueller, 2019).

From a societal point of view, there is a threat implied in GM foods production. Many people around the world, systematically scourged by hunger, might choose to eat such products even jeopardizing their health, as potential long or mid-term risky aftermaths of doing so would overweigh their need to survive (Carter et al., 2016). In the meanwhile, people with lower economical income would not be able to afford more expensive GM foods, whereas those with more purchasing power would be able to either prevent themselves from eating such foods or to choose to consume them.

In this scenario, plenty of ethical quandaries, a stark question remains: when genome editing is used to create a loss of function of a target gene with no foreign DNA, should we view the end-product different from those coming from conventional mutagenesis? Hundleby and Harwood (2019: 5–6) give some light of the international state of the art of such matter. They expound that in many countries, such as Argentina, Brazil, Canada, Chile, Israel, the USA, and Japan, the regulation

of genome editing, in cases where new genetic sequences have not been directly inserted, that is, when the changes have been created by indels resulting from non-homologous end joining (NHEJ) repair or deletion of existing genetic sequence, should be no stricter than a product of mutagenesis. As a matter of fact, Argentina, Chile and Brazil regulate gene-edited products case-by-case and excuse them from regulation when there is no transgenesis.

On the other hand, some countries of the EU (Sweden leading) interpreted the 2001/18 EU directive on GMOs to propose that in cases of genome editing, where the changes to the genome are similar to those resulting from conventional mutagenesis techniques, they should fall within the same exemption clause as exposed in Article 3 and Annex 1 of the directive (Hundleby & Harwood, 2019: 6). Nevertheless, while in most jurisdictions science treats the resulting plants as equivalent, some techniques of producing such plants remain within the scope of the GMO legislation (though others fall outside), by proving GMO definition to be quite conflictive.

Other countries, such as Germany and the Netherlands are in favor of ruling a non GMO label for crops produced through genome editing (Spicer & Molnar, 2018). Countries making their national recommendations certainly defers from EU rulings, by pointing out the need to redefine the concept of GMOs, their social implications as well as their associated risks and regulations (Zhang et al., 2020). As conflicts and complexities of regulation, policy and governance display some barriers for genome editing techniques, especially those using gene knockout or nucleotide variants, a wise balance between protecting human beings, animals and environment, and fostering biotechnological development is needed.

As addressing both global food security and sustainability is nothing less and nothing more than urgent (Valdés & Rendtorff, 2022), genome editing has the potential to make a noteworthy contribution. Given the EU's policies to assist developing countries in addressing food security challenges, especially in response to climate change (Valdés & Rendtorff, 2022), the EU could contribute to the long-term goal of global food security, by implementing specific regulation of improved crops. In addition, developing principles and instruments for international global governance can be seen as a significant contribution to understanding the ethical and legal framework of the United Nation's sustainable development goals (Valdés & Rendtorff, 2022). In this fashion, regulation, policy, governance and oversight should harmonize different jurisdictions all over the world to prevent these new breeding technologies from being underrated and underexploited.

Concluding Remarks

GM foods' negative effects for human health and natural environment have been disaccredited by systematic research and specialized literature. This, in the circle of what we call transgenesis. Probably, the only concerns that, in this context, deserve more attention, are those related to potential social threats with implications for economy, food sovereignty and international governance.

Yet, in genome editing setting things may change as governing CRISPR-Cas9 is not merely reduced to predict potential aftermaths and side-effects, but also implies societal concerns and a huge diversity of moral positions about the need and plausibility of tailoring and even commodifying nature for any human endeavor. Certainly, trivializing the issue is not the way. Overlooking some fundamental implications of governing CRISPR-Cas9 genome editing, by discarding supposed mythical risks such new technology encompasses may have counterproductive effects.

Many say that talking about the risks posed by current CRISPR-Cas9 genome editing technique involves "irrational fears" (Huang et al., 2016; Pollock, 2016; Araki & Ishii, 2015). Thus, regulating this technique as it brings up a set of new biotechnological risks would be an exaggeration that lacks objectivity, since biotechnology still does not reach perfection, so thinking about its potential threats only would beget a hypothetical scenario. However, using diffuse arguments to cast aspersions on possible risks of genome editing techniques is unhelpful. If we even were not able to prove that there is an objective risk in biotechnology, the only fact of seriously considering such a possibility implies at least a subjective risk. And either objective or subjective, risks associated to new technologies deserve special consideration, as even accepting that trying to distinguish between objective and subjective risk is a hesitant task, biotechnological practices tolerate their ontological and ethical degradation and, although their aftermaths may not occur in our interval of time, they may impact the near future.

Therefore, affirming that CRISPR-Cas9 genome editing only contains apocryphal threats is, at worst unreasonable, and at best, unconvincing. Sound policy and governance need to be made to ensure, among others, success in reaching global food security and interjurisdictional sustainability when exploiting the potential of this new breeding technology.

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Chapter 39
GMOs and Human and Environmental Safety

Ignacio Chapela and Angelika Hilbeck

Abstract The 50-year anniversary of the first 1972 laboratory demonstration of transgenesis resulting in biotechnology (or Biotech for short), provides an opportunity to review this historical development with real evidence. Our evidence-based review shows a field dominated by high, unmet expectations, and underplayed damage and failure. Biotech's agricultural promises and hopes, as well as its few commercial products, raise questions of centralization and control, erosion of diversity, emergence of new dependencies, and more. But institutions have also changed; in this chapter, we analyze transformations of regulatory frameworks and ask how Biotech forced institutional trajectories. Each application of Biotech carries ethical questions – most of them unresolved and often not even acknowledged – including Biotech-generic questions, as well as those specific to the application. Biotech's history would demand extensive ethical questioning impossible to do here. Instead, by focusing on a few examples we aim at providing a frame of analysis that may be useful for further application as the extraordinary history of Biotech's failures, and its counted successes, continues to evolve.

Keywords GMOs · Human safety · Environmental safety · Ethics · Transgene contamination

The Stakes

We stand at the half-century mark of a major undertaking for humanity. The 50-year anniversary of the first laboratory demonstration of transgenesis in 1972 provides an opportunity to review this historical development and offer a reality check.

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Unlike other fields, such as material-science or informatics, where scientific advances lead to material technical developments and economic growth in rapid succession, transgenic techniques in biology have had a less-than-brilliant history with failures dominating outsized expectations. Highlighting either the expectations or the failures alone makes for a polarized discussion in the field that resembles a debate among the deaf. We propose instead a recognition of the historical context in which transgenesis came into existence, and where it developed into what became known as Biotechnology (or Biotech) to conduct a critical evaluation of realities. We posit that Biotechnology continues to be misunderstood when viewed solely through the filter of twenty-first-Century politics, and that a sober historical account provides clarity about how it became a misguided and even dangerous enterprise. A review of how it went from a proposition "too sweet not to taste" in the mid-twentieth Century to an edifice "too big to fail" in the 21st can give useful guidance for this and other science-based fields of social importance.

The beginning of the age of biotech may best be marked, not by the 1972 "DNA splicing" that later would be called transgenesis, but by the 1944 letter of US-president Franklin Delano Roosevelt (FDR) to his main advisor, and promoter of the new role of technology as an economic force, Vannevar Bush (Roosevelt, 1944). In his famous "New Frontiers of the Mind" letter, FDR outlines the future Biotech (not known by this name yet) as a US national plan. Having demonstrated the power of atomic theory in physics not least through the nuclear bomb, little doubt remained among the small group of insiders in 1944 that the same impetus would produce equally stunning results in biology. FDR asked Bush:

> *With particular reference to the war of science against disease, what can be done now to organize a program for continuing in the future the work which has been done [i.e. the successes of WW II] in medicine and related sciences?*

Having the resources of the victorious US State at his disposal, Vannevar Bush's response to this question would become the animating force in the future of biological education, training, infrastructure and financialization for many decades to come, indeed to our days. Almost 80 years later, the concept of manipulating the "unit of life" in the same way that "units of matter," atoms, were manipulated through the Manhattan Project continues as foundational to the Biotech project.

Biotech, as the intentional manipulation of the foundational particles of life, must accept a few items of faith: first, the centrality and absolute dominance of DNA not only in heredity, but also in the metabolic (physiological) maintenance of life-forms; second, the atomistic behavior of discrete DNA sequences, more or less identified with "genes" that could be "moved" from one context to another without changing "meaning" or function; third, the universality of that "meaning," in physiological terms. Taking these assumptions at face value, transgenesis can be simply defined as the movement of genes (= DNA sequences) from one context to another. It is the combination of simplicity of concept and universality of potential application that carries the overwhelming power of the Biotech promise to this day.

Nevertheless, while the decades since 1944 saw exponential growth in the expectations of Biotech, actual applications continued to disappoint even the most enthusiastic proponents, as we will show with a few examples. Many other successful economic applications of physical technologies, including the personal computer, space-travel, home-internet or the nuclear bomb, did not take half as long from laboratory- to market scale, yet Biotech continues to stumble and limp without reaching unalloyed success in material terms. However, in the process, whether it succeeds or fails on specific projects, Biotech does produce physiologically active, reproducing life-forms that change the environments where they live, mostly in unsuspected and unaccountable ways. In this mismatch between presumed and actual effects of Biotech lie many of its most vexing ethical questions.

This chapter does not aim to be exhaustive or extensive about all the many questions, within the realm of ethics, that Biotech's history would demand. Instead, by focusing in a few examples we aim at providing a frame of analysis that may be useful for further application as the extraordinary history of Biotech's failures, and its counted successes, continues to evolve.

The Starting Gun

What is the scope of Biotech? Uncountable pages have been written on the subject, yet weak and variable definitions plague the field. Authors wishing to play-up a perceived success of Biotech will include in their definitions activities that collectively reach into the trillions of dollars yearly – from agriculture and animal nutrition to fisheries, medical diagnosis and instrumentation, as well as the production of pharmaceuticals. From this perspective, "Biotech" becomes substantially equivalent with "Biology" (e.g. Carlson, 2010). On the other extreme, when it comes to expose a specific sector of a future industry to regulation, the subject of Biotech can become extremely reduced. Thus, for example, current efforts to label transgenic manipulations through techniques such as CRISPR are often presented as standing in their own class, most often when seeking a regulatory environment more friendly to industrial development than what, for example, Ag-Biotech through so-called GM-crops has received. Indeed, the business of instrumentation centered on subjects close to Biotech, in particular the synthesis of DNA sequences, the use of DNA sequences for forensic and diagnostic uses, and the sequencing of DNA from various sources, have spurred extraordinary growth. Yet, these instrumental developments fit squarely with developments in material science, nano-manufacturing, electronics and cybernetics, not actual biological manipulations.

Here, we focus attention on all the various and outwardly different methods which have the one key manipulation in common: transgenesis. Thus, we can clearly delineate a field of analysis without distraction from either over-reaching definitions that claim to include all biological activities under the sun, or over-specializing definitions which tend to exclude important examples from analysis. Transgenesis *per se* is important because it is in fact the goal of Biotech as defined above (i.e. the

movement of a "unit of biological meaning," or "gene""from one context into another), and because transgenesis is the one manipulation that generates a life-form (cell, organism, population, species, etc.) that has the potential for reproduction beyond the moment of conception in the lab.

From an ethical viewpoint, transgenesis is indeed the central point of human intervention that makes of Biotech a subject of attention/concern, unique among many other interventions: through transgenesis, life-forms are conceived with unprecedented configurations of heritable materials that have not gone through testing and trialing and, indeed, the guidance of evolution. This would be important enough even if the newly conceived life-forms were truly and reliably contained in a laboratory. But the great difference lies in the fact that the vast majority of transgenic life-forms will have at least the opportunity to break out of their conditions of conception, with many of them intended for open-air release. Herein lies a specific set of ethical questions unique to Biotech.

The perception of this problem is not new. Indeed, if the concept of transgenesis has been current for centuries, its practical demonstration by Boyer and Cohen in 1972 (Cohen et al., 1973) was concerning enough to the very people engaged in it that they self-regulated via a short-lived moratorium on the practice, preceding the famous Asilomar Conference on Recombinant DNA of 1975 (Berg et al., 1974, 1975). The conference was the medium that allowed the practitioners of transgenesis at the time to socialize their concerns (many of them ethical, others technical), as they shared them not only among themselves but with media and most importantly government (in the US). This ad-hoc "ethics committee" at the cradle of Biotech considered, without resolving, specific questions of potential harm but also many unanswerable questions about a field that had been mostly science-fiction up to that point. Although this conference is often presented as an example of scientist's mature ethical behavior, the reality is that the only clear conclusion reached there was not better than a punt into the future: after some months of further consultations, scientists agreed that they did not really need to deal with the host of questions associated with the potential release of transgenically-manipulated life-forms, since they all considered that their laboratories—all in elite institutions—would not allow such releases. Asilomar attendees thus defined away vast swaths of ethics concerns, in particular those associated with environmental releases and medical interventions.

In keeping with the spirit of FDR's and Vannevar Bush's "Frontiers of the Mind" foundational stone, a series of institutional transformations quickly followed the laboratory transformations in the Boyer and Cohen labs, as well as the Asilomar Conference. These are too many to include here, but key among them are an Act of Congress (US) and a Supreme Court (US) decision. The Bayh-Dole act of 1980 and the Supreme Court decision that same year in the case of Chakrabarty v. Diamond (Silver, 2020) established a new legal and institutional framework that allowed indeed for the organization of (in FDR's words) "*a program for continuing in the future the work which has been done in medicine and related sciences*" that would "*help us stimulate new enterprises, provide jobs …, and make possible great strides for the improvement of the national well-being*."

If there was a foundational ethics problem with Biotech (transgenesis), the institutional transformations also baked-in institutionalized conflict of interest at the deepest levels. The Chakrabarty decision established that "human-made" life-forms were "patentable subject matter" and, thus, open to ownership, while Bayh-Dole inserted an unavoidable conflict of interest in all institutions of research in the US, and its individual researchers, who all of a sudden saw themselves not as disinterested observers of nature, but as entrepreneurs-in-the-making, able to set up businesses based on the discoveries of their publicly-funded labs – since the vast majority of biological research in the US took place under such funding, this meant, for all intents and purposes, that all biological research would be fair-play for commercialization and speculation. This model would be copied throughout the world.

The historical capping-stone of these developments was the predictable onslaught of money interests on the previously tranquil biology labs of every university and research institute. Eventually, these relationships became common currency at every academic and research facility under the term "PPP" for "Private-Public-Partnerships." In a historically-appropriate development, all these new institutional experiences were pioneered in the same locus, the University of California in Berkeley and the San Francisco Bay Area in general.

Ag-Biotech

A "Land Grant University", Berkeley had one of the country's premier standing in forestry and agriculture, particularly in its College of Natural Resources. It is not surprising that it would be within the aegis of this college that the first environmental release of a transgenically-manipulated life form took place. The release in a well-monitored and -fenced field near Lodi of the so-called "Ice-Minus" bacterium by the laboratory of Steven Lindow in 1987 was indeed scrutinized and challenged to the point of exhaustion. The release could have been possible 4 or 5 years before, were it not for the challenges, and the initiative was eventually abandoned—a foundational failure at the very inception of Biotech. Media and activists, as well as committees in- and outside academia provided what could be described as a high level of scrutiny. Forms were filled, permits assigned and disclaimers filed. The problem, however, continues to be that the technical instrumentation and expertise (certainly not cameras or eye-witnesses) that would have been necessary to follow what happened with the ice-minus bacterium and its descendants was simply not available, nor even imaginable within the future horizon—and it is not available even today; it is impossible to comprehensively trace the fate of descendants of transgenic life-forms as they move out from their original release in space, in time and in phylogenetic terms as they evolve.

In other words, the Ice-Minus bacterium was released soon after the Asilomar Conference had declared that no environmental releases should happen for the foreseeable future, under the conditions that Asilomar attendees feared and sought to

prevent (at least on paper). Nevertheless, over the years, Lindow declared multiple times that he was acting on entirely clear legal (and presumably ethical) grounds. In his 2020 retirement lecture as Berkeley's awardee of the once-a-year Meyerson Lecture, Lindow still declared the experience as a success, and pointed to "critics" as the source of the commercial limbo into which ice-minus "tech" drifted (Lindow, 2020). Critics, averred an unrepentant scientist, were simply ignorant and should be swayed into compliance through public education. In making this statement, Lindow was signaling a further institutional "capture" of the Biotech program, the capture of the educational system for the purpose of, again in FDR's words, "*making possible the great strides for the improvement of the national well-being*" through Biotech. In the view of Dan Koshland, a major Berkeley and science figure at the time, the well-being of the industry could be identified with the well-being of the Nation (pers. comm. to ICh).

The capture of regulatory institutions in the US followed apace. Two central examples include the controversial workings of the Committee on Competitiveness, set up in 1989 during the Bush/Quayle administration and charged with removing regulatory "hurdles" to the free operation of the Biotech and other industries, and the coining of the 'Substantial Equivalence' principle. This principle declared, without evidence, that the products of transgenesis were not different from their predecessors, and thus not liable for special regulation (nor responsibility) as long as the newly created life forms, that were 'novel' enough to be awarded the status of a human invention for patenting purposes, fell within the broadest range of variation of its basic compounds (proteins, lipids, carbohydrates, etc.), notably with no threshold ever defined for what would constitute a non-substantially equivalent novel transgenic life form. Hence, 'regulations' were designed, from its inception, to deflect and "externalize" ethical and other questions about Biotech.

With an environment purposeful and willing, including enthusiastic media and scientific literature, permissive regulatory and financial incentives and much hope and expectation, transgenic crops, here called GMOs, were introduced into the environment and became part of the feed and food chain since the mid 1990s. Two traits were introduced then and remain to this day the overwhelming majority of acreage devoted to these crops: herbicide-tolerance (HT) and insecticidal toxins, produced by transgenesis from the bacterium *Bacillus thuringiensis* (Bt). Almost 90% of transgenic crops contain one or several HT traits (ISAAA, 2020) which allow for the blanket-spraying of crops with broad-spectrum herbicides, eliminating every plant (and associated life) without the trait. About 99% of GM crop plants sold today contain traits from either one or both categories, herbicide and pest resistance (ISAAA, 2020). The remaining 1% of transgenic crops occupy niche markets with little to no global agronomic or economic significance. All GM crops in this "First Generation" of GMOs were heralded as "super tools" for increasing agricultural sustainability and productivity. They failed on both counts, but they did create super problems.

The Failure – A Reality Check

In practice, the adoption of "First-Gen" transgenic crops brought a variety of problems, including the emergence of 'superweed' resistance to herbicides and 'super bug' resistance to Bt toxins, leading to increased pesticide use (Almeida et al., 2017; Benbrook, 2018; Bonny, 2016; Campagne et al., 2013; Carrière et al., 2016; García et al., 2019; Gould et al., 2018; Kilman, 2010; Kranthi, 2016; Mortensen et al., 2012; Stone & Flachs, 2018; Tabashnik & Carrière, 2017; Strydom et al., 2019). For example, overall pesticide use in the US had grown by 7% already in 2016 (Perry et al., 2016), while in Argentina, government estimates show an increase of glyphosate use from 13.9 million litres in 1996, to 200 million litres in 2008 (Secretaría de Ambiente y Desarrollo Sustentable, 2008).

Chemical Abuse and the Expected Rise of Superweeds

Serving as platforms for delivery of corporate chemistry through both transgenesis and the old means of synthetic production and application, today's transgenic crops, in particular HT, have now been associated with a variety of detrimental environmental effects and biodiversity damage. These include but are not limited to the decline of monarch butterflies in the Americas, a marker species for many other insects, due to blanket spraying with glyphosate (Roundup) and the simultaneous expression of vast amounts of insecticidal toxins (Pleasants & Oberhauser, 2013; Flockhart et al., 2015; Pleasants 2017; Thogmartin et al., 2017; Saunders et al., 2018; Taylor Jr et al., 2020), widespread contamination of water and air with herbicides (Sanchís et al., 2012; Chang et al., 2016; Battaglin et al., 2014; Majewski et al., 2014; Aparicio et al., 2013; Bohm et al., 2014; Bento et al., 2016; Mendez et al., 2017; Aparicio et al., 2018; Okada et al., 2019). Downstream, toxic and chronic sub-lethal effects of weedkillers, increasing with the expansion of HT crop production and the escalating resistance evolution in superweeds, eventually altered aquatic environments, affecting nontarget species including duckweed, tadpoles, frogs, snails, crayfish, crabs and fresh-water fleas (Relyea, 2005a, b, c; Relyea & Jones, 2009; Pérez et al., 2012; Cuhra et al., 2013, 2014, 2015; Rzymski et al., 2013; Avigliano et al., 2014a, b; Sikorski et al., 2019) as well as soil-living species such as earthworms (Santadino et al., 2014; Zaller et al., 2014; Gaupp-Berghausen et al., 2015; Domínguez et al., 2016; García-Pérez et al., 2020). Detrimental farmer practices induced by GM crop cultivation, include abandoning integrated pest management practices (applying pesticides only when and where thresholds are exceeded), and the reduced practice of sustainable techniques such as crop rotation, biological control, cover cropping and short-season crops (see Wilson, 2020). These damaging practices far outweighed the vaunted no-till practice that was driven solely by economic considerations and not ecological concerns.

Of particular concern was the emergence of superweeds, as the agronomic ecosystem became flooded with herbicides selecting those plants that would survive. When the first generation of glyphosate-resistant GM crops were introduced in the mid 1990s, the widely promoted 'benefit' of these GM crops was that it would allow growers to stop using other, more toxic compounds like 2,4 D, glufosinate, dicamba etc. and that resistance evolution against glyphosate would be highly unlikely (Bradshaw et al., 1997). After a few early successes, the usefulness of the herbicide/HT crop combination did not last long. In response to escalating and out-of-control resistance evolution against the first generation of Roundup/Glyphosate resistant GM crops, a new generation of herbicide tolerant GM crops, which are tolerant to additional herbicides such as the more toxic glufosinate, 2,4-D, isoxaflutole and dicamba, has led to additional concerns about the effects of blanket spraying of these pesticides on human health and the environment, including pesticide residues on crops, increased weed resistance and the adverse effects of dicamba drift on neighbouring crops (Mortensen et al., 2012; Miyazaki et al., 2016; Wechsler et al., 2019). 2,4-D has, for example, been linked to increased cancer rates in farm workers (Hardell et al., 1994; McDuffie et al., 2001; Zahm et al., 1990). Widespread chemical contamination, including aerial spraying of HT crops, has also been linked to concerning rises in cancer and birth defect rates in Argentinian GM crop production regions (Lapegna, 2016; Avila-Vazquez et al., 2017, 2018). These reports are consistent with the IARC (2015) designation of glyphosate as a probable human carcinogen, and with other studies suggesting that chronic exposure to glyphosate and other pesticides can cause a range of other adverse health effects. Needless to say, the amount of research effort going into such precautionary studies is a tiny fraction compared to the funding and other support of promotion of the crops, including widespread efforts to discredit research showing negative effects. This dramatic unbalance between promotion and precaution has remained a hallmark of Biotech products to this day.

Expected Effect of Evolution: The Rise of Superbugs

The aim of Bt crops was to overcome the limitations of topically applied, Bt-based pesticides by making plants express the mostly activated forms of the toxin continuously (Latham et al. 2017). While both persistence and increased efficacy are promoted as beneficial for target pest control, their effect on non-target organisms continues to be ignored. Continuous exposure to Bt toxins, expressed within the plant throughout the season, drastically differs from pulsed spraying of Bt crystals and spores only when a pest problem arises, and causes chronic exposure of all organisms feeding on these plants as well as their predators and parasites. Target pest species under continuous exposure develop resistance, negating the sustainability of the desired effect. This risk was successfully posited during the deregulation process of Bt-crops in the US (and subsequently elsewhere), leading to the mandatory requirement of pest-resistance management programs (e.g. Bourguet

et al., 2005). This probably extended the shelf-life of Bt crops beyond those of transgenic HT crops where no such management programs were required. But given the massive selection pressure on the target pest species caused by the almost complete adoption of Bt-transgene containing maize and cotton, pest resistance evolution eventually gave rise to "super bugs." The fall armyworm, a major crop pest that is now spreading from the Americas has documented resistance to all Bt toxins except for one. Reflecting the dimension of this problem, the US EPA recently proposed the complete phase-out of all Bt corn and cotton crops unless they carry the only Bt toxin (VIP protein) still without documented insect resistance (Agfax, 2020). After 35 years of attempts with this Biotech application, its failure in the US could not be clearer.

Similar insect resistance has now been documented in South Africa (Bengyella et al., 2021), where Bt crops were heralded by developers as a solution for small-holder farmers across African countries (e.g. CropLife, 2018). Nevertheless, massive amounts of funding, public and private (e.g UASAID and the former Gates Foundation), continue to lure receptive African leaders into the trap of promise and hype. Of particular ethical concerns are "humanitarian" interventions, such as donations of off-shelf-life (off-patent) 'transgenes' to African researchers, including generous funding to put them into African crops. These outdated traits are largely non-functioning under field conditions (e.g. due to resistance, Fischer et al., 2015) but come with no transparency regarding their documented failures[1] or risks, nor accountability or ethical responsibility for the consequences among unknowing small-holder farmers.

Super Spread – Transgene Contamination Causes Economic, Societal and Environmental Harm

Transgene contamination has been another problem resulting from both commercial cultivation and field trials of unapproved GM crops. Unintended contamination from field trials is a regular occurrence despite the use of containment practices, with 396 incidents being recorded across 63 countries from 1997–2013, and this is despite the lack of detection practices being deployed (Price & Cotter, 2014). The real extent of contamination worldwide is unknown due to lack of will and funding into proper detection practices and programs, and can thus be expected to be much higher than the reported levels.

Commercial cultivation has led to significant economic consequences for farmers and wider food markets from the efforts required to ensure co-existence. In Europe, ensuring legally mandatory co-existence has a significant impact at

[1] https://www.iol.co.za/saturday-star/news/agriculture-minister-says-no-to-monsantos-drought-tolerant-maize-seed-34072840?fbclid=IwAR21PuKCRWOQCgb-4zBhO7VMai7RISiGfiTHvOF_WFMsU9HLc8DQSnl151Q

different levels of non-GM supply chains, amounting to up to 14% of total product turnover (Gabriel & Menrad, 2015). In Switzerland, costs of co-existence measures have been estimated to be even greater, between 5–20% (Albisser Vögeli et al., 2011); while in the US, organic farmers have reportedly spent $6532–8500 per farmer in 2014 (FWW & OFARM, 2014). For organic farming, the European Commission has noted that stricter segregation methods are needed (European Commission, 2010).

Contamination of farmer fields has also led to serious economic consequences. A 2015 USDA Organic Survey reveals that 92 U.S. organic farms suffered combined monetary losses of over $six million between 2011 and 2014 due to GMO contamination (USDA NASS, 2015). Others have estimated that contamination of the total organic maize crop could cost U.S. organic farmers $90 million annually (Hewlett & Azeez, 2008). In Brazil, farmers lost higher premiums for organic products because of GM contamination of organic soybeans (Hewlett & Azeez, 2008). Inadvertent contamination has also resulted in international bans on imports, as has been experienced with Japan banning Canadian wheat after contamination occurred from a field trial. The EU also banned Thai tinned papaya after it was contaminated from a research center (ICTSD, 2004). The EU has also banned Canadian flax following contamination events, while recalls of US corn following contamination was estimated to cost the company over $1 billion to compensate producers (Schaefer & Carter, 2015). EU honey shipments from Canada severely impacted by GM canola contamination cost $4.8 million due to the dropping of shipments (Smyth et al., 2002). Contamination events are also likely underestimated, with some only detected years after the event, if at all. Herbicide-tolerant rice trials conducted in 199–2001 in the US were only found to have contaminated rice shipments to the EU in 2006 (Schaefer & Carter, 2015). Contamination of wheat with unapproved varieties also led to class action lawsuits as a result of temporary bans by Japan and South Korea, forcing Monsanto to compensate farmers with $350,000 (NBC News, 2015). Feral plants have also been detected in Austria, where transgenic corn is not cultivated, encroaching on semi-natural environments under Central European climatic conditions (Pascher, 2016). Similarly, establishment of unapproved transgenic rape seed along railroad tracks and in ports have been reported for Switzerland and Japan invoking additional costs for its control, all paid with tax money.

Contamination events also have had real life impacts on biodiversity. In Spain, organic maize contamination led to the loss of farmer varieties adapted to the local climate (Cipriano et al., 2006). Such events threaten the availability of high-value germplasm in breeding programs (Burgeff et al., 2014), a risk that is extremely concerning considering the loss of crop biodiversity already taking place over the twentieth Century (FAO, 2010), reducing food security, particularly during the current ecological and climate crises.

Failed GM Traits

Complex traits promoted to herald a new era of climate resilient or more nutritious crops have failed to materialise. One case in point is the drought-tolerant maize developed by Bayer (formally Monsanto), already commercialised in the US, and now targeted at Southern and Eastern Africa. South African authorities have rejected this maize due to its failure to increase yield and the lack of the claimed drought tolerance: MON87460, concluded South African authorities, "*did not provide yield protection in water limited conditions*" (DAFF, 2019), while "*some trials even showed lower yields than conventional maize*". The claim of drought tolerance has never been established independently in the scientific literature. That the integration of a single transgene, the *cspB* transgene, improves tolerance against drought, rests entirely on claims by the producer. A study by Monsanto reports a disappointing, expected 6% reduction in yield loss from the 15% loss observed under water-limited conditions over three seasons in the US, with one season observing a 0% change in yield in comparison to conventional varieties (Nemali et al., 2015). Though this study purported to show a "yield increase" there was, in reality, still a 9% yield loss under water-limited conditions. How *cspB* maize performs comparatively to known and documented maize varieties with tolerance to drought, in particular those that emerged from the non-GMO Drought Tolerant Maize for Africa (DTMA) project, is also unstudied and undocumented.

Another case in point is the engineering of vitamins into crop plants that has also been a failure. The most prominent and historic example, as it started on its journey over three decades ago, is the 'Golden Rice' (GR). Variety GR2-R1 was hampered by low yields, dwarfism, bushy stature, pale leaves, late flowering and low fertility (Bollinedi et al., 2014; Stone & Glover, 2017). The later GR2E version has suffered degradation of beta-carotene during storage (Bollinedi et al., 2014, 2019; Paine et al., 2005), with negligible evidence of health benefits (see Wilson, 2020). A study of the seed selection practices of Philippine rice farmers has concluded that farmers are unlikely to plant Golden Rice in its current varieties, unless induced to do so (Glover et al., 2020).

Against a historical backdrop of failure, permits for trial releases in the US alone exceed 22,000 to date, concordant not with 'excessive' regulations, but with the permissive 'de-regulation' model supposed to promote Biotech (Goodman, 2002). Meanwhile, both agroecological and conventional methods have delivered the adapted varieties that transgenesis has been promising for decades but has yet to produce (Gilbert, 2014, 2016; Bardgett & Gibson, 2017; IPES, 2016). The huge number of field trials run annually is a testament not to great successes, but to a Biotech marked not by engineering-like precision and predictability but by almost blind trial-and-error approaches resulting in ineffective results.

The 'Success' of Biotech

The Ag-Biotech enterprise grew to unwarranted proportions thanks to the intentional convergence of governmental, private, corporate and other subsidies, exemptions, promotional schemes, and the advent of public-subsidization of high-risk enterprises through the financial markets and venture-capital dynamics. All these were historically unprecedented conditions that were intentionally managed to promote what was declared *a priori* a future success story. However, what began as a promotion of exaggerated hopes and suppression of criticism would eventually come to interfere with reality-based checks on an unwieldy multitude of start-up companies as well as the larger, well-established ones.

The dynamics of venture-capital economies, recently exploding from the successes in electronics and cybernetics, intruded into the already fraught situation of Biotech towards the end of the twentieth Century. Large amounts of capital became available in the 90 s from funds with little or no capacity to truly evaluate the promises of Biotech. Venture capitalists, eager to find new investments to "plant" and "grow" their recently-found riches, were willing to give credence to practically any promise, no matter how large, provided enough credentialed experts were recruited into the start-up companies. With professors and researchers already primed by the recent transformation of their institutional boundaries (see above), there was almost no limit to the abundance of experts willing to partake, with various degrees of intentionality, of the bounty.

Perhaps the best example of these dynamics was the emergence of a plethora of start-ups promising through transgenesis to resolve, or at least address, the growing problem caused by the burning of fossil fuels. Riding under the flag of 'Synthetic Biology', a new term for the process of transgenesis, the offerings were somewhat varied, but they all shared in common the promise to "create" microbes (and plants) which would produce fuels to replace diesel, gasoline, and even jet fuel. The proposal was enticing, as it avoided questioning consumption of energy per-se, instead promising to increase fuel consumption while reducing the environmental footprint of that fuel – akin to the eternal dream of reducing body weight without changing calorie intake or life-style.

We present three examples for illustration of countless others. Two examples, again from the San Francisco Bay Area, are Amyris and Solazyme. A third was conceived in Oxford. In addition to the public subsidization of the academic research needed to produce lab-scale prototype processes, these companies received millions in governmental subsidies and exemptions, foundation grants, venture capital and eventually public money directly through Initial Public Offerings of shares.

Amyris

Amyris was born in the hallways of the engineering departments at Berkeley, both the public university and the National Laboratory of Manhattan Project ancestry. Berkeley's role, as a public institution, in midwifing the early stages of the nascent biofuels industry cannot be overlooked; it was through deft jockeying of networks of influence and credibility that the university promoted not only the technical aspects of biofuel production, but also its political and policy implementation, to the extreme of managing to place a trusted hand from the Berkeley National Laboratory, Steven Chu, as Secretary of Energy under president Obama. An extraordinary level of promotion in academic, industrial and governmental circles ensured a dazzling growth of Amyris, which moved in leaps and bounds to the point of establishing large-scale facilities in Brazil where it was supposed to produce high-energy-density liquid fuels from sugar-cane using transgenically modified yeast in large fermentation vats.

Judging by the enthusiasm of people willing to buy Amyris shares in its Initial Public Offering in 2010, one could conclude that their storyline was strong and sensical, a new birth after the failures of the ag-biotech version of transgenesis. But time and biological reality have shown the contrary: the financial performance of Amyris shares since its IPO can instead be seen as pioneering a pattern that would become common in the field, with a giddy early stage followed by an unavoidable crash. In fact, Amyris is unusual in its persistence over 10 years (a long history in the world of fast-paced "unicorn" companies often going under within months of their emergence) despite nagging evidence against their storyline; thanks to their exceptional influence and contacts, Amyris has raised an extraordinary US$ 1.4 billion in 26 rounds of financing (as of August, 2021), but this does not change the lackluster performance of its profit or stock (Fig. 39.1).

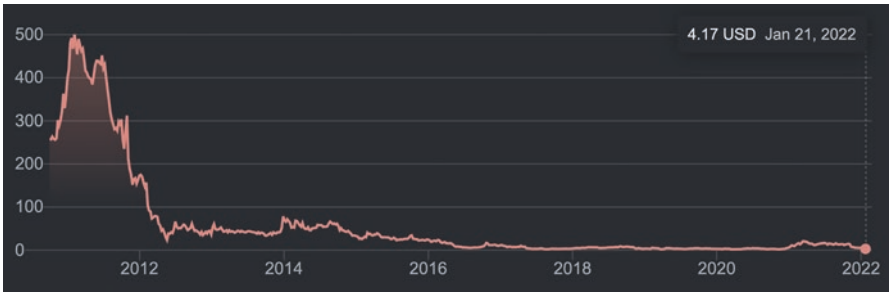

Fig. 39.1 Stock Price of Amyris in the Nasdaq market, 2010–2022 (US Dollars)

Amyris' persistence and relatively long history is useful to visualize how a failure of concept (the original biofuel-through-transgenesis dream) can be re-worked in a way that deflects attention from the failure itself. Instead of the millions of tons of biofuel that were promised to the enthusiastic early investors (many of them with lofty environmental ideals), the company now produces kilograms of chemicals for cosmetics and will try anything a fermentation plant can do, including cannabinoids and even recently CoviD-19 vaccines. In the process, however, uncountable billions of life-forms have been produced both in the Amyris laboratories in California, but also in the facilities they have spread around the world, particularly in its six 200,000 liter fermenters in Brazil. Nobody knows what these life-forms and their descendants have done or will do in the future, or where, as they become released into the environment. Indeed, nobody can know, since the technical capacities necessary to monitor such life forms are still not even near the horizon of the possible, just as it was during the first release of the Ice-Minus bacterium mentioned above.

Rather than facing the consequences of failed promises, the operation of financialization through venture capital and public offerings of stock allowed individuals and institutions to simply leave behind their unfulfilled promises by doubling-down on their claimed powers and moving on to new promises (often more modest in scope). Individuals are rewarded for this behavior, as they leave a trail of unproductive companies that failed, usually in public hands, while the individual has the necessary information, credibility and contacts to leverage not only large profits from the folding of those companies, but also new investments in their newfound promises. In Amyris' case, the main promoter (Prof. Jay Keasling) started promising a cheap cure for malaria to found the company, followed by biofuels, and from there a continuously-changing palette of smaller promises. Emblematically, Amyris' Chief Technology Officer, Neil Renninger, who spent his formative years as an MIT student, is quoted as saying: "*The biggest thing I learned at MIT was [to say] go ahead and take risks because if you fail, you'll land on your feet*" (Grushkin, 2012).

Solazyme

Another company founded on the now-forgotten promise of supplying the world with environmentally-neutral fuels rests now as a contrasting example to the zombie-like evergreen survival of Amyris. Solazyme was founded in 2003 and raised over the years US$ 484 million in eight rounds of funding up to 2016 (including 21.8 million from Steven Chu's Department of Energy, and 52 million from Chevron), only to file for bankruptcy months later in 2017. Similarly to Amyris, Solazyme experts promised to come up with plentiful biofuels produced by algae (as opposed to yeast), through transgenesis (at the time called Synthetic Biology). They also set up production capacity in Brazil, near sugarcane plantations which were supposed to have been their source of raw material to feed their algae. In addition to Chevron, this promise also attracted the attention of many others, including two of the world's largest agriculture transnationals, Bunge and ADM (Archer

Daniels Midland). The Clinton Global Initiative awarded Solazyme's CEO, Jonathan S. Wolfson, its "Green Leap" award in 2009, while Forbes included him in their list of 12 "Most Disruptive Names in Business, 2013." No amount of corporate or venture capital support, however, was sufficient to prevent the failure of Solazyme's unwarranted promise, leading to its bankruptcy. Nevertheless, Wolfson did not miss a beat as a *serial entrepreneur*, shifting the fermentation capacities of the company to the production of the more expensive (and not idealistic at all) supplements for the cosmetics and nutritional industry, as well as pigments and specialty oils, echoing Amyris' similar move, under a new company name, TerraVia.

Oxytec – Intrexon

Similar business performance can be found in the interfacing sector of environment and health where dreams of finally eradicating disease transmitting insects, like mosquitoes, or pests have been nurtured. One such example is Oxitec which was founded in 2002 by three Oxford University researchers who genetically engineered mosquitoes to carry a conditional lethality gene, where in the absence of tretracyclines, the mosquito larvae will die prematurely. Male transgenic mosquitoes, bred *en masse* in laboratories on tretracycline diets, are expected to mate with wild-type female mosquitoes upon their release to produce offspring that will then prematurely die before reaching the adult stage. With this mechanism, coined as 'self-limiting', it is hoped that mosquito populations can be knocked out and with it any diseases they transmit, be it malaria, dengue or chikungunya. Although this could never be demonstrated it was computer-modeled. According to Oxford University information, the university assisted with patenting the initial intellectual property, setting up the company and raising investments. The university also 'invested £248,000 in seed funding from the Oxford University Challenge Seed Fund for proof-of-concept research'.[2] Much of these starting funds stemmed, again, from typical public subsidization of academic research. In 2015, Intrexon bought Oxitec for 160 Mio USD leaving the university and its founders rich without any marketable product beyond the proof-of-concept stage regarding disease reductions in humans. However, Intrexon in turn notoriously underperformed at the stock market (Fig. 39.2), after buying several of these hyped start-ups,[3] including Okananga, the official inventors and owners of the non-browning, transgenic 'artic' apple and Aquabounty, the official inventors and owners of transgenic, faster growing salmon (literally saving it from bankruptcy – Waltz, 2015). Intrexon recently received 'a

[2] https://innovation.ox.ac.uk/news/oxford-spinout-oxitec-sold-to-intrexon-corporation-for-160-million/;https://www.prnewswire.com/news-releases/intrexon-to-achieve-175m-cash-goal-appoints-helen-sabzevari-phd-as-new-president-and-ceo-and-will-change-name-to-precigen-to-reflect-healthcare-focus-300980434.html

[3] https://www.nature.com/articles/nbt1015-1017/tables/1 Waltz, 2015.

Fig. 39.2 Stock Price of Precigen in the Nasdaq market, 2013–2022 (US Dollars)

little facelift'[4] involving not only the rebranding of the company by a new name, now called 'Precigen', but also a new CEO.

Most notably, as part of this 'facelift', Precigen sold its smaller non-healthcare businesses for $65.2 M, including but not limited to Oxitec, to a firm called 'Third Security' run by another 'serial entrepreneur'[5] Kirk Randal, previous CEO of Intrexon. 'Third Security' was described as '*a venture capital firm characterized by an expanding global perspective and a distinctively patient approach*'. And 'patient' it must be, because Oxitec has not delivered a tangible marketable product in its 20 years of existence. All applications on offer rest on the more than decade-old patents tried on various insect species, none of which have passed beyond a limited release-recapture proof-of-concept stage (e.g. Shelton et al., 2020, https://www.oxitec.com/en/news/projectbmediaadvisory) with mixed and often rather discouraging outcomes (GeneWatch 2015[6]). None could demonstrate to even begin to reach their bold ultimate claims of reducing disease prevalence in people or pest problems for farmers after decades of research and astronomical financial support including public tax monies and IPOs.

Conclusions

A historically contextualized approach to the field of environmental Biotech allowed us a glimpse past the momentary "debate among the deaf" that has characterized it for the better part of half a century. From this vantage point, several major watersheds of understanding can be discerned:

First, biology has not yielded to the enticements of the technologist in the same way as physics has done, consistently, for well over 200 years since the successful

[4] https://www.biospace.com/article/intrexon-changes-name-to-precigen-taps-new-ceo/

[5] https://synbiobeta.com/from-biotech-to-biotech-meet-serial-entrepreneur-randal-kirk-ceo-intrexon/

[6] http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_GWbrief_Mar15.pdf

application of thermodynamics and fluid physics to the use of steam in industry. Where nuclear physics yielded a successful—if also terrible—nuclear bomb, the conceit of the "gene" as the "atom" of biology continues to yield at best extremely patchy results, to this day.

Second, despite this questionable performance, the deployment of Biotech in the environment has had major consequences. Self-replicating life-forms, unlike the objects of physics from the steam-engine to the router on a satellite, go on with their interactions, mostly unaccountably, after their release. The early warnings by skeptics of Biotech have generally come true, as amply demonstrated now in agricultural applications where we have at least a minimum degree of monitoring; even though the vast majority of transgenic life-forms exist in the microbial world (consider algae and yeast, bacteria and many others) for which we do not have even the beginning of an idea of what their actual impact on their environment might be, not even where they are.

Such a disparity between actual performance in the real world on the one hand, and general consequence—mostly negative— in the environment and in society for a technological intervention has rarely, if ever, been seen in history. More commonly, an intervention that does not work or has major deleterious consequences (or both) becomes, normally, quickly discontinued. In this case, however, the evidence shows that other forces and other logics must be taken into account to understand Biotech's development and continued existence despite its dismal performance.

We wish that a focus purely on the biological aspects of these developments could be enough, but a sober and specifically ethical consideration of the evidence makes it impossible not to consider forces of local, national and international politics, including the specifics of transformations in media, economic and academic/scientific milieus in the late twentieth Century and into the 21st. The development, status and future of Biotech cannot be understood—let alone comprehended in the framework of ethics—without understanding that we are dealing not only with the momentous transformation of life forms in their heritable characteristics, but also with the transformation of institutions and social processes that undergird such biological transformation — an "Institutional Engineering" of sorts. While this recognition also applies to medical applications of transgenesis, it becomes truly critical when the environmental lens is used to observe the peculiar field of Biotech. Discussions are often curtailed through a misleading appeal to small technical details: maybe some yield increases might have taken place, for some time, in some transgenic crops somewhere; maybe more and new technical innovations in the lab could have bought months of life to the doomed anti-malaria mosquito. But the fact remains that neither the lofty goals promised again and again (particularly "ending world hunger", "curing cancer" and "saving the planet") have even been approached.

We observe a historically unusual dissonance between material reality and perceived value of a unique technical intervention, transgenesis. This observation is supported by so many evidentiary cases that we feel compelled to ask not whether a risk/benefit analysis of environmental Biotech should be done more carefully, but rather what might help in explaining the exceptional afterlife of a proposition, transgenesis, after it invariably failed to deliver on its promise while consistently causing

foreseeable, documented and also unaccountable negative consequences. We have provided examples that underline the complex nature of possible answers to this question. In each of these examples, we find individuals who operate on very different value-levels compared with the institutions in which they find themselves involved: the scientist turned into entrepreneur, the graduate student working both as publicly-supported intellectual and as privately-committed research and development officer; the university drop-out boldly forging a fortune in the wild steppes of venture-capital (beautifully exemplified by, but by no means exceptional in the Theranos case (Carreyrou, 2018)), the venture capital investor, trusting the promise of technical "disruption" from a reputable scientist only to find that this reputation became compromised by the very promise of venture-capital investment; the regulatory agency caught between roles as both promoter (for the National interest) and watch-dog (also for the National interest); the country and multi-lateral body seeing a mirage of a promise for future economic benefit in the turbulence of the field; the small-time online investor, oblivious to the fundamental scientific contradictions and complexities yet playing the roulette of stock prices; and so many more. All these players, however, are joined in a collective that tends, in its composite totality, to maintain a steady force of promotion of Biotech, with little or no regard for consequences, other than short term profit opportunities.

Public opposition to the original event in Biotech's material environmental history, the release of the Ice-Minus bacterium made it impractical for fast development of new "products" of Biotech that could identify with this event. The terms "gene-splicing" or "genetic-engineering" that were used at the time were promptly avoided in favor of "genetic-modification," which produced "genetically modified organisms" or "GMOs". As critical public discourse followed the deployment of GMO crops over vast areas (principally the US, Canada, Brazil and Argentina), the need arose to utilize "Second Generation-" and "Third-Generation GMOs," shortened to "First-Gen" and "Second-Gen" respectively. As these changes in nomenclature still did not change substantially the nature of the life-forms in question, nor their performance, new labels began to multiply and appear at increasingly shorter intervals from one another. "Synthetic Biology" or "SynBio" and "Gene-Editing" became the most recent titles that make it difficult, except to the dedicated, to trace to the original "gene-splicing" reference to transgenesis. Each new label has been typically accompanied by efforts to remove special considerations to the products of transgenesis by the public or regulatory agencies. The current situation in Europe, after a so-far failed attempt at deregulation of "Gene-Editing," could not be more exemplary: the European Food Safety Agency (EFSA) is faced with a need to establish policy guidelines, presumably different from those already available for GMOs, for not one or two different labels for transgenic manipulations, but a plethora of them, including the following acronyms and neologisms: SDN1, SDN2, SDN3, ODM, Cis-genesis, and Intra-genesis.

Reflecting on the ethics of the nuclear bomb, Robert Oppenheimer remarked (Personnel Security Board, 1954): "*When you see something that is technically sweet, you go ahead and do it and you argue about what to do about it only after you have had your technical success. That is the way it was with the atomic bomb*."

Seen in its historical context, the process is clear, yet for Biotech, history was to unfold further from such a technical dream "too sweet not to taste" into an unexpected direction, towards a self-perpetuating edifice that became "too big to fail." Faced with a less-than-stellar performance and poor public acceptance, it became easier for Biotech to seek institutional and semantic changes than to provide products with better performance or acceptance. Self-reflection and critical analysis of the underlying reasons for the disappointing performance became taboo, unchartered territory in Biotech circles, likely because following them would inevitably lead to questioning the scientific foundations of the entire field, undermining belief systems that sustain careers and businesses.

The questions raised in Asilomar in 1975 remain unanswered even though the serious concerns of participants in that conference continue to apply undiluted. In the process of evolution, two forces are at play: reproduction with change (via mutation, recombination, symbiogenesis, etc.), and selection. Transgenesis is an unprecedented technical manipulation of the former, no matter how precise in scale or location. Whether a technical manipulation of the first force of evolution (reproduction) is performed via biolistics (as with early GMO techniques) or oligonucleotide-directed mutagenesis (ODM, including most "gene-editing" methods such as CRISPR-Cas), does not change the fact that such a transformation takes place outside of the choreography and script of a reproduction that guides the evolution of life-forms. Nevertheless, a narrow, a-historical and decontextualized representation of transgenesis continues to lead many into presuming that with each wave of "New-Gen" Biotech, some mysterious transformation will happen that will erase the obvious questions still pending since the 1970s. Herein lies the agnotological veil that, laid over the entire field, continues to provide a thin but powerful cover for each actor in the field to short-circuit not only biological understanding, but ethical behavior, in favor of some long-promised revelation that has no sign of ever materializing.

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Chapter 40
GMOs and Sustainable Agriculture

Sheldon Krimsky

Abstract The introduction of genetically engineered crops in agriculture in the mid-1990s has been heralded as the advent of the Second Green Revolution. Among the expectations were high yields, fewer inputs like pesticides, and new nutritionally enhanced foods. Around the same period that traditional breeding was eclipsed by molecular breeding, the concept of sustainability was introduced into the working lexicon of many disciplines, practitioners, and corporations. This chapter discusses the principles of sustainability and their applications to agriculture, evaluates specific GMOs against the criteria for sustainable agriculture, and argues that GMO crops must be understood within an agro-ecological system.

Keywords GMOs · Sustainable Agriculture · Agro-ecological systems · Sustainability · Ethics

Introduction

Agriculture had its origins in the Middle East between 10,000–12,000 years ago in the region called Mesopotamia also referred to as the Fertile Crescent, which covered parts of modern-day Syria, Lebanon, Jordan, Israel, and Northern Egypt. Up until that time, human societies were organized around hunting and gathering. Sustainable agriculture was introduced as a concept in 1987 with the publication of *Our Common Future* also known as the Brundtland Report, issued by the World Commission on Environment and Development of United Nations. The Commission

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was chaired by Norwegian Prime Minister Gro Harlem Brundtland. The application of biotechnology through recombinant DNA techniques to produce food crops was introduced in the mid-1990s. Large scale agriculture began its transition from traditional breeding, which included selection, exposure of plant cells to radiation and chemical mutagens, and hybridization, to molecular breeding, which included genetic modification or genetic editing, applying CRISPR (clustered regularly interspaced short palindromic repeats) to plant cells for creating desirable traits.

The introduction of genetically engineered seeds, beginning with insect resistant and herbicide tolerant crops brought international opposition from environmental groups like Greenpeace as well as several nations. In response to the controversy over genetically modified organisms (GMOs) introduced into agriculture, the European Union established a regulatory system that included risk analysis, testing programs, and restricted criteria for adoption of GMOs into agricultural production and in GMO food shipments to European nations. In contrast, the United States did not require testing but began with the assumption of "substantial equivalence." Unless otherwise proven, the U.S. regulatory agencies considered GMOs as safe as traditionally bred crops and that the process utilizing recombinant DNA techniques or gene editing was not a factor in assessing risks.

While new biotechnology products were entering the farming sector, the interest in sustainability had been growing globally, in part spurred on by an awareness of climate change, the pollution of oceans, the loss of biodiversity, the decline in soil quality, and the rise in the use of agro-chemicals. The United States and Brazil were world leaders in the use of GMOs in large scale agriculture. Most of their staple crops of corn and soybeans consisted of GMOs. With such large sectors of the agricultural economy devoted to GMOs, agricultural scientists and environmentalists began to ask whether GMO applications was or could be consistent with sustainable agriculture. By the new millennium, this question began to receive serious attention. This paper will explore the issue of GMOs and sustainability first outlining some core principles in sustainable agriculture, and then exploring whether GMO agriculture meets these standards and how one can answer that question.

Principles of Sustainable Agriculture

The terms sustainable or sustainability are among the most widely used terms in the title of scientific papers. From Web of Science, I found 122,744 titles containing one of those two words. In 2021 and 2020 the terms were found in 14,896 and 20,760 titles in scientific papers, respectively, while 19,255 books had the root "sustainable" in their titles. Before we can ask "Is X sustainable," where X is a product, system, or technology we must be clear about what we mean when people use the term "sustainability." (Shearman, 1990: 1–8). Some believe the term is kept deliberately ambiguous to satisfy stakeholders with different political and economic agendas. We can begin by examining how the term has been used in agriculture.

The Brundtland Report referred to sustainable development as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs." Specifically, with respect to sustainable agriculture the report states:

> …rapid growth combined with deteriorating income distribution may be worse than slower growth combined with redistribution in favour of the poor. For instance, in many developing countries the introduction of large-scale commercial agriculture may produce revenue rapidly but may also dispossess many small farmers and make income distribution more inequitable. In the long run, such a path may not be sustainable; it impoverishes many people and can increase pressures on the natural resource base through over commercialized agriculture and through the marginalization of subsistence farmers. Relying more on smallholder cultivation may be slower at first, but more easily sustained over the long term.

It also states that the rate of depletion of topsoil, fish stock and forest resources should not exceed the rate of regeneration. The operative term is "regenerative agriculture" also referred to as "sustainable agriculture." Practitioners of sustainable agriculture seek to integrate three main objectives into their work: a healthy environment, economic profitability, and social and economic equity. I shall use as guiding points that promoting sustainable agriculture means advancing agroecology, protecting the resource base of natural systems (maintenance of natural assets) for future generations including and especially the soil, protecting plant and animal species biodiversity, and enhancing the quality of life and health for farmers, farm workers and society. When we ask: "will the technology of genetically modified organisms (crops) support agricultural sustainability, we shall refer to these contributing factors".

These factors may be interpreted differently by different scholars and stakeholders. Constance (2010) noted: "because the concept of sustainability is deeply contested, agribusiness is able to exploit the ambiguity surrounding the definition of sustainable and exercise power in attempts to frame sustainable agriculture in their favor." Also, we can find a different emphasis in the literature on the core factors of sustainable agriculture. Gaffney et al. (2019) emphasize four factors: ensure production of an adequate food supply; alleviate poverty; achieve better nutrition; and conserve natural resources, which must be balanced against one another (Gaffney et al., 2019).

Sustainability is rooted in the living world's moral obligation to future generations. Our obligation to future generations falls into four archetypal positions. The first and strongest obligation I refer to as "family values" because it seeks to make future generations better off than the current generation. This is reminiscent of the parental exhortation "we want our children to be better off than their parents." The second moral position is that we want to ensure that the next generation is no worse off than the current generation. This viewpoint implies that we wish to protect biodiversity, natural resources, sources of energy, the climate so that the next generation can experience life as comparable to how it is experienced by the current generation.

The third position is to ensure that future generations have the knowledge to address the problems of scarcity and loss of raw materials, species or what we consider a favorable climate. I call this the knowledge-based response to our obligation to future generations. We do not know who these people will be or what their needs and desires will be, so fulfill our obligation to them by ensuring that the knowledge we preserve and transmit will guide them to a favorable future. Regarding preserving resources, this position places our obligation only to the current generation of people. Finally, the fourth position extends beyond the knowledge-based response by placing no restrictions on our consumption or depletion of natural resources nor does it obligate us to create a survival knowledge for future societies. This is the position of pure hedonism, with no obligations to the future. It is sometimes referred to as "cornucopian." Consume what you want without any moral constraints. Future generations will find their own path.

Within these archetypal positions, sustainability is associated with position #2, ensuring that future generations are not worse off than we are. For sustainable agriculture this means protecting the soil (soil conservations), preserving wildlife, maintaining forests, and protecting the biodiversity of the planet as well as the climate for human habitation.

Building on the Brundtland criteria for sustainable development, Karlsson (2003) proposed three ethical principles for GMO sustainability. Karlsson echoes the three cornerstones of sustainability: environmental, economic, and social. His ethical principles are process, rather than outcome- based. The first is the Precautionary Principle. Applied to GMOs it means that the lack of scientific certainty of the adverse effects of a living genetically modified organism on the food or the environment for which there is credible concern, shall not be used stop the health and environmental assessment in favor of release. The second principle is commonly known as "The Polluter Pays." The responsibility for the costs of preventative action on a GMO, including risk assessment, is placed on the polluter prior to release into the environment. Finally, Karlsson (2003) cites public participation for decisions on risk management as part of the social dimensions of sustainability.

Sustainable Applications of GMOs

Genetically modified organisms (GMOs) include any biological species that is genetically modified in a laboratory (in vitro) by either recombinant DNA molecule technology or the more recently discovered CRISPR (gene editing) technology or any of its variant methods. The technology itself cannot be said to be sustainable or unsustainable without understanding how it is used and the products it has created. There is no inherent reason why GMOs should be used to exacerbate or ameliorate unsustainable agricultural practices. As Russell (2008) has stated: "…it is not feasible to ask whether a particular system, industry or technology is 'sustainable' or

'unsustainable,' but useful to consider whether it is associated with a tendency towards or away from sustainability." (Russell, 2008: 214). Herrero et al. (2015) noted that "agricultural biotechnologies cannot be usefully assessed as isolated and technological entities but need to be evaluated within the context of the broader socio-ecological system that they embody and engineer." Following Russell's analysis that no product or process is inherently sustainable or unsustainable, I shall examine several crops that could progress toward sustainability and in the next section outline several products that are antithetical to sustainable agriculture.

In Hawaii, papaya tree plantations were blighted by the papaya ringspot virus (PRV), which could not be controlled by pesticides or netting to stop its spread by the aphid vectors. A laboratory technique initially called "coat-protein gene-mediated transgenic resistance" was developed for papaya cells. A protein from the capsid coat of a mild form of the PRV was inserted into papaya cells. Under the right conditions, plants can be sensitized with a coat protein of an invading pathogen, which sensitized the plant to induce an immune response (RNA or proteins) against the invading pathogens. In some respects, it is like a vaccination in mammals that induces an immune response against a viral pathogen. Once vaccinated, the animal's immune system remembers the invading virus and can launch an antibody defense.

The GMO papaya has been widely heralded as a success, which can be adapted to any sized farm. Its use mitigates against the use of insecticides and other environmentally damaging methods to destroy the aphids carrying the virus. However, some studies have found effects of the GMO papaya on the soil microorganisms in the rhizosphere (Wei et al., 2006; Phironrit et al., 2007). Thus far these observed effects have not altered the use of GMO papaya in the Hawaiian plantations although other genetic approaches to the PSRV such as RNA silencing have shown favorable outcomes mitigating effects on rhizosphere.

While the GMO papaya is an actual example of a GMO in use, there are also potential applications of transgenic crops that show a favorable approach to sustainability. One of these applications is the genetic modification of bacteria and plants to extend nitrogen fixation to new plants. The massive application of inorganic nitrogen fertilizers in agriculture is a well-documented environmental contaminant. The fertilizers drift away from agricultural fields leaching into lakes, rivers, streams, and aquifers creating eutrophication. The excessive nitrogen sources, providing a richness of nutrients in bodies of water, frequently causes a dense growth of plant life and results in the death of animal life from lack of oxygen.

All plants require nitrogen for growth. There is a small sub-group of plants, including peas, beans, soybeans, alfalfa, clover, and peanuts, which have a symbiotic relationship with soil bacteria that reside at the root nodules of the plants. These bacteria located in the rhizosphere of the plant, called nitrogen-fixing bacteria, can draw nitrogen from the air and make it available to the selected plants. The process is called nitrogen fixation. A set of genes called nif genes are genes that encode enzymes involved in the fixation of atmospheric nitrogen into a form of nitrogen available to living organisms.

One of the earliest projects for the new biotechnology industry during the last quarter of the twentieth century was the transformation of plants that cannot naturally fix nitrogen to become nitrogen fixers. This involved genetically modifying bacteria that are symbiotic to these plants with nif genes or to genetically modify the plants with the nif genes with the role of the bacteria. One of those projects was to turn cereal crops into plants that could utilize nif bacteria.

While creating new plants with nitrogen-fixing properties would contribute to sustainable agriculture, there were many obstacles.

The primary obstacle to expanding nitrogen fixation to non-leguminous plants is the difficulty of restructuring a plant to bear root nodules similar to those of legumes where nitrogen fixation works (Krimsky & Wrubel, 1996).

Research continues to design bacteria to deliver fixed nitrogen to cereal crops. No commercial applications have yet been developed as it has proven more challenging than originally believed (Ryu et al., 2020). Other prospects for social sustainability, or the development of new positive social applications of GMOs, are products that are improved nutritionally without creating any detriment to the environment. The first application of this came with Golden Rice. The rice genome was genetically modified to contain a precursor to vitamin A, which the body can turn into the vitamin. In vitamin A, scarce communities' blindness is common. This product would help reduce the worldwide prevalence of child blindness.

In 2000, the international media proclaimed that a new variety of GMO rice could save the lives of one million children a year. A Swiss scientist Ingo Potrykus had genetically modified the rice endosperm to be beta carotene enriched. Consumption of the rice converts the beta carotene to vitamin A. The idea of beta carotene conversion or biofortification was a new strategy for the biotechnology to elevate the public's acceptance of GMOs. Research into biofortified rice began in 1982 under leadership of the Rockefeller Foundation.

The GMO rice was called "Golden Rice" reflecting its orange carotene color. The availability of Golden Rice to poor developing nations in South Asia and Sub-Saharan Africa where vitamin A deficiency (VAD) was prevalent could in theory prevent countless cases of blindness and death. VAD increases the risk of measles and diarrhea in children. It was estimated that 93% of VAD-related deaths could be traced to those regions.

In nearly 40 years of research into beta carotene-fortified rice, the primary concerns were over its safety and efficacy. Another concern was whether consumers would accept rice of a different color to which they had been accustomed. For the GMO rice to be successful, it had to exhibit a sufficiently high conversion factor from beta carotene to vitamin A in order that standard dietary amounts of rice would prevent VAD.

A sustainable approach to bioconversion would have to ensure that it was safe over a person's lifetime and that the agricultural fields of Golden Rice would be safe for the environment. Some scientists expressed concern that the new beta carotene pathways in rice created by the gene insertion could produce toxic by-products including retinoid compounds.

In 2019 Golden Rice was approved for use as s human food in the Philippines. It was permitted for planting in July 2021. The American Society of Human Nutrition reported that a cup of Golden Rice consumed daily could provide 50 percent of the Recommended Daily Allowance for vitamin A (Tang et al., 2009).

Unsustainable Applications of GMOs

While the examples of GMOs given in the previous section show the possibility that these crops can contribute to sustainable agriculture, the next examples will illustrate how other GMO crops are unsustainable under the criteria discussed in the introduction. One of the earliest GMOs to enter commercial markets were herbicide tolerant crops. The premise behind developing these crops was that they would resist any damage from spraying herbicides, which could then be used to eliminate weedy competitors of the crops.

In 1970 Monsanto synthesized the herbicide glyphosate. It was approved by the Environmental Protection Agency as a broad-spectrum herbicide in 1974. Glyphosate's herbicidal property is based on its inhibition of 5-enolpyruvylshik imate-3-phosphate (EPSP) synthase, the enzyme catalyzing the final step of the shikimate pathway, which is necessary for the plants to synthesize amino acids. Monsanto scientists delivered genes into crop cells that produced proteins which interfered with glyphosate's pathway for inhibiting EPSP synthase, which makes the crops glyphosate tolerant. Corn and soybeans were among the first crops genetically modified to become glyphosate tolerant. Monsanto called these products "Roundup-Ready" seeds. Roundup was its patented formulation of glyphosate.

Glyphosate-based herbicides (GBH) have proven to be highly controversial as they are implicated in causing human cancers and because they have been found detrimental to the environment. In 2015 the International Agency for Research on Cancer (IARC), an independent research arm of the World Health Organization, issued a report that glyphosate is a probable human carcinogen. Other studies have found GBH deleterious to many species, including butterflies, quails, frogs, fish, tadpoles, and soil microorganism (Krimsky, 2021). Given the extensive environmental impacts of GBH and its suspected effects on humans, this class of herbicides does not meet the standards of agricultural sustainability. Thus, the system that GBH is embedded and co-dependent, namely, GMO transgenic crops, cannot be sustainable.

Since the publication of *Silent Spring* by Rachel Carson, the role of insecticides to prevent crop damage has been extensively studied. The impacts of insecticides (or biocides as Carson would call them) on non-target species and its toxicity to humans have been the primary considerations in excluding them from sustainability regimes.

The prospects of genetically engineering plants with insecticidal proteins provided another approach to the management of insects. It has been estimated that 37 percent of what is planted is lost from insect herbivores. In the mid-1970s, scientists discovered a plasmid (circular piece of DNA) in the bacterium *Bacillus thuringiensis* (Bt), which encodes crystalline proteins (more than 200 types) that is toxic to specific insects.

Natural forms of Bt have been used by farmers since the 1920s and was approved in the form of granules or as a liquid under the organic standards as a natural microbial pest control agent. The term Bt-transgenic crops had the insecticidal properties of Bt built into the genome of the plant. The first approved Bt crops were introduced into commercial agriculture in 1995 and included potatoes, corn, and cotton. Its application was expanded to many other crops after the Environmental Protection Agency and the Food and Drug Administration declared that the Bt δ-endotoxin expressed in crops is not hazardous to humans.

The prospect that Bt transgenic crops would substitute for billions of pounds of chemical insecticides that are sprayed promiscuously on farmland leaching into waterways made these GMO crops a prospect for sustainable agriculture. There were several problems that arose from the extensive use of Bt crops. First, insects became resistant to them. Because the presence of Bt endotoxins were on the crops at every stage of growth, the pressure on insects for mutations was great. According to Tabashnik et al. (2013): "The increase in documented cases of resistance likely reflects increases in the area planted to Bt crops, the cumulative duration of pest exposure to Bt crops, the number of pest populations exposed and improved monitoring efforts."

Much has been learned about the effect of Bt crops on non-target species in cases where insects and animals consume the crop and when the breakdown products of the Bt crops leach into water systems. In his dissertation at the University of Bern Yi Chen (2021) wrote:

"even after 100 days, plant-derived Bt protein can be detected in water. These studies indicate that the Bt protein released from remnants of Bt plant tissue remain in water for quite some time. The Bt protein from transgenic crops can get into water through the pollen, rhizosphere secretion, post-harvest crop residues and other forms of diffusion, so that organisms in aquatic ecosystems are principally exposed to Bt protein. The Bt protein can potentially aquatic organisms when they are susceptible to the protein at the encountered concentrations."

Once the insects became resistant to Bt crops, farmers had to either use chemical pesticides or accept crops that had more than one toxic protein. Thus, plants had to be genetically modified to contain a pyramid of toxic proteins, imposing additional risks on the crops and the environment (Huang, 2021). Many of the early gains of reduced insecticide use had diminished. Tabashnik and Carriere (2019) wrote in the *Journal of Economic Entomology* that "the global monitoring data reviewed here reveal 19 cases of practical resistance to Bt crops, which is field-evolved resistance that reduces Bt crop efficacy and has practical consequences for pest control."

Secondly, organic farmers, who used Bt sparingly at the times that insects were invading their crops, could no longer used the pesticide because of the rise of Bt resistant insects. For these reasons, transgenic Bt GMO crops are not likely to be sustainable. Some commentators believe the only limit to Bt crop sustainability is the growth of insect resistance (Glaser & Matten, 2003). But there are other issues affecting sustainability such as the effect of ubiquitous Bt on non-target insects and other arthropods. Notwithstanding the skepticism about BT crop sustainability, there have been very favorable reports. One 2011 report indicated that Bt cotton may serve as an example of how African countries can achieve sustainable agriculture. "Bt cotton increased yields, raised income, saved energy use (increased productivity and economic returns" (Vitale et al., 2011). In contrast, an analysis of GMO sustainability in Switzerland where transgenic crops were reviewed on both socio-economic and environmental sustainability reached an unfavorable conclusion. "Results show that the six out of seven scenarios showed a lower socio-economical sustainability for genetically modified crops compared to conventional systems." They did report a slight improvement in the environmental component (Wohlfender-Bühler et al., 2016). Question the long-term sustainability of Bt crops. "The evolution of resistance and cross-resistance threaten the sustainability of genetically engineered crops that Bt crops produce insecticidal toxins derived from the bacterium *Bacillus thuringiensis*. And Li et al. question whether Bt crops will be sustainable. "The current trend of increasing proportion of cultivation of transgenic Bt crops is pushing towards dramatic destabilization of the agroecosystem, thus raising sever concerns about the sustainability of transgenic Bt crops as an effective management tool for the control of target insect pests in the future" (Li et al., 2019). The National Research Council issued a report in 2010 on how genetically engineered crops impact farm sustainability stating that "the application of genetic-engineering technology to crops has not developed novel means of pest control, such as developing plant mechanisms to resist pest damage, nor has it reached most minor crops" (National Academies of Sciences, 2010).

Because GMOs cover a wide range of crop phenotypes, including disease resistance, herbicide tolerance, biofortification, a broad-brush assessment of a crop's contribution to sustainability cannot be made a priori. It must be assessed in the context of the agricultural system. Myhr and Myskja (2018) note:

"With NBTs [new breeding technologies] it may be possible to develop plants that have increased drought and saline tolerance relevant for the developing world. Such gene-edited plants can have positive, stable long-term effects on environment, economic and social conditions, and hence be argued to contribute to sustainability. Conversely, the same plants may also have adverse long-term environmental effects." Sustainability means more than high yield or improving the commercial value of crops to farmers, but as Azadi et al. (2015) note: sustainability must respect natural resource preservation, biodiversity, and the beauty of the environment, which without an ethical support system cannot compete with agricultural economics.

Conclusions

Sustainable agriculture is not premised on a particular crop of set of crops, but rather on an integrated ecological system. A GMO crop cannot be assessed for its sustainability by itself without considering the system in which it is embedded. While a single crop or procedure cannot turn a non-sustainable agricultural system into a sustainable one, it can turn a sustainable system into a non-sustainable one. This has been shown in the example of glyphosate-based herbicides (GBHs), which are paired with herbicide tolerant crops (i.e., Ready Roundup crops). Even for a sustainable agricultural system, GBHs will turn it into a non-sustainable one.

The ethics behind sustainability is fundamentally in the selection of a system, where all the parts fit together to preserve the ecology for future generations. Some refer to the system as Integrated Pest Management, agro-ecology, or more generally integrated agriculture. The animal systems interact with the crops; the soil microbes interact with the plants; the diversity of crops support stability. Or as Shearman (1990) noted, "sustainability is a concept in search of a framework instead of a definition." Anderson et al. (2019) argue:

> Sustainable, eco-rational IPM strategies rely on a diversified portfolio of tactics, of which GE crops represent a valuable tool. By leveraging the experiences gained with GE crops, understanding the limitations of the technology, and considering the successes of GE traits in IPM plans for different crops and regions, we can enhance the durability and versatility of IPM plans for future crops.

Transgenic crops that work effectively within the integrated system can contribute to sustainable agriculture. Tabashnik and Carriere (2017) state: "Transgenic crops are most desirable when used in combination with other control tactics in integrated pest management. The sustainability of transgenic crops for pest control depends largely on the will to implement this [IPM] knowledge." Azadi et al. (2015) acknowledge the higher productivity of some GMO crops but they assert that "it remains questionable whether GM crops can result in a revolution towards 'agricultural development' and 'sustainability' or make only a significant change in 'agricultural growth'."

What this paper has shown is that GMO use is embedded in a system. If the system meets the criteria of sustainability, the individual GMO may either contribute to or violate the criteria. That can only be decided after a full analysis of each GMO product is completed including how it interacts with the agro-ecological system.

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Correction to: Limits of Debate: Governance of Human Embryo Research and the Making of the Fourteen-Day Rule

J. Benjamin Hurlbut

Correction to:
Chapter 9 in: E. Valdés, J. A. Lecaros (eds.), *Handbook of Bioethical Decisions. Volume I*, Collaborative Bioethics 2, https://doi.org/10.1007/978-3-031-29451-8_9

The last name of J. Benjamin Hurlbut was unfortunately published with an error. The initially published version has now been corrected.

The updated version of this chapter can be found at
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