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Comparative Issues in the Governance of Research Biobanks

Property, Privacy, Intellectual Property, and the Role of Technology

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Contents

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Chapter 1
Introduction: A Law and Technology Approach to the Law of Biobanking

Umberto Izzo, Matteo Macilotti, and Giovanni Pascuzzi

This book constitutes the proceedings of the International Conference entitled "Comparative Issues in the Governance of Research Biobanks: Property, Privacy, Intellectual Property, and the Role of Technology", held in Trento, in May 2010. The Conference saw the participation of eminent scholars from Italy, US, UK, Canada, Germany, and France that gave rise to an engaging debate about the legal issue related to the biobanks.

This event was organised by the *Trento LawTech Research Group*,[1] a research team established at the Department of Legal Science of the University of Trento. In general, the group has a primary aim of exploring the complex interactions between law and technology. In particular, it has a special focus on the peculiar field of the biobanking technology.

The idea of exploring the relationship between law and technologies originates from the belief that for a deeper understanding of a given technological phenomenon, a strictly legal analysis is not sufficient. Instead, it is necessary to embrace an overall approach in order to combine the technical and social analyses of the phenomenon with the legal one.

It is self-evident that in nature, there are only "phenomena" and the distinction between legal, social, and technical aspects is only a *fictio*, which is functional to study these phenomena. The legal analysis represents only one factor for the comprehension of the "technological fact", and this analysis must be combined with the results of the studies conducted by other disciplines to understand the phenomenon. Therefore, a multidisciplinary approach is an "imperative" and the main issue is to find a method and a language that can be used in communicating with the different sciences involved.

[1] http://www.lawtech.jus.unitn.it/.

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Every science has its own technical language and its own point of view, but all sciences share the same "fact". Therefore, one safe starting point is the analysis of the fact. Nowadays, technology grows fast and the understanding of the "technological fact" becomes increasingly complex and requires the constant support of experts in the specific field involved. On one hand, the necessary recourse to the experts implies the risk of increasing the fragmentation of the knowledge, but from the other hand, it pushes (even) the legal scholars to invest more energy into the debate with the other branches of science. In particular, the complexity of "technological phenomena" highlights the needs for the jurists to acquire the fundamental technical notions of the phenomenon that they intend to study. Examples of this fact are innumerable in the field of human biotechnology. One glaring instance is the famous and controversial judgement of Judge Swift in the case *Association for Molecular Pathology, et al.* v. *USPTO*, which has been carefully analysed in one of the contributions proposed here. In this case, Swift spent most part of the judgement in the explanation of the biological characteristics of DNA, an essential premise to understand the meaning and the consequences of the patent on DNA.

Against this backdrop, this book bucks for representing an occasion of the debate about law and technology through the analysis of the legal issues related to a peculiar "technological fact", the "research biobanks", a phenomenon which has become increasingly relevant in the medical research landscape.

Before exploring the structure of this book, it appears relevant to investigate more deeply into the complex relationship between law and technology, starting from the thesis developed by the Trento LawTech research group.

As a first remark, it is worth noting that if, on one hand, law is used for the regulation of technology; on the other hand, law employs technologies to pursue its own goals, the relationship is bidirectional. We may observe this feature in different contexts.

Firstly, technology may change the contents of protected legal interests. One clear example is the right to privacy, which has been transformed by the rise of IT from the "right to be let alone" to the "right of controlling the information" pertaining to the individual (so-called right of "informational self-determination"). In the biobank context, this aspect assumes a crucial role. As we will appreciate, by virtue of the change of contents of the right to privacy, persons involved in the biobanking are not only entitled to the right to be protected from illegitimate intrusion, they also have the right to control the data stored in the biobank and eventually to withdraw their consent. In biobanking, the right of "informational self-determination" constitutes the rationale that gives rise to the debate between scholars who deem it necessary to obtain a strict consent for every use of tissue and data and scholars who consider a broad consent sufficient. Secondly, the emergence of new technologies can transform well-established scenarios. If, in the past, the research opportunities were limited by the possession of adequate numbers of biological samples, biobanks permit a greater number of researchers to have access to biological resources and facilitate data sharing between researchers. As we can appreciate in the articles concerning open-access in biobanking, the biobanks could unhinge the "market" of medical research, thus, making it more competitive.

Thirdly, the features characterising a given technology shape the rules linked to this technology. It is one thing to have rules concerning a material entity; it is another to have rules concerning the bits. In some cases, this implies the need to re-frame concepts that traditionally refer to material things, such as ownership and possession, and to draw on new concepts shaped on the reality of the immaterial entities. As it can be verified in some contributions of this book, the double dimension of human tissue, both material entity and source of genetic data, represents the main challenge in the definition of the legal status of human tissue. This double dimension stresses the need to create a new legal paradigm to define the relationship between person and human tissue detached from his body. Whilst tissue is commonly referred to property rights, the information obtained from tissues are not considered as property and their protection is based on the protection of personality rights.

Fourthly, technologies create new commodities and the law is continuously faced with the need to regulate these commodities, which were unknown in the past. Biobanks *per se* could be seen as a new "commodity", even if a particular one. Some contributions of this book clearly portray the new challenges related to the access to this new commodity and the efforts that numerous legislators are spending to regulate it. The difficulty to provide a regulation derives from the crisis of the classical categories of law that seem unable to encompass the new issues raised by this phenomenon. The new interests linked to human tissues and their crucial role in the biomedical research transform the concept of "human body" and create an inedited tension between the interests of the medical research, the interests of the market, and the protection of human dignity.

Fifthly, the development of new technologies also influences the source and the structure of the rules. In the biobanks context, this feature is particularly evident. The reconstruction of the regulatory landscape shows that in this field we assist to a constant overlap of regulations made by international entities and national institutions with guidelines and best practise written by technical committees and other stakeholders. It seems increasingly difficult for the operators who work in the biobanking to "juggle" in this "tangle" of regulatory instruments and technical norms. This aspect is underlined in the major part of the contributions and highlights the need to rationalise the regulatory framework.

Moreover, in the European countries, the lack of harmonised legislation in this matter represents an obstacle in building common scientific infrastructures and suggests the need for an intervention of the European legislator.

Sixthly, technology not only changes the law setting, but also sometimes guarantees the enforcement of the norms. In biobanking, one of the clearer examples of this fact is the encryption and anonymisation systems that are used to ensure that the privacy of the people involved is respected. These technological measures reduce the risks related to the spread of data and enable the building of a safe environment for data sharing.

IT systems increasingly assume a pivotal role in the governance of biobanks. The P3G and EnCoRe projects, for instance, prove the trend of using technology to assure the exercise of patients' rights (the right to withdraw the consent, the right to

control the data flow, and the right to know in which research project tissue and data are used), embedding the legal norms into the technological infrastructures. Technology achieves levels of protection and interaction that law instruments solely cannot assure. Law and technology become two complementary factors for protection and promotion of the patients' rights in medical research.

As to the analysis of the structure of the book, it seems important to state that every essay presents an autonomous point of view, and, in some case, the views differ, which is normal in debate. The scope of this volume is not to underpin a particular thesis, but to give an account of the debate that has arisen in the biobanking context, and above all, to put on the arena some original ideas and re-interpretations of old questions.

This book is composed of three parts. The first one is devoted to the analysis of the issues related to property and privacy in the biobanking context. These themes are analysed from different perspectives. Below is a brief excursus of the contributions.

The contribution of Stephen Munzer introduces us in the discussion about research biobanks and synthetic-biology repositories with respect to autonomy and ownership, through a detailed examination of a pair of examples, the autonomy-based interests of the Havasupai Indians in their blood samples, and ownership structures for zinc finger proteins.

Starting from another perspective, Roger Brownsword draws a larger regulatory picture of biobanking, with its own triple bottom line (i) that participation and the use of participants' samples and data are based on free and informed consent; (ii) that the privacy, confidentiality, and fair data processing rights of participants are respected; and (iii) that the proprietary rights (if any) of participants are respected.

The article of Eric Feldman and Chelsea Darnell focuses the attention on the US Genetic Information Nondiscrimination Act (GINA) and its consequence on biobanking. In particular, the Authors, moving from the question does genetic information warrant special legal protection, and if so, how should it be protected, analyse how GINA regulates genetic information, and conclude with the provoking assumption that GINA seems to be a "solution in search of a problem", an "unnecessary piece of legislation that creates more problems than it solves".

The contribution proposed by Naomi Hawkins et al., offers an interesting analysis about the ownership of biomedical information in biobanks. Through a careful study of the concept of property applied to the biomedical information, the authors show that, "the notion of ownership of information in the context of translational research in genomics is legally meaningless". In particular, they conclude by establishing that, "[T]here is no such thing as ownership of information as a matter of law, and to discuss such matters using the language of property does not benefit any of the parties involved in research, whether they are participants, researchers, research institutions or research funders".

In her essay, Mariachiara Tallachini aims to overcome the property/privacy dichotomy in the regulation of human tissue. The author explores the main existing legal framing of biological materials, both in the US and the EU contexts, and the potential for reconciling individual and collective dimensions in biobanking

through a participatory approach. She draws an intriguing comparison between the regulation of human tissue and the environment, showing that the notions of both the subject of rights (the rights holder) and the object of property (the object held) have failed to fully represent the potential of collective sharing.

In his essay, Amedeo Santosuosso addresses the provocative question of whether privacy should be abolished in genetics and biobanking. Starting from a meticulous analysis of the interests at stake on the genetic information, he reaches the conclusion that the answer could be twofold: "The answer is yes, if privacy claims to extend biologically to any (even smaller and less significant) biological connection at any time. The answer is no, if privacy refers to people directly involved, their free determination and, in a wider area, only to those who have, or are able to, demonstrate a concrete interest, provided that public interest to the "common genetic railway" is properly stewarded".

The contribution of Paolo Guarda aims to analyse the interaction between research biobanks and the Electronic Health Records (EHR) systems. The interaction between these two technological tools represents a step toward the definitive breach of the wall between clinical medicine and research, and it is one of the key points in order to build a process of personalised medicine. From the legal point of view, this interaction changes the role of the patient and, as remarked by the Author, "allows us to 'spotlight' the patient as both the person from whom tissue samples are collected and managed within the biobanks and also as a main character in the informational flow that must return to him as the result of the analysis undertaken by biobank research".

The last article of the first part of the book, presented by Matteo Macilotti, dealt with the issue of informed consent in biobanking. In this contribution, the Author tries to overcome the debate about the possibility or impossibility of configuring a broad consent in biobanking, through the study of the legal status of human tissue. In particular, Macilotti proposes to modulise the level of information given to the patient on the specific interests that are recognised on the human tissue. Therefore, the main issue shifts from the acceptability of the broad consent to the proof of whether the information provided are sufficient to permit to the patient to protect his interests.

The second part of the book is devoted to the analysis of the issues related to intellectual property in the biobanking context. This topic is particularly complex and involves numerous stages of the biobank activity, the access to the resources collected in the biobanks (both tissue and data); the sharing of the data obtained through the analysis of tissue and the related information; the database protection, the patents developed, thanks to the tissue stored in a biobank, and the certification of the biobanks.

In the first contribution of the second part, Donna M. Gitter examines several challenges to widespread application of open-source principles to biobanks. In particular, she analyses the "reluctance among researchers to share their data; the challenge of crafting appropriate publication and intellectual property policies; the difficulties in affording informed consent, privacy, and confidentiality to research participants when data is shared very widely; controversy surrounding the issues of

commercialisation and benefit-sharing; and the complexity of establishing a suitable infrastructure". Her study is not limited to open-source model, but she proposes an alternative approach towards biobanks, the "fair access" model.

In a different perspective, the same topic is discussed in the essay written by Richard Gold and Dianne Nicol. Starting from the observation that in the last decade, the costs of drug discovery have grown exponentially while innovation has at best remained stable, or, at worst, in decline, the Authors recognise that collaborations and data sharing could offer important tools to rationalise the cost in time and money of drug discovery. Gold and Nicol carefully examine two models of collaboration through biobanks: open-access and open-source biobanks. Although the Authors highlight the problems that characterise each of these models, they reach the conclusion that, "where there exists a clearly defined community in which norm development and enforcement is possible, open-access would seem to be the preferred route. Where this feature is missing—the community may be too large and heterogeneous, there may be resistance to the use of norms and guidelines, or there may be a lack of leadership within the community—open-source may be the better option".

In the third contribution, Roberto Caso and Rossana Ducato dealt with the same general topic discussed in the two former contributions, but they pay more attention to the concrete biobanks governance. Biobanks are considered here not only as a provider of tissue and data but also as "data-centre" that collect the data derived from the researches conducted on tissue. Firstly, the Authors examine how IP, technology, social norm, and contracts interact in the specific context of data sharing in research biobanks. Secondly, they analyse the reasons why researchers should share the information with others, emphasising the crucial role of the contract as legal tool to encourage the researchers to share data with each other.

The contract represents the focus of the Thomas Margoni contribution. He analyses the role that Material Transfer Agreement (MTA) has accrued in the exchange of bio-materials between research institutions. Starting from the importance which MTAs have acquired in the most recent years, the Author remarks how an uncontrolled proliferation of MTAs could bring about a highly inefficient market situation. Showing how standardisation could partially fix these problems connected to the exchange of bio-materials and bio-samples, Margoni stresses on the importance of foreseeing a minimum level of flexibility in order to catch the huge varieties of situations involved. Finally, Margoni observes how new digital and web-based technologies can contribute in achieving such trade-off between standardisation and flexibility.

Going one step further, Michael Mattioli and Gideon Parchomovsky describe two new models for managing patents, raw data, and research findings at biobanks: quasi-patents and semi-patents. Quasi-patents are patents which can only be enforced against one's competitors and are a specially-tailored type of traditional patent that respect the importance of basic research. Differently, in the semi-patents model, researchers would be free to assert their patents against whoever they wish, but their right to exclude would be contingent on cooperation, with a mandatory data sharing policy. As highlighted by the Authors, both models can be understood

"as reconfigurations of property's fundamental components: quasi-patents represent a shift of dominion, while semi-patents involve a splitting of the asset combined with new rules of acquisition and retention".

The contribution proposed by Mark Perry offers an early study on a variety of practise of biobanks with regard to accessibility of materials and data, and the types of their collection. The study takes into consideration both human and non-human biobanks. While human biobanks are more regulated, with regard to the non-human biobanks, Perry observes a great divergence between how biobanks manage their material accessions, whether it is a physical sample use or even access to the data.

In the last article of the second part, Matteo Ferrari examines an unusual but crucial topic that has profound practical impact on the regulation of biobanking, the certification. After a description of the notion of certification, the Author tries to provide a taxonomy in terms of functions and types of certification and offers an analysis on how certification bodies can be rendered accountable for the service they provide. Afterwards, Ferrari focuses his attention on the biobanks' context, adapting the general features of certifications described so far to the peculiar aspects characterising biobanks. Finally, he explores some of the possible benefits and problems that certifications can generate for the biobank domain.

The last part of the book presents three contributions by scientists who are involved as operators in the real world of biobanking.

The first one, by Mattia Barbareschi and his collaborators, focuses the attention on the workflow and organisation of a specific type of biobank, the tumour biobank. The analysis is based on the experience developed in the recently established Trentino Biobank (TBB), one of the most developed Italian biobanks based in Trentino Autonomous Province.

Moving from the Italian context to the European scenario, Giuliano D'Agnolo and Elena Bravo examine the Italian prototype networks of research biobanks. In particular, they give a report of the Italian participation to the Biobanking and Biomolecular Research Infrastructure (BBMRI), a European network that aims to harmonise standards for sample collection, storage, and analysis; to harmonise data collection and database infrastructure; to provide ethical and legal guidance; and to develop a sustainable funding model for biobanks.

In the third and last contribution, Barbara Parodi, Paola Visconti, Tiziana Ruzzon, and Mauro Truini dealt with the complex issue of the governance of biobanks for cancer research and they propose a peculiar model of material transfer agreement. Authors base their report on the experience gained, thanks to the IST Biological Resource Centre experience.

The editors gratefully acknowledge that the present book has been made possible thanks to a grant from the MIUR (Italian Ministry of Education) obtained, after a scientific selection by a national commission, with the FIRB project "Genetic testing and biobanks: bioethical issues between law and society".

Part I
Property and Privacy in Biobanking

Chapter 2
Research Biobanks Meet Synthetic Biology: Autonomy and Ownership

Stephen R. Munzer

Abstract Two examples of research biobanks are discussed. The first is a set of stored blood samples taken from Havasupai Indians by scientists at Arizona State University (ASU). The second is a set of zinc finger proteins (ZFPs) and zinc finger nucleases (ZFNs) assembled by Sangamo BioSciences, Inc. of California. Both examples involve individual and group autonomy, informational asymmetries, and exchange. Both examples are controversial but for different reasons. In the Havasupai case, the Indians claimed that the scientists used the blood samples to analyze a Havasupai predisposition to diabetes, to which they consented, and to extract information about Havasupai inbreeding, schizophrenia, and geographical origins, to which the Indians did not consent. Eventually, ASU returned the blood samples and compensated the tribe and some individual members. Scrutiny shows that the Havasupai complaints were mainly justified. As to ZFPs and ZFNs, some lawyer-scientists contend that Sangamo's preeminent patent and trade secret position unfairly hinders others from benefiting from Sangamo's knowledge. Close examination shows no unfairness in the Sangamo case, for two reasons. First, the Zinc Finger Consortium provided an open access alternative to dealing with Sangamo. Second, under standard economic criteria Sangamo did not have a monopoly on zinc finger technology.

2.1 Introduction

This article discusses research biobanks and synthetic-biology repositories with respect to autonomy and ownership. My conclusions rest on both philosophical and economic considerations. These considerations pertain to the interests and rights of

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sample donors, as well as inventors and their assignees. Instead of abstract, highly theoretical article, I examine a pair of examples in detail, the autonomy-based interests of the Havasupai Indians in their blood samples and ownership structures for zinc finger proteins (ZFPs). These examples differ from each other in many ways. However, they share more features than might readily appear, which makes it both feasible and instructive to treat them in the same paper. Among the shared features are the use of biological repositories, the exercise of both individual and group autonomy, some informational asymmetries, and an element of exchange. To illustrate the latter, the Havasupai case involves autonomously granted informed consent to donate blood samples in return for more information about Havasupai propensity to diabetes, and the zinc finger technology example involves the receipt of patent rights in return for teaching others how to make these biotechnological inventions.

One set of conclusions I draw centres on the special case of securing informed consent from indigenous peoples for donating their blood and tissue samples. (1) Indigenous peoples are more likely than members of the culturally dominant population of a country to misapprehend what is being given up in return for what is promised. (2) They are also less likely to see the risks that some genetic testing poses to their conceptions of themselves and their way of life. (3) The root value underlying the most promising approach to this special case is autonomy. This value undergirds self-governance and rights of control, which are in turn fundamental to privacy, confidentiality, and informed consent.

A different set of conclusions relates to the combination of intellectual property and open-source alternatives in one area of protein engineering. (4) The growing area of zinc finger technology has a pre-eminent player in Sangamo BioSciences, Inc. because it holds a larger share of patents and trade secrets in this technology than any other entity, whether private firm or academic institution. (5) At the same time, a loose association of scientists called the Zinc Finger Consortium has placed its independent contributions to the field in the public domain and made some of its physical embodiments, such as reagents, available at a lower price than reagents sold by Sangamo. (6) However, one cannot be confident that the counterweight the Consortium poses to Sangamo will endure or that it is generalisable to other areas of biotechnology.

2.2 Research Biobanks

Research biobanks are repositories of biological samples, especially human samples. Synthetic biology is a relatively new discipline that seeks to build more complicated biological structures out of basic biological bits.[1] Synthetic biologists

[1] A recent achievement of synthetic biology was the transplantation of a synthesised genome into a recipient cell whose genetic material had been removed (Gibson et al. 2010, p. 52).

often use repositories of biological samples. The MIT Registry of Standard Biological Parts, for example, records and indexes the following in ascending order of complexity: functional DNA sequences, parts composed of functional DNA sequences, devices composed of parts, and systems built out of devices.[2] Repositories are thus central to both research biobanking and the practice of synthetic biology. Moreover, the repositories can overlap if, say, at a given time a biobank and the MIT Registry contained only DNA sequences. Typically, though, research biobanks and synthetic-biology repositories contain different items, different purposes, and raise different issues.

Among the issues raised by biobanks are privacy, confidentiality, and informed consent. Very few biobanks state squarely on their consent forms that donor privacy and confidentiality will not be protected at all. If a competent, informed donor consents to having no privacy or confidentiality, his or her consent should be honored in the name of donor autonomy. Of course, researchers may be unaware at the time of donation of all the possible uses of the sample years later. A donor could give consent for all possible uses, although it is debatable whether the donor's consent could be informed in the case of uses that did not exist at the time of consent. However, in most cases of genetic sampling, donors have well-founded concerns about privacy and confidentiality. An example is the denial of health coverage in some countries to individuals who have a known genetic propensity to contract certain diseases. These cases require researchers to uncouple the identity of the donor from a number or other marker assigned to the sample. Further, researchers should use various mechanisms, such as confidentiality requirements imposed on secondary researchers who might be careless in handling sensitive data or a Certificate of Confidentiality or some other means to protect the donor's identity from legal discovery. No single model of property rights perfectly balances the biobanks' interests with donors' interests in privacy and confidentiality.

[2] The DNA sequences must have some known function in a cell, such as coding for the protein keratin. Parts consist of at least two functional DNA sequences that produce something in a cell, such as coding for conjugation plasmids. Devices consist of at least two parts that together perform a more complicated function in a cell—for example, a ribosome binding site, a protein coding region, a promoter, and a terminator can form an inverter (repressor), which lowers an intracellular signal in order to reduce the amount of a target protein. The MIT Registry has not yet carefully defined a system, but Jha 2005 suggests that a collection of devices that performs a task would be a system. For instance, three inverters working together could form a system for quantifying gene expression in terms of PoPS (Polymerase Per Second). Part Types, http://partsregistry.org/Part_Types. Accessed 25 October 2010. Parts, Devices, and Systems, http://partsregistry.org/cgi/htdocs/AbstractionHierarchy/index.cgi. Accessed 25 October 2010. Part Types: Measurement Systems, http://partsregistry.org/wiki/index.php/Part_Types:Measurement_Systems. Accessed 25 October 2010.

2.3 Havasupai Blood Samples

First, I take up a case involving the acquisition of blood samples for a research biobank by Arizona State University (ASU) scientists led by Dr. Therese Markow. Here, philosophical considerations of autonomy loom larger than economic analysis. The Havasupai Indians, who live deep in the Grand Canyon, have a high rate of diabetes. In 1990, they gave blood samples and, hence, DNA to ASU researchers to find out why. Over time, researchers used these and later DNA samples to investigate genetic causes of schizophrenia, in which inbreeding among the Havasupai might be a factor. Other research on the DNA samples confirmed that Havasupai ancestors had crossed over the frozen Bering Sea into North America, which conflicted with traditional Havasupai stories that they had always lived in North America, specifically the Grand Canyon.

The Havasupai sued the Arizona Board of Regents, which governs ASU, in state[3] and federal[4] courts. The Havasupai alleged that they had consented only to research on diabetes, not on schizophrenia, inbreeding, or migration.[5] On 20 April 2010, the Board of Regents agreed to a settlement with the Havasupai.[6] It would pay $700,000 to 41 of the tribe's members. It would return all blood samples to the Havasupai and provide educational and other assistance to members of the tribe. By the time the Board of Regents settled, it had spent US$1.7 million in litigation.[7]

My intention here is to get to the root of the matter. Therefore, I defer momentarily comments on privacy, confidentiality, and informed consent, as well as remarks on disputed issues of fact. The root of the matter, I suggest, lies in the autonomy of the tribe and its members. By "autonomy" I mean, in the case of individual human beings, the psychological capacity to be self-governing. Because this understanding of individual autonomy refers to self-governance, I must say something about it. To be self-governing is to determine, guide, and control one's behaviour and character over time based on reasons.[8] The possession of autonomy does not entail the possession of self-governance, for two reasons. First, an individual might have the capacity to be self-governing but neglect to exercise that capacity. Second, an individual might want to exercise her autonomy, and indeed struggle to do so, but might not succeed because of external factors beyond her

[3] *See*, e.g., Havasupai Tribe v. Ariz. Bd. of Regents, 204 P.3d 1063 (Ariz. App. Div. 2008) (reversing the Superior Court's grant of summary judgment in favor of the tribe and its members and remanding for further proceedings).

[4] *See*, e.g., Tiloussi v. Ariz. State Univ., 2005 WL 6199562 (D. Ariz.) (dismissing some claims but allowing others to proceed).

[5] Second Amended Complaint, Havasupai Tribe v. Ariz. Bd. of Regents, CV2005-013190 (filed 22 February 2006) (on file with the author).

[6] Settlement Agreement and Mutual Release, Exhibit C, Havasupai Tribe v. Ariz. Bd. of Regents, CV2005-013190 (6 March 2010) (on file with the author).

[7] Harmon (2010); Tribal Genes and a Fair Settlement, N.Y. Times, 27 April 2010, at A22.

[8] My argument is compatible with various accounts of autonomy and self-governance. I am sympathetic to the (different) accounts of Bratman (2007) and Christman (2009).

control. To illustrate the latter point, a woman might want to protest working conditions by participating in a strike against her employer, but if she has a family and little money, and if the strike might go on for some while, then economic factors over which she has no control may hinder her from acting on her reasons to participate in the strike.[9]

The autonomy of a group depends on the autonomy of the individuals, past and present, who comprise it. The group autonomy of a tribe, then, involves the self-governing behaviour and character of members of the tribe across time. Groups, like individuals, can be autonomous without being self-governing. Once more, this is true for two reasons. Groups might neglect to exercise their autonomy. Or they might want to exercise their autonomy and struggle to do so, but external factors beyond their control may block them from acting on the reasons they have. If a group is both autonomous and self-governing, it need not be the case that all members of the group unanimously favor a particular course of action. Still, there must be some institutions or other means by which the members, or at least the competent adult members, of the group can discuss and decide which action to take.[10] Neither autonomy nor self-governance is an all-or-nothing affair. There can be degrees of each, whether we are talking about individuals or groups.

The keys to individual and group self-governance are rights to control certain aspects of the situation in which individuals and groups find themselves.[11] It is for this reason that I earlier deferred comments on privacy, informed consent, and confidentiality. If a person did not have autonomy, self-governance, and some rights of control, one would be hard put to explain why privacy is valuable and important. To have privacy is to have some control over access to one's person, knowledge of one's location, and information about oneself. In order to give, or withhold, informed consent to the use of one's blood samples, it is necessary to have information about what is at stake, a capacity to absorb and evaluate that information, and the absence of internal or external factors that preclude one from acting on reasons in deciding whether to give or withhold consent. Similarly, confidentiality requires that one have justifiable confidence that, whatever one's reason for consenting to donate blood for research, the entity to which the blood is given will respect the parameters of one's consent. Hence, in my view, privacy, informed consent, and confidentiality are intellectually dependent on autonomy,

[9] Faden and Beauchamp (1986), pp. 235–273, draw a useful distinction, which I happily accept, among autonomous persons, autonomous choices and autonomous actions. However, their book was written before the contemporary philosophical discussion of autonomy, self-governance and control rights, which are important to my analysis, had reached its current maturity. Neither do they devote much attention to groups.

[10] I take no position on which institutions or means Indian tribes in the United States should use in governing themselves. For the view that they should use principles drawn from their own tribal tradition and culture, see Riley (2007).

[11] Christman (1994) describes the centrality of "control rights" to autonomy and their relation to property. Christman (2009) elaborates on this position by drawing attention to the surrounding social relations and the historical embeddedness of autonomy and self-governance.

self-governance, and control rights. This proposition holds, in different ways, for both individuals and groups.

Once we have these considerations securely in hand, we possess the philosophical bases for a preliminary analysis of the Havasupai consent, or lack of it, in donating blood samples to ASU researchers. Havasupai autonomy and self-governance help to ground a right held by the tribe and its members not to donate blood samples unless they give informed consent. In an unproblematic situation, the tribe and its members could, upon receiving adequate information, decide to donate blood samples for research on diabetes but not on schizophrenia or population genetics. In the actual situation behind the litigation, we see informational asymmetries. The ASU researchers know, better than the Havasupai, what scientific information blood samples can supply.[12] The Havasupai know, better than the researchers, the tribe's beliefs, practices, and stories. The actual situation also involves an element of exchange. The Havasupai want to know more about their propensity to diabetes. In return, the ASU scientists want to use Havasupai blood samples not only for diabetes research, but also research on schizophrenia and population genetics. What makes the actual situation problematic is whether the Havasupai gave informed consent for the scientists to investigate schizophrenia and population genetics.

It is exactly here that we must be aware of disputed issues of fact. The litigation ended in a settlement. The plaintiffs made certain allegations of fact. The defendants denied some of those allegations.[13] No judge or jury made findings of fact. The absence of such findings stymies the most desirable sort of analysis and renders many questions unanswerable. To what did the plaintiffs consent? What information did the defendant researchers give the plaintiffs? Did that information suffice for informed consent and, if so, consent to what, precisely? If the defendant researchers were partly in the wrong, was this because they intentionally deceived the plaintiffs, or because they did not give the plaintiffs enough information to make informed consent possible? If the defendant researchers obtained written informed consent from the plaintiffs, did the researchers archive the consent forms so that they could be retrieved during the course of litigation?

[12] No researcher can predict all possible uses of blood samples many years down the road. Austin and Lemmens (2009) call this "the problem of the unknown future". They wisely distinguish between consent to participate in a biobank and consent to participate in specific research projects of the biobank. They argue plausibly that if a biobank satisfies certain conditions, then we can relax strict requirements for informed consent despite the problem of the unknown future. Among these conditions are (1) the biobank has a governance structure that provides consistent information practices across all projects, (2) the biobank uncouples health information from individuals' identities, and (3) the biobank's governance structure protects individual privacy interests (Austin and Lemmens 2009, pp. 111, 112–113, 118–121). This possible solution may work less well for informed consent by groups, which they do not address.

[13] Defendant Arizona Board of Regents' Answer to the Havasupai Tribe's Second Amended Complaint, Tiloussi v. Ariz. Bd. of Regents, CV2005-013190 (30 October 2006) (on file with the author).

Although historians may eventually be able to answer at least some of these questions, in this article, I must focus on such evidence as is readily available. An important feature of Havasupai autonomy and self-governance is the tribe's interest in controlling representations of its beliefs and stories. To modern ways of thinking, some Havasupai choices seem irrational. If inbreeding conduces to schizophrenia, it seems important to know that.[14] If Havasupai ancestors came from Asia, that seems worth knowing. But modern ways of thinking are not the only ways. The Havasupai alleged that they were consenting to give biological samples only for research on diabetes. They saw the other uses as objectionable. One member of the tribe explained: "We say if you [inbreed], a close relative of yours will die"; she found a research article reporting "a high degree of inbreeding" to be offensive.[15] Another member said that, "when people tell us, 'No, [the Grand Canyon] is not where you are from,' and your own blood says so—it is confusing to us. . . . It hurts the elders who have been telling these stories to our grandchildren".[16] There was also concern that population-genetics analysis could undermine tribal land rights. "Our coming from the canyon", said another member, "that is the basis of our sovereign rights".[17] The Havasupai are not incompetents, and they have an autonomy-based interest in controlling representation of their culture.[18] It would take more argument than space would allow to show that they have a *right* to their individual and group autonomy.

Yet, how strong is their *interest* in autonomy? To answer this question, it is essential to look at the experience of the Havasupai and indeed a great many Native American tribes. In the United States, scientists since the nineteenth century and earlier have frequently treated Native Americans as a repository of specimens for measurement, experiment, and deeper understanding of human beings. To this end, scientists have exhumed the bodies of American Indians and studied them. Even today, some thousands of these bodies are kept in museums. A still more dramatic example is the case of Ishi, who, after he emerged from the wilderness, resided in a California museum as a living exhibit, and, in that capacity, served as an educational tool for those, mainly whites, who came to watch him.[19] Thus, the American Indian experience with science reflects colonial domination. White scientists in the

[14] Horvatta et al. (1999), p. 1114. There are many varieties and subtypes of schizophrenia. Am. Psychiatric Ass'n, Diagnostic and Statistical Manual of Mental Disorders 297–323 [4th ed. Text Revision (2000)].

[15] Harmon (2010), *supra* note 7.

[16] *Id.*

[17] *Id.*

[18] Rohter (2007) recounts the giving of blood samples by the Amazonian Karitiania Indians in return for promises of medicine, even though they never received any medicine, and cell lines and DNA from their blood were distributed to scientists world-wide at $85 per sample by Coriell Cell Repositories of Camden, New Jersey, USA.

[19] Ishi (c. 1860–1916), the last of the Yana people of California to live most of his life outside European–American culture, spent almost all of his final years in the University of California at Berkeley Museum of Anthropology. For further information, see Kroeber (1961, 2002).

United States, at least from perspective of Native Americans, often treated them as raw material to advance "science" and a way to get at the "truth" about them that would somehow satisfy non-Indians' curiosity about Indians.[20] At the turn of the millennium, different tribes had varied attitudes on this matter. Some tribes wanted to engage with contemporary science, but desired to have some control over the process so that they were not simply used as raw material to advance the aims of non-Indians. One can look at the Havasupai litigation in this way. The Havasupai autonomously submitted to study in the hope that it would lead to greater understanding of their propensity to develop diabetes. From that one cannot validly infer that they autonomously submitted to be studied for purposes of learning more about their risks of schizophrenia or the population genetics of their geographic origins.

The strength of the Havasupai interest, and the interest of other indigenous peoples, in autonomy and self-governance, depends partly upon the distinction between practices and beliefs, and the reasonableness of these practices and beliefs. Consider the disturbing example of practices of female genital cutting in sub-Saharan Africa and scattered areas of the rest of the world. These practices range from nicking the clitoris to removing all or part of it, to cutting away the labia minora, removing the inner portion of the labia majora, and, ultimately, to infibulating the labia majora or vagina after all or some of these other parts have been removed. I refuse to call such practices "female circumcision", for almost none of them involve removing only the prepuce of the clitoris, which would be the closest analog to male circumcision. Nor is it generally accurate to describe these practices as "female genital surgery", because that phrase suggests a precision that is lacking when using a razor blade or a piece of glass to cut away part or all of the external female genitals. Female genital cutting is typically done on young to pubescent girls, whose power to act autonomously in this matter is almost nil. There may be some positive effects: social approval and access to marriage. They pale in comparison to the enduring adverse effects: infections, pelvic pain, loss or diminution of sexual response, compromised urination, uncomfortable vaginal intercourse, complications in childbirth, and death.[21] Practices of female genital cutting depend partly on some questionable, even outrageous, beliefs: that the clitoris is "poisonous" and can kill any man whose penis touches it in intercourse, that the clitoris interferes with "menstruation, impregnation, and childbirth", that female genital cutting protects "a woman from aggressive males" and prevents her from acting on an otherwise "unbridled and voracious appetite for promiscuous sex".[22] So far as I can see, the interest in the group autonomy of a tribe or other indigenous group, in the form of attachment to long-standing practices of female

[20] One can see a related phenomenon in scientists' treatment of African Americans in the Tuskegee Syphilis Experiment (1932–1972). Office of the Sec'y (1979), also known as the Belmont Report, summarizes ethical principles for the treatment of human research subjects in the wake of the Tuskegee Experiment, which let blacks with syphilis go untreated. Thomas and Quinn (1991), p. 1498.

[21] Lightfoot-Klein (1989).

[22] *Id.* at 38–39.

genital cutting based on many false beliefs, is not nearly strong enough to overcome the physical and psychological harm done to young and pubescent girls.

The Havasupai, it will be said, have no such harmful practices. The Havasupai themselves may urge that their beliefs about inbreeding, schizophrenia, and their origins are not harmful. I agree that these beliefs are not remotely as harmful as the false beliefs some use to justify female genital cutting. Still, one can see Havasupai beliefs as beneficial in some ways and harmful in others. They are beneficial insofar as stories about origins give comfort to older members of the tribe as valued and respected members of the community. They are also more broadly beneficial insofar as their beliefs about themselves and their origins tie the community together and enable it to survive as a distinct group in an otherwise non-Havasupai world. Nevertheless, these beliefs can cause some harm insofar as they mask the risks of inbreeding and schizophrenia, foster empirically incorrect, or at least highly implausible, views of tribal origins, and hold the Havasupai back from participating in a larger world.

With respect to these beliefs, it is important to separate the origin stories from the connection between schizophrenia and inbreeding. To have false beliefs about your geographic origins when better information is available is undesirable in obvious ways. In most instances, though, it inflicts little, if any, physical or psychic harm on those who hold these false or at any rate implausible, beliefs. The connection between schizophrenia and inbreeding is a rather different matter. If there is a genetic predisposition to schizophrenia, and if intermarriage practices persist, then some Havasupai children will develop schizophrenia at a greater than normal rate. This mental illness causes extraordinary suffering. In that respect, one might think that having schizophrenia could be akin to the horrors of female genital cutting.

Even though the results of female genital cutting and inbreeding-related schizophrenia are both very bad outcomes, there remains a difference between the two cases. One can prevent the adverse consequences of female genital cutting by not performing it on young to pubescent girls. What philosophers call the "non-identity problem" is not at issue.[23] A Sudanese girl who might have her genitals cut is already in existence. She is still the same person, according to most philosophical views of personal identity, whether she is cut or not. In contrast, the non-identity problem is at the root of the schizophrenia/inbreeding case. If a Havasupai man and woman decide to marry outside the tribe, or if they decide to adopt rather than have their own biological children, and if they make these decisions to avoid the risk of schizophrenia in their biological offspring, then the biological children who might otherwise have been born would never exist. These possible children, who never come into existence, are not identical with any children the man and woman would have if they marry outside the tribe or if they adopt. In short, the non-identity problem is central to the schizophrenia/inbreeding case, whereas it is wholly absent from the case of believing tribal origin stories.

[23] Parfit (1984), pp. 351–379, formulates the non-identity problem and discusses whether the fact of non-identity makes a moral difference.

Now, we would do the Havasupai and other indigenous peoples a great disservice by characterising their practices, beliefs, and stories as pre-modern or ignorant while letting pass some of the harmful practices and false beliefs held by non-Indians. On the one side, many indigenous beliefs relating to respect for the earth and its creatures, the natural balance of the environment, and the value of a sustainable way of living are hardly irrational. In fact, the beliefs just listed are starting to seem more enlightened among non-Indians than ever before. On the other side, a good many non-Indian practices and beliefs are vulnerable to criticism. Unbridled consumption of recreational drugs is a harmful practice. Many beliefs of the major world religions, such as Christianity and Islam, are non-scientific and, in the eyes of many adherents, not even claimed to be scientific. Those Christians who believe, based on Genesis 1:1–31, that God created the earth in 6 days of 24 h each will find it difficult to square this belief with a university-level course in evolutionary biology.

Taking into account all of the circumstances, I think that most Havasupai beliefs in this area represent a trade-off between holding onto a traditional belief system and way of life, and recognising the scientific evidence thought to be persuasive in the broader culture. The trade-off is often defensible, even if it is also a matter of regret for both Havasupai and members of the dominant culture. In that respect, it is somewhat like the practices of some American parents to home-school their children so that "creation science" may be taught to them instead of prevailing hypotheses and theories about human evolution.

All the same, the schizophrenia case does not seem to offer an acceptable trade-off. We do not yet know enough about the genetics of schizophrenia to say how much risk inbreeding creates of developing it in different populations. However, if it is the case that there is a significantly higher risk that inbreeding Havasupai couples will have a child who eventually develops schizophrenia, then it is not justifiable for them to take the chance of having a biological child who could become schizophrenic. Out-marriage and adoption are acceptable ways of precluding this possibility. Other ways might exist. For instance, if pre-implantation genetic diagnosis is a highly reliable way of determining whether an ovum fertilised in vitro carries the undesirable gene or genes, and if there is no moral objection to terminating this fertilised ovum should it have the relevant gene or genes for schizophrenia, then that appears to be another defensible way to act on a moral decision.

2.4 Synthetic Biology

2.4.1 Repositories of Biological Materials

I turn now to synthetic biology in the United States. Here, economic rather than philosophical considerations are paramount. The MIT Registry is by far the main synthetic biology repository in the United States. Though MIT may own the

Registry in some sense, it does not own the contents of the Registry. In fact, the contents of the Registry are open to all academic and industry laboratories; thus, it is an open-access repository. The justification usually given for this open access is that the contents should be available to all in the interests of scientific progress. The expectation is that those who use items from the Registry will contribute any new DNA sequences, parts, devices, and systems back to the Registry. However, the Registry imposes no legal duty on its users to conform to this expectation. It is therefore possible that a user could access certain items, create a new device or system, and seek to patent the invention.

A related endeavor comes from the BioBricks Foundation (BBF).[24] The BBF is a not-for-profit foundation formed by scientists at MIT, Harvard, and the University of California, San Francisco. It aims to encourage biological engineering and give the public access to such technologies. To these ends, the BBF has legal documents addressing the ownership and use of various biological parts once they enter the public domain. It gives free access to all through the MIT Registry. The BBF also aims to set scientific and legal standards for submissions to the Registry.[25]

The openness of the BBF is guaranteed by the BioBricks Public Agreement (BPA). The BPA is not yet in force but a draft is available for public comment.[26] In its draft form, the BPA is a bilateral agreement between contributors and users of genetic parts. As with the Registry, the BPA expects that users will contribute any new parts to the BBF, but the BPA does not require them to do so. Hence, some users could seek patents on inventions involving, say, biological devices or systems. If they do so, under the BPA, they would almost surely have to provide attribution to some other contributor.

Not all repositories used in synthetic biology are open-source, for some firms protect the contents of their repositories by patents or trade secrets. Patents on biological items can impede other researchers in two main ways, which are not mutually exclusive. One way is "royalty stacking", sometimes also called a "patent thicket". These terms apply to any situation in which a product reads on many patents and patentees demand licenses from potential users. Even if no patent is foundational, the various owners of non-foundational patents can insist on licenses from users of their patented technology. At worst, anticommons might develop.[27] At a minimum, royalty stacking increases the costs of future research and the prices to buyers at all levels.

[24] The BioBricks Foundation, http://openwetware.org/wiki/The_BioBricks_Foundation. Accessed 25 October 2010. BBF links to the MIT Registry are informal. However, both organizations support openness in synthetic biology and technical standards for DNA parts.

[25] Anderson et al. (2010); The BioBricks Foundation, http://biobricks.org. Accessed 25 October 2010.

[26] Comments on Draft Version 1a, dated January 2010, may be sent to Drew Endy or David Grewal. The BioBricks Public Agreement, http://www.biobricks.org. Accessed 25 October 2010.

[27] Heller (1998), p. 621.

Another way to impede research is enforcement of patents that are foundational to related work in the field. The expression "foundational patent" is not a statutory term like "written description" or "enablement". Nor do judges use it very often. However, the term has become part of the patter of some academic patent specialists, and one might associate its use with the playing out of the debate over anticommons issues in the law and policy pertaining to biotechnological patents.[28] Some scholars use the term "foundational patent" to mean a patent "with broad claims that appear [. . .] important to a large percentage of work in [a] field",[29] or a patent "with claims covering a basic aspect of [a] technology"[30] This usage is akin to the label "pioneering" applied to both inventions and patents, which some suggest might merit interpreting the scope of their claims more broadly, with or without help from the doctrine of equivalents.[31] Beyond these few possibly helpful remarks, it is doubtful that calling a patent "foundational" has any very precise meaning or any rigorously articulated criteria of application.

If that is correct, then it makes sense to ask who might create, in the minds of some legal scholars, the impression that a particular patent is foundational. There are two obvious sources: patent lawyers[32] and experts in the field of invention. I suggest that both are involved. On the one side, patent lawyers are conversant with the drafting of claims. If a scientist has invented something which he or she thinks of only narrowly, and if the scientist has little knowledge of or experience with the patent system, then a patent lawyer will often draft claims language so as to broaden the scope of the invention, and thus obtain for the scientist the most powerful body of rights surrounding the invention. Indeed, a lawyer has a professional obligation to clients to advance their interests by securing the broadest possible claim scope without infringing another's patent or repeating prior art.[33] On the other side, experts, be they scientists or engineers or others, are apt to have a deeper and broader understanding of the field of the invention than the patent lawyer. Thus, once an expert's patent lawyer has alerted him or her of a possible broadening of claim scope, the two can work together to evaluate how to broaden the claim without trenching on another's patent or prior art. For instance, they might collaborate in describing an invention as not merely using a complicated protein to insert a new gene in a particular plant, but using that protein to insert various new genes in plants of different sorts. Ultimately, the drafting will fall to the lawyer, for why else would a scientist or biotechnology company seek a legal counsel at the stage of patent prosecution?

[28] Heller and Eisenberg (1998), p. 698 and Munzer (2009), p. 271.

[29] Kumar and Rai (2007), p. 1751.

[30] Cahoy and Glenna (2009), p. 426.

[31] Duffy (2004), pp. 440–441 and Lichtman (2005), p. 2013.

[32] Here I would include registered patent agents along with patent lawyers.

[33] Solomon v. Kimberly-Clark Corp., 216F.3d 1372, 1382 (Fed. Cir. 2000).

2.4.2 Zinc Finger Technology

A prominent example of allegedly foundational patents has to do with "zinc fingers", which are small protein structural motifs that coordinate zinc ions so as to stabilise the folding of proteins. Whether certain patents on zinc finger (ZF) technology really are foundational will be left open until an account of the technology has been presented.[34]

The "fingers" part of the label comes from the fact that their shape "holds", "grasps", or "pinches" a DNA sequence. A protein containing ZF components is called a ZFP. ZFPs bind DNA (or RNA) sequences through helical and sheet-like components which are themselves bound to a zinc ion through cysteine and histidine amino acid residues. ZFPs are not the greatest thing since cold beer, but they are useful as transcription factors and as regulators of gene expression. Most are found in nature. Some are engineered; they are products of synthetic biology. Zinc finger nucleases (ZFNs) are synthetic restriction enzymes that fuse a ZFP-domain to a DNA-cleavage domain. ZFNs are used to cleave certain DNA sequences and then insert a new or repaired gene into a particular region of an organism's genome. ZFNs are useful in recombinant DNA technology. They do not occur in nature.

ZFPs fall into five main groups based on the protein folds near the zinc finger motif. The most common fold group is Cys_2His_2-like. Over 10,000 members have been found, of which more than a thousand are thought to be transcription factors.[35] Cys_2His_2-like ZFPs can bind up to four DNA base pairs because of their tandem helical structure. Other fold groups include the gag knuckle (in HIV proteins), the treble clef (in some transcription factors), the zinc ribbon (in many proteins), and the Zn_2Cys_6-like (in some yeast transcription factors). Which fold group a ZFP falls into affects how many DNA base pairs it can bind.[36]

ZFPs and ZFNs are valuable in contemporary biotechnology, and collections of them held by firms and research institutions are specialised biobanks. Protein engineers use ZFPs to control levels of gene expression. Other uses of ZFPs include angiogenesis and the targeted introduction of specific genes into cells. Protein engineers use ZFNs to advance basic research and therapeutic applications. The main players in ZF technology are research universities and biotechnology firms. Sometimes, access to the fruits of this technology is open, and sometimes it is not. When access is not open, ZFPs and ZFNs may be protected by trade secret or patent law.

The most significant player in ZF technology is Sangamo BioSciences, Inc., of Richmond, California. With any new technology, it is often hard to be certain which patents are foundational. Sapna Kumar and Arti Rai, writing in 2007, characterised

[34] For a good summary of the structures and functions of ZFPs, see Klug (2010).

[35] US patent no. 7,705,139 (filed 19 October 2006) (issued 27 April 2010).

[36] Krishna et al. (2003), p. 532.

Sangamo's patents on certain technologies to be "arguably foundational".[37] As to Sangamo's ZFP technology, Kumar and Rai were more cautious. They called Sangamo's ZFP patents "quite powerful" even though "none of these is necessarily a foundational patent".[38] Shubashini Chandresekharan, Sapna Kumar, Cory M. Valley and Arti Rai, writing in 2009, gave a new picture based on additional information and further analysis.[39] They identified four Sangamo patents as "foundational" on the ground that it is hard to work around them.[40] Three of these patents protect a modular design strategy for three-finger ZFPs.[41] A fourth patent protects the best methods for improving binding specificity in certain situations.[42] This second article no longer speaks of patent thickets, though there is a brief reference to an "anticommons".[43] Instead, its authors emphasise the technological and economic power of Sangamo's portfolio of forty-two ZFP patents as of 31 December 2007. Sangamo, they write, "has now consolidated the majority of [the] patent estate"[44] for ZFPs. It has the "dominant position in ownership of patents covering relevant research tools and methods, including foundational patents on enabling technologies".[45] Sangamo exercises "a powerful monopoly over an important platform technology".[46]

Much more of great interest lies in the article by Chandrasekharan and her colleagues, but before exploring it, I wish to supplement some of their data. Their closing date for ZFP patents was the last day of 2007, as indicated in Fig. 2.1.[47] I have, with help, identified 12 ZF patents acquired by Sangamo in the period from 1 January 2008 to 1 June 2010, along with other ZF patents obtained during this period by other institutions working in this area of biotechnology.[48] Figure 2.2 puts

[37] Kumar and Rai (2007), *supra* note 29, at 1755 (using their definition from 1751 quoted at text accompanying note 29 *supra*).

[38] *Id.* at 1756. For critical but appreciative discussion of their article, see Munzer (2009), *supra* note 29, at 290–297.

[39] Chandrasekharan et al. (2009), p. 140. Their article is by far the ablest short account of the patent/trade-secret/open-source landscape of zinc finger technology.

[40] *Id.* at 141.

[41] *Id.* US patent no. 7,177, 766 (filed 2 April 1001) (issued 13 February 2007) (incorrectly numbered in Chandrasekharan et al. 2009, *supra* note 39, at 141); US patent no. 6,785,613 (filed 28 March 2002) (issued 31 August 2004); US patent no. 6,453,242 (filed 19 January 1999) (issued 17 September 2002).

[42] US patent no. 6,794,136 (filed 20 November 2000) (issued 21 September 2004).

[43] Chandrasekharan et al. (2009), *supra* note 39, at 140.

[44] *Id.*

[45] *Id.* at 141.

[46] *Id.* at 143.

[47] *Id.* at 142 (Fig. 2).

[48] For help I am most grateful to Jamie L. Summers and UCLA reference librarian Stephanie Plotin. The Appendix lists these patents.

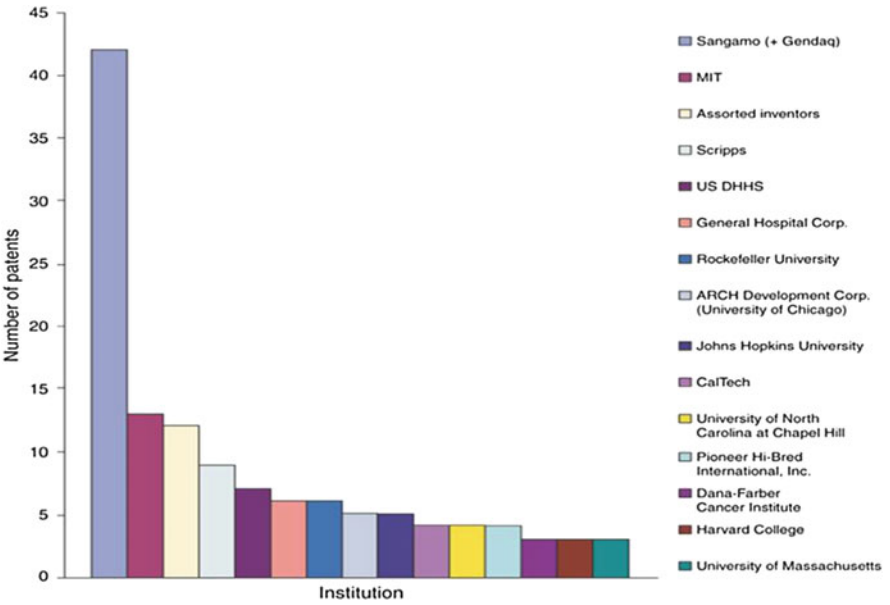

Fig. 2.1 Ownership (assignees) of US ZFP patents by institution, 1993–2007. Institutions with three or more US ZFP patents are shown. Data are complete as of as of 31 December 2007. *Source*: Chandrasekharan et al. (2009), *supra* note 39

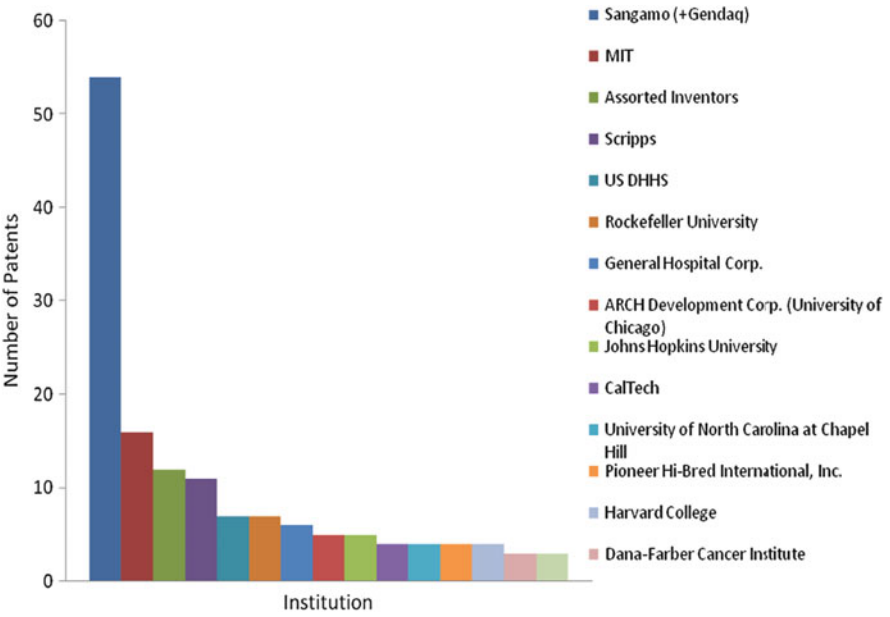

Fig. 2.2 Ownership (assignees) of US ZFP patents by institution, 1993–2010. Institutions with three or more US ZFP patents are shown. Data are complete as of as of 1 June 2010

the two data sets together.[49] The overall picture remains largely the same: Sangamo is still the pre-eminent player in zinc finger technology. As of 22 October 2010, the company had no marketable products besides reagents and other supplies sold to researchers. It had a market capitalisation of US$178.54 million as of that date.[50]

2.4.3 *Intellectual Property Rights and Open-Source in Zinc Finger Technology*

As Chandrasekharan and colleagues explain, Sangamo's success depends on many factors besides its patent portfolio. First, Sangamo is able to attract public funding and private capital. Second, it acquired Gendaq Ltd. and its ZF patents in July 2001, obtained licenses from other institutions, issued licenses on Sangamo's own patents, and executed material transfer agreements with other companies and academic research groups. Third, it has protected its unpatentable or not-yet-patented ZF technology by trade secrets. Fourth, it has rarely enforced its patents against academic researchers, who often pay no attention to whether something they want to use is under patent; leaving them alone may actually increase the worth of the company. And fifth, "Sangamo's consolidation of relevant IP rights may ease negotiation cost burdens for commercial entities that want to work in this area, as they will have to negotiate licenses with only one institution instead of several".[51] Given that Sangamo lacks the financial resources to develop its platform all by itself, the company may be one of those rational maximizers economists like to tout.[52]

At this point, reactions often divide according to viewpoint. Those who are generally skeptical of biotechnology patents might well see Sangamo as just another time-limited monopolist. Those who believe that patents give an incentive for useful biotechnology inventions may see Sangamo as a paragon of how our system of intellectual property should work.

However, there is another side to this matter besides patents and trade secrets: the availability of open-source alternatives. The most substantial of these is the Zinc Finger Consortium. It aims to further research and development in engineered ZFPs and ZFNs, make this engineering platform liberally available to academic scientists, and promote the application of designer zinc finger technology.

[49] The methodology used to obtain the new data was almost exactly the same as that employed by Chandrasekharan et al. (2009), *supra* note 39, at 141 (Fig. 1). For the details, see the end of the Appendix. There is a counterpart to Appendix 1 in the online supplementary materials to Chandrasekharan et al. (2009), *supra,* which are available at http://www.nature.com/nbt/journal/v27/n2/extref/nbt0209-140-S1.pdf. Accessed 25 October 2010.

[50] Sangamo (SGMO) trades on Nasdaq and closed at US$4.01 on 21 October 2010, with a 52-week range of US$2.81–6.82. The stock pays no dividend and showed earnings per share of negative US $0.34. *See* http://finance.yahoo.com/q?s=sgmo. Accessed 25 October 2010.

[51] Chandrasekharan et al. (2009), *supra* note 39, at 142.

[52] *Id.*

To achieve these aims, it has brought together many scientists, and made its software, protocols and reagents available to academic scientists. The Consortium offers a pair of web-accessible software tools: Zinc Finger Targeter (ZiFiT) for the design of zinc finger arrays, and ZiFDB as a database of these arrays. It has a protocol called OPEN, which gives a publicly available method for engineering ZFNs. It also has a set of reagents for zinc finger domains, which it sells for less than comparable reagents available from Sangamo. The Consortium's scientists often publish papers in this area of biotechnology. Their research papers, of course, count as prior art, and thus can thwart the patenting of some advances in zinc finger technology by commercial firms like Sangamo.[53]

The net effect of these open-source alternatives is to serve as a counterweight to Sangamo's patents, trade secrets, and pre-eminent intellectual property position. This effect should reduce the hand-wringing over Sangamo's intellectual property rights in zinc finger technology. One might well conclude that we have reached a healthy accommodation between private property rights held by Sangamo and a few other commercial entities, the interests of academic scientists, and the desires of open-source advocates reflected in the operations of the Zinc Finger Consortium and similar groups. Indeed, Sangamo's patents do not elicit the furious opposition that some unpopular patents do, such as those held by Myriad Genetics and the Wisconsin Alumni Research Foundation (WARF). Myriad insists on a high price for its tests for the breast and ovarian cancer genes *BRCA1* and *BRCA2,* including mutations of these genes—currently about US$3,000 for the most thorough test.[54] No doubt there was rejoicing in some quarters when a federal district court held Myriad's patents invalid.[55] WARF's patents on human embryonic stem cells were long the bane of many academic scientists and consumer groups. When the USPTO Board of Patent Appeals and Interferences rejected one of the patents, some regarded it as a major victory.[56] In contrast, Sangamo has no genetic test for which it is extracting a high cost from patients and health insurers. Nor are any of

[53] *Id.*; The Zinc Finger Consortium, http://www.zincfingers.org. Accessed 25 October 2010. Sander et al. (2007). The Consortium also archives plasmids that code for zinc finger modules, which Addgene distributes to academic scientists. Addgene, http://www.addgene.org. Accessed 25 October 2010.

[54] Genetic Testing Facilities and Cost, 19 March 2009, http://www.breastcancer.org/symptoms/testing/genetic/facility_cost.jsp. Accessed 25 October 2010.

[55] Ass'n for Molecular Pathology v. U.S. Pat. & Trademark Office, 702F. Supp. 2d 181 (S.D.N.Y. 2010) (holding that Myriad's method and composition of matter claims are invalid under 25 U.S.C. §101). The case is on appeal to the Federal Circuit.

[56] Foundation for Taxpayer & Consumer Rights v. Patent of Wisc. Alumni Res. Found., 2010 WL 1734377 (Bd. Pat. App. & Interf.) (reversing the Examiner's decision to withdraw the rejection of claims 1–3 of US patent no. 7,029, 913 under 35 U.S.C. §103(a) as obvious and anticipated by prior art); PRN Newswire, Patent on Human Embryonic Stem Cells Rejected After Consumer Groups' Appeal, 3 May 2010, *available at* http://www.prnewswire.com/news-releases/patent-on-human-embryonic-stem-cells-rejected-after-consumer-groups-appeal-92668229.html (last visited 25 October 2010) (reporting that "two consumer groups . . . praised [the decision] as a victory for open scientific inquiry"). WARF is appealing. The decision does not affect WARF US patents nos. 5,843,780 and 6,200,806, which also cover embryonic stem cells.

Sangamo's patents remotely as fundamental as the three embryonic stem cell patents issued to WARF.

The foregoing assessment of the ZF landscape reflects my fascination with "ownership structures" for various areas of technology. For me, this phrase includes not only which firms or other entities hold patents and trade secrets in a technological area. It also includes the placing of information and inventions in the public domain by entities of various sorts, from individuals to firms to open-source organisations. Software is a conspicuous example of an area of technology in which the aggressive assertion of intellectual property rights is sometimes the exception rather than the rule.[57] So my interest in ZF inventions hardly lies in the belief that ZF technology will turn out to be remarkably successful. Rather, it springs from my interest in the various ownership structures that have emerged in different fields of biotechnology. These structures have arisen against the backdrop of the following features at least: the use of biological repositories, the existence of informational asymmetries (for instance, Sangamo knows, better than its competitors, which "rule sets" connect modular multi-finger ZFPs to like-numbered DNA subunits), and the element of exchange in the "teaching bargain" that is part of receiving a patent. Features of this sort, though exhibited in different ways, help to understand some of the similarities between the Havasupai case and ZF technology.

It is useful to elaborate on the Havasupai and ZF parallels. Just as the tribe and its members and the ASU researchers sought to exercise and protect their autonomy, so do the individuals who work for biotechnology firms or universities as research scientists or executives, as well as those active in open-source organisations. As to group autonomy, the analogs of the Havausupai tribe and, in some ways, the Arizona State University, are corporate firms like Sangamo and open-source entities like the Zinc Finger Consortium. In regard to the element of exchange, the Havasupai litigation turns on what the ASU researchers gave the tribe in return for blood samples. Apparently, they gave them, or were on the way to giving them, information the tribe sought about its members' predisposition to diabetes. They also gave them, or were on the way to giving them, information about inbreeding, schizophrenia, and geographical origins—information that the tribe claimed it neither sought nor wanted. Sangamo occupies a position that is partly similar to that of the ASU researchers, for Sangamo can give information to others who want ZF technology. The issues then become what others are willing to give Sangamo in exchange for access to its technology, and whether Sangamo's pre-eminent patent and trade secret position unfairly hinders others from benefiting from Sangamo's knowledge.

Reasons abound for seeing no unfairness here. Sangamo's researchers and executives are exercising their individual autonomy in making scientific

[57] Mann (2006), p. 1, Roberts et al. (2006), p. 984 and Zittrain (2004), p. 265.

breakthroughs. The Zinc Finger Consortium provides an open access alternative to dealing with Sangamo. Sangamo is often willing to license its ZF technology to others, which allows its knowledge to be exploited by competitors in the field, which in turn leads to efficient proliferation of output and innovation. In this connection, the heart of the wrangle over supposed foundational patents is not so much whether they are hard to work around but whether Sangamo needs to license its portfolio to capitalise on it. Because Sangamo is a relatively small company that has few in-house products, frequently, outside laboratories and firms are the most efficient practitioners of Sangamo's discoveries.

Let us now see if we can press more deeply on the ownership structure in zinc finger technology by considering two questions. First, how and why has a nice balance been achieved between patent protection for Sangamo and other entities and the open access made possible by the Zinc Finger Consortium? Five factors seem to be important. (1) The basic science grew out of the discovery of the structure of DNA and the study of nucleic acids in the middle of the twentieth century. Investigations into the structure of chromatin in the mid 1970s led to a greater understanding of the nucleosome, its structure and the folding of DNA in chromatin by the early 1980s. From there, interest emerged in the sort of chromatin that is involved in transcription, which issued in research on ways to control gene expression.[58] The analysis of transcription factor IIIA revealed the repeating motif now called zinc fingers.[59] Eventually, scientists seized on the interaction of ZFPs with DNA, classified ZFPs into different groups and created ZFNs.[60] (2) At this point, scientists in the industry, as well as academia, explored the practical uses for ZFPs and ZFNs. Because synthetic biology was taking off as a new and enterprising field of research, it became easier to put samples into biological repositories and create databases on what the various samples could do.[61] Because so many ZFPs occur in nature, scientists could identify their different uses, come up with ways to engineer synthetic ZFPs, and eventually harness ZFP-domains to DNA-cleavage domains in order to invent ZFNs. (3) Because ZF technology is less capital-intensive than the other areas of biotechnological research, small firms like Sangamo and academic researchers could work in the field without undue barriers to entry. As often happens, some innovators concern themselves chiefly with making money and others with gaining fame or contributing to society. There was room for both in ZF technology. Detailed economic analyses are best left to

[58] Brown (1984), p. 359.

[59] Miller et al. (1985), p. 1609.

[60] Klug (2005), p. 213.

[61] A good review of the development of synthetic biology and the state of the art may be found in Special Issue: Synthetic Biology (2010) BioEssays 32:265–363.

others,[62] but the different motives and incentives in this technological field understandably generate a complicated ownership structure. (4) There are not yet explosive commercially useful applications for ZF technology. ZFPs and ZFNs are a niche market. The same might not hold for stem cell technology, whose applications might prove to have great commercial success. (5) All the same, the emergence of the nice balance of ownership structures is not serendipitous. Neither did it emerge as if guided by an invisible hand. The determination of scientists associated with the Zinc Finger Consortium to place their results in the public domain was a mighty contribution to the resulting balance.

Second, is this balance likely to endure? It is far harder to answer this question than the first. A promising place to start is with the proposition that a given ownership structure is apt to remain in place unless something occurs to destabilise it. From that point, it makes sense to inquire what sorts of occurrences might destabilise that structure. One is the invalidation of a patent that is so fundamental to the field that the patentee loses its leverage over the other players. Something like this might be in process with WARF's three stem cell patents, each of which has been invalidated, even though appeals are in progress. This possibility seems unlikely in ZF technology, for, as explained earlier, various Sangamo patents that some consider foundational are not nearly as central to further research and invention as the WARF patents were to hESC research.

Another possible destabilising occurrence is the granting of a new patent that utterly transforms the landscape. An example is the Myriad Genetics patent on the *BRCA1/BRCA2* genes. It is common knowledge in the industry that Myriad was in an extremely close race with another biotechnology company, and that Myriad hit upon the solution shortly before a competitor. As a result, Myriad has made a great deal of money in subsequent years, even though its hegemony is under threat from the adverse decision in the *Association for Molecular Pathology* case.[63] It is improbable that this situation will be replicated in ZF technology. Prior to Myriad's hitting the jackpot, scientists in the field were inclined to believe that genes existed which could predispose individuals to breast and ovarian cancer. The issue was which genes, and which mutations of those genes, were the culprits. Myriad was the first to identify them and create a workable diagnostic test. In ZF technology, there is as yet no holy grail that is known to exist and it is only a matter of finding it.

Still another possible destabilising occurrence is the exit of key players. For instance, the market might lose interest in ZF technology, and Sangamo's business might collapse. Or the scientists behind the Zinc Finger Consortium might lose their passion for ZF technology and begin to work in other fields; then the counterweight that the Consortium poses to Sangamo might wane or disappear. The highly speculative nature of this last possibility suggests that it is time to stop trying to predict the future.

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[62] Lerner and Tirole (2005), p. 99, Lerner and Tirole (2002), p. 197 and Roberts et al. (2006), *supra* note 57.

[63] 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

2.4.4 Why We Should Have Few Reservations About Sangamo's Preeminence

Chandrasekharan and colleagues express at least three concerns over what they call Sangamo's "dominant position".[64] First, "economic theory has ... identified a variety of situations in which increased negotiation costs in concluding licensing deals, as well as other distortions, could impede a monopolist's optimal deployment of a research platform".[65] The authors suggest that foundational patents in the automobile and aircraft industries impeded development.[66] But these industries are so different from zinc finger technology that the analogy is weak. Further, the term "foundational patent" is, as we have seen, so malleable that it has little precise content. The authors also point to Sangamo's failure to conclude a licensing agreement with Phytodyne, a start-up plant biotechnology firm.[67] This example seems inconclusive because both Sangamo and the Zinc Finger Consortium have substantial plant technology underway that uses zinc finger technology. Moreover, the Consortium makes relevant ZFP and ZFN plant technology freely available.

Second, Chandrasekharan and colleagues claim that Sangamo is fastidious in choosing companies with which it will share its technology through licensing or material transfer agreements.[68] This concern has, I think, little weight. Almost any company that has a patent portfolio and trade secrets will have to decide with whom to deal. Business judgments of this sort are sometimes straightforward and sometimes highly complicated. Part of what it means to have intellectual property is to have the legal power to make choices of this kind. That is one reason why open-source alternatives such as the Zinc Finger Consortium are a valuable counterweight. An appropriate response to the authors' concerns about "optimal development" is that, even in the case of open-source platforms, development is often suboptimal.

Third, Chandrasekharan and colleagues express concern about inadequate patent disclosure. They find "problematic" the "strong possibility that at least part of this proprietary information should, under standard doctrines of patent disclosure, be disclosed in the patents themselves".[69] The heart of this concern is that whereas Sangamo's patents on modular three-finger ZFPs should reveal the "rule set" connecting these modules with three-base DNA subunits, in fact, they fail to do so.[70] Underlying this concern is the worry that biotechnology patents might be

[64] Chandrasekharan et al. (2009), *supra* note 39, at 141.
[65] *Id.* at 142, *citing* Farrell and Weiser (2003), p. 85.
[66] The authors cite Merges and Nelson (1990), p. 839.
[67] Chandrasekharan et al. (2009), *supra* note 39, at 142.
[68] *Id.* ("Sangamo ... appears to be highly selective in its choice of collaborators").
[69] *Id.* at 143.
[70] *Id.*

starting to ape the inadequate disclosure associated with patents on information technology.[71]

The authors make a good point. They are well aware that patent applicants often try to disclose as little as possible and claim as much as possible; almost always the applicant and the USPTO go back and forth on this matter. The authors are also aware that the onus rests on patent examiners to make sure that the patent bargain is met: In return for a patent, the patentee is to teach those having skill in the art of zinc finger engineering how to make the patented invention. They express uncertainty on whether academic scientists would be willing to contribute their expertise to make sure examiners get enough disclosure.[72] One possibility, unmentioned by Chandrasekharan and her colleagues, would be to use "peer review" in the patent process.[73] A "Peer to Patent" system has been available in the US for several years for a small number of patent applications. Unlike some, I do not think that, as a general matter, either that informed reviewers will have little incentive to participate or that they will join eagerly.[74] I venture that the constabulary of zinc finger scientists who have an interest in open-source technology can be plausibly seen as providers of peer-to-patent review. If their personal commitment to open-source alternatives disqualifies them for this task, then the same disqualification should apply to industry scientists who are willing to serve as "Peer to Patent" reviewers.

Although Chandresekharan and colleagues offer a remarkable contribution to our understanding of the ZF patent landscape, my ultimate conclusion is that they overstate their case. Sangamo, they tell us, has "consolidated the majority of [the ZF] patent estate".[75] True, but somewhat misleading. The statement is true because, in light of the authors' supplementary Table 1 and my Appendix, as of 1 June 2010, Sangamo owned 54 out of a total of 103 ZF patents, which gives Sangamo a 52.4 % share.[76] That percentage figure is nonetheless a bit misleading because we need to take into account the patentable discoveries and inventions that the Zinc Finger Consortium has placed in the public domain. Chandrasekharan and colleagues also say that Sangamo exercises "a powerful monopoly over an important platform technology".[77] It is correct to say that Sangamo has a time-limited monopoly over the inventions, distributively, claimed in each of its patents. But it does not follow from this proposition that Sangamo has a monopoly (time-limited or not)

[71] *Id.*

[72] *Id.*

[73] Noveck (2006), p. 123; Ctr. for Patent Innovations, N.Y. Law Sch., Peer to Patent: Second Anniversary Report (June 2009), http://dotank.nyls.edu/communitypatent/CPI_P2P_lo.pdf. Accessed 25 October 2010.

[74] *See* Munzer (2009), *supra* note 28, at 276–280.

[75] Chandrasekharan et al. (2009), *supra* note 39, at 140.

[76] The authors' Supplementary Table 1, which is available online (*see* note 48 *supra*), lists a total of 68 patents, and my Appendix lists an additional 35 patents.

[77] *Id.* at 143.

over the inventions, collectively, that make up ZF technology.[78] The context and phrasing of the quoted sentence indicate that Chandrasekharan and colleagues are making a claim about Sangamo's patents collectively—namely, that they gave the company a monopoly on ZF technology at the end of 2007.

I recognise that they are especially concerned about difficulties in accessing ZF technology given Sangamo's patent estate. But perhaps, to give this concern stronger impact, they slide to the idea of a monopoly. Although their concerns about patent disclosure are partly justified, concerns about monopoly are much less so, for two reasons.

First, given the Consortium's work placed in the public domain, and the twelve ZF patents held by MIT and the eleven held by Scripps, it would appear that Sangamo does not exert the dominance that they claim. The lower level of dominance typically requires a "market" share of 65–70 %, so Sangamo's 52.4 % share would not qualify.

Second, Sangamo does not have a monopoly on ZF technology under standard economic criteria. The company appears unable to charge supra-competitive prices without substantial erosion of its allegedly dominant position. In fact, Sangamo has very few products. It has not made a profit since it came into existence in 1995. Even though Sangamo has a slight majority of the patents on ZF technology, there are almost no significant barriers to entering ZF research, and Sangamo has not enforced its patents against university laboratories. Sangamo seems to have caused, at most, minimal anticompetitive harm, for it has not reduced output in order to increase prices. Frankly, the market for ZF products was weak both at the end of December 2007 and on 1 June 2010. To the extent that Sangamo's practices have any anticompetitive effects, they are more than offset by their procompetitive benefits, such as making the ZF field more attractive to other scientists and firms. And yet, investors do not seem to view Sangamo to be on the verge of substantial profits; its stock price has dropped over the last 5 years. Sangamo's 2009 Form 10-K contains over 14 pages recounting the risks to which the company is exposed, including the limited testing performed on ZFP therapeutics, the firm's modest experience with clinical trials, the chance that it cannot get regulatory approval for product candidates, the prospect that competitors will develop superior ZF technologies, and the potential inability to raise additional capital.[79] In my view,

[78] A university might have a rule that students may not enroll in more than six courses per semester. Understood distributively, this statement is true, for each student may take no more than six courses per semester. Understood collectively, this statement is false, for all of the university's students taken together may enroll in hundreds if not thousands of different courses each semester. Copi (1972), p. 96.

[79] Sangamo Biosciences, Inc., 2009 Form 10-K (5 March 2010), at 27–41, *available at* http://files.shareholder.com/downloads/SGMO/1025588598x0x358508/F33603B8-8846-4AB7-9429DEAA74-B57B76/65269_002_SANGAMO_BIOSCIENCES_INC_BMK.pdf. Accessed 25 October 2010.

it is a strange monopolist that has so little power and so few anticompetitive effects.[80]

2.5 Conclusion

The Havasupai example and the zinc finger technology example have more in common than might at first appear. Both involve research biobanks, individual and group autonomy, informational asymmetries, and exchange. As to exchange, the Havasupai litigation turns on what the Arizona State University researchers gave the tribe in return for blood samples. Apparently, they gave them, or were on the way to giving them, information the tribe sought about its members' predisposition to diabetes. They also gave them, or were en route to giving them, information about inbreeding, schizophrenia, and geographical origins—information that the tribe claimed that it neither sought nor wanted. Sangamo Biosciences occupied a position similar to that of the ASU researchers, for Sangamo can offer legally protected information to others working on zinc finger technology. The question then becomes what others are willing to give Sangamo in return for access to its technology, and whether Sangamo's pre-eminent patent and trade secret position unfairly hinders others from benefiting from Sangamo's knowledge. Among the reasons for seeing no unfairness in the zinc finger example are that Sangamo's researchers and executives exercised their autonomy in making scientific breakthroughs, that the Zinc Finger Consortium provides an open access alternative to dealing with Sangamo, and that under standard economic criteria Sangamo does not have a monopoly on zinc finger technology.

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Appendix

To determine the ZF patent landscape from 1 January 2008 through 1 June 2010, UCLA School of Law reference librarian Stephanie Plotin searched the USPTO patent database. Using Dialog®, she searched with the same algorithm used by Chandrasekharan and her colleagues.: (((ZFP) <in> (TITLE,ABSTRACT,

[80] Scott (2005), p. 915, claims that Sangamo has a "monopoly" on ZFNs and a "stranglehold" on ZF technologies. His antitrust analysis in support of these claims is pretty much nonexistent. Whether he would make the same claims in 2010 like he did in 2005, I do not know.

Table 2.1 Ownership and licensing of US patents on the engineering and use of designer ZFPs from 1 January 2008 through 1 June 2010

Patent no.	Title	Patent owner	Licensee	Patent category
US7705139	Zinc finger proteins for DNA binding and gene regulation in plants	Sangamo		ZFP design/ selection
US7605140	Regulation of angiogenesis with zinc finger proteins	Sangamo		Angiogenesis
US7585849	Position dependent recognition of GNN nucleotide triplets by zinc fingers	Sangamo		Modify/affect gene expression
US7560440	Regulation of angiogenesis with zinc finger proteins	Sangamo		Angiogenesis
US7534775	Methods and compositions for modulating cardiac contractility	Sangamo		Modify/affect gene expression
US7491531	Randomised libraries of zinc finger proteins	Sangamo		Screen for targets
US7407776	Engineered zinc finger proteins for regulation of gene expression	Sangamo		Modify/affect gene expression
US7361635	Simultaneous modulation of multiple genes	Sangamo		Modify/affect gene expression
US7358085	Anti-angiogenic methods and compositions	Sangamo		Angiogenesis
US7700523	Nucleic acid binding polypeptide library	Sangamo[#]		ZFP design/ selection
US7521241	Regulated gene expression in plants	Sangamo[#]		Modify/affect gene expression
US7595376	Poly zinc finger proteins with improved linkers	MIT	Sangamo	ZFP design/ selection
US7485441	Chimeric DNA-binding proteins	MIT	ND	Modify/affect gene expression
US7393318	Methods and compositions for interaction trap assays	MIT	Sangamo	ZFP design/ selection
US7442784	Ligand activated transcriptional regulator proteins	Scripps Res Institute	ND	Modify/affect gene expression
US7378510	Synthetic zinc finger protein encoding sequences and methods of producing the same	Scripps Res Institute	ND	Modify/affect gene expression
US7615380	Methods for modulating an immune response by modulating KRC activity	Harvard	ND	ZFP design/ selection
US7601490	Development of influenza A antivirals	Univ of Texas	ND	Screen for targets
US7659362	Metal-binding motif compositions and methods	Academia Sinica	ND	ZFP for non-gene uses

(continued)

Table 2.1 (continued)

Patent no.	Title	Patent owner	Licensee	Patent category
US7365181	Probes for chondrogenesis	Case Western Reserve Univ	ND	Screen for targets
US7335760	Nucleic acid sequences encoding zinc finger proteins	Ceres Inc	ND	Gene modification
US7553659	CHD5 encoding nucleic acids, polypeptides, antibodies and methods of use thereof	Children's Hospital of Philadelphia	ND	Screen for targets
US7407745	Method for screening anticancer agent	Chugai Seiyaku Kabushiki Kaisha	ND	Screen for targets
US7485714	Transcription factor having zinc finger domain	Sangamo	ND	Modify/affect gene expression
US7402436	Lentiviral vectors for site-specific gene insertion	City of Hope	ND	Gene modification
US7598031	Method for the detection of gene transcripts in blood and uses thereof	GeneNews Corp	ND	Screen for targets
US7413863	Identification of substances that inhibit NEMO oligomerisation	Institut Pasteur	ND	Screen for targets
US7592146	Protocol for detecting proteins in a culture containing an embryo	Inventors	ND	Screen for targets
US7354766	Modification of plant crossing properties via gene transfer	National Inst of Agrobiological Sciences	ND	Modify/affect gene expression
US7368293	Liver enriched transcription factor	Rockefeller Univ	ND	ZFP design/ selection
US7514257	Zinc finger transcription factor differentiation proteins	ToolGen Inc	ND	Modify/affect gene expression
US7666591	Single stranded DNA binding proteins from Archaea and uses thereof	Univ of California	ND	ZFP design/ selection
US7576263	Gene OSISAP1 of rice confers tolerance to stresses and a method thereof	University of Delhi	ND	Modify/affect gene expression
US7716030	Target ligand generation	Vertex Pharma Inc	ND	ZFP design/ selection
US7435806	Nucleic acid binding of multi-zinc finger transcription factors	Vlaams	ND	ZFP design/ selection

Patents obtained through Sangamo's acquisition of Gendaq are indicated by the symbol #

CLAIMS)) *OR* ((ZFP) <in> (TITLE,ABSTRACT,CLAIMS)) *OR* ((Zinc finger) <in> (TITLE,ABSTRACT,CLAIMS)) *OR* ((zinc finger binding protein) <in> TITLE,ABSTRACT,CLAIMS)). Although Chandrasekharan et al. used Delphion analysis tools for their search, I believe that Delphion and Dialog would have turned up exactly the same patents. Dr. Mark Metzke and Ms. Jamie L. Summers read and categorised the patents independently. They made appropriate judgments in regard to noise and ZF category. In the case of initial differences of opinion, they discussed the patents in question until they reached consensus. One cannot be certain that the Metzke-Summers team classified the patents issued between 1 January 2008 and 1 June 2010, exactly as the Chandrasekharan-Valley team would have done. The initial categories used were the same as those in Chandasekharan et al.: (1) design or selection of ZFPs, (2) angiogenesis (including methods or applications affecting Vascular Endothelial Growth Factor gene expression using ZFPs and "anti-angiogenesis" applications), (3) modify/affect gene expression (use of engineered fusion ZFPs and/or ZFP transcription factors to alter or regulate gene expression in different cell types), (4) screen for molecular targets using ZFPs (e.g., methods of screening for drug/protein/nucleic acid interactions, or screening for target interaction with drug compounds or ligands), and (5) gene modification (use of an engineered ZFP or ZFN to alter DNA content and make targeted changes in genes). As a result of Metzke's and Summers' discussions, they concluded that an additional category was needed: (6) ZFP for non-gene uses (for ZFPs that are used as metal scavengers or other uses not involving nucleotides). Munzer cross-read the patents but did not depart from the Metzke-Summers conclusions, which this Appendix displays (Table 2.1).

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Chapter 3
Regulating Biobanks: Another Triple Bottom Line

Roger Brownsword

Abstract In European societies, where there are clear political and legal commitments to respect human rights, it is axiomatic that the regulatory environment for biobanks—by which I mean public health research facilities, such as UK Biobank—should be compatible with those commitments; in particular, it is essential that the rights of participants are respected. During the start-up period for such biobanks, regulators will be expected to ensure: (i) that both participation and the use of participants' samples and data are based on free and informed consent; (ii) that the privacy, confidentiality, and fair data processing rights of participants are respected; and (iii) that the proprietary rights (if any) of participants are respected. While the scope and substance of these rights are much debated, it is broadly agreed that the adequacy of the regulatory environment will be judged by reference, so to speak, to this triple bottom line.

In this paper, I will sketch a larger regulatory picture with its own triple bottom line. The larger picture is of a community with rights commitments (a community of rights) for which one of the bottom lines is, indeed, that the rights of its members, including the rights of biobank participants, should be respected. Thus, the early-stage debates about privacy, property, and consent are debates about one of the larger bottom lines as, indeed, are the debates that follow about feedback to participants and third-party access to the collection. In this larger picture, though, there are two other bottom lines: one is that regulators should act as stewards for the agency commons (for the infrastructural conditions that are essential to human life); and the other is that the regulatory environment should not become so reliant on coding, design, and technical fixes that the conditions and context for moral community are compromised. While biobanking for public health purposes might seem to be an unimpeachable act of stewardship, we need to be careful that it does not contribute to the corrosion of the conditions for moral community.

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3.1 Introduction

In European societies, where there are clear political and legal commitments to respect human rights, it is axiomatic that the regulatory environment for biobanks—by which I mean public health research facilities, such as UK Biobank[1]—should be compatible with those commitments; in particular, it is essential that the rights of participants are respected. During the start-up period for such biobanks, regulators will be expected to ensure (i) that participation and the use of participants' samples and data are based on free and informed consent; (ii) that the privacy, confidentiality, and fair data processing rights of participants are respected; and (iii) that the proprietary rights (if any) of participants are respected. While the scope and substance of these rights are much debated, it is broadly agreed that the adequacy of the regulatory environment will be judged by reference, so to speak, to this triple bottom line.

In this paper, I will sketch a larger regulatory picture with its own triple bottom line. The larger picture is of a community with rights commitments (a community of rights) for which one of the bottom lines is, indeed, that the rights of its members, including the rights of biobank participants, should be respected. Thus, the early-stage debates about privacy, property, and consent, are debates about one of the larger bottom lines as, indeed, are the debates that follow about feedback to participants and third-party access to the collection. However, in this larger picture, there are two other bottom lines: one is that regulators should act as stewards for the agency commons (for the infrastructural conditions that are essential to human life), and the other is that the regulatory environment should not become so reliant on coding, design, and technical fixes that the conditions and context for moral community are compromised. While biobanking for public health purposes might seem to be an unimpeachable act of stewardship, we need to be careful that it does not contribute to the corrosion of the conditions for moral community.

The paper is in four principal parts. First, I outline my understanding of the concept of a "regulatory environment", together with the way that it applies to biobanking. Secondly, I review the upcoming issue of feedback to participants, highlighting the approach of a community of rights and contrasting it briefly with that of its principal ethical rivals. Thirdly, I sketch the special jurisdiction that attaches to the responsibilities of regulatory stewardship with regard to the agency commons, and I ask whether it will be possible to distinguish between those biobanking activities that relate to the protection of the essential infrastructure and those that simply concern human actions, transactions, and interactions on the commons. Fourthly, noting the tendency of technologically advanced communities to focus resources on ex ante prevention, control, and the management of risk, I caution that biobanking might be another practice that accelerates the corrosion of the conditions for moral community.

[1] McHale (2004), Campbell (2006) and Brownsword (2007), p. 11.

My conclusions are already implicit in these introductory remarks. In a community of rights, it is important that there is an ongoing reflection with regard to the precise scope and substance of its moral commitments. It follows that it is right to initiate and to persist with debates about the best interpretation and application of such commitments in relation to the development of biobanking practices. The fact that there are unresolved questions about privacy and property or about feedback and the right to know (or not to know) or about the informational requirements for an informed consent is not at all pathological—to the contrary, these are indications of a healthy moral community. However, as biobanking begins to generate data about the patterns of disease, there will be larger questions that arise. In particular, while the agency commons needs to be preserved and improved for the well-being of agents, it is important to leave space for agents to make their autonomous choices, and while controlling disease makes an important contribution to the quality and length of life enjoyed by agents, we need to be careful that a focus on risk and prevention does not overwhelm our opportunities for moral development.

3.2 The Regulatory Environment and Biobanking

Generally speaking, the idea of regulation is taken to refer to a sustained, focused, and organised attempt to steer conduct. As Julia Black puts it, we think of regulation as: "the sustained and focused attempt to alter the behaviour of others according to standards or goals with the intention of producing a broadly identified outcome or outcomes, which may involve mechanisms of standard-setting, information-gathering and behaviour-modification".[2]

Regulation is thus operationalised through a combination, or cycle, of direction, detection, and correction. It follows that, in a regulatory environment, there will be various signals that are intended to direct the conduct of regulatees; there will be various means of monitoring conduct to see whether the directions are being followed, and, where defection is detected, there will be measures for correction. In other words, regulatory environments are coded for action, the coding signalling whether particular acts are permitted (even required) or prohibited; whether they will be viewed positively, negatively, or neutrally; whether they are incentivised or disincentivised; whether they are likely to be praised or criticised; even whether they are possible or impossible; and so on.[3]

To be more specific about the characteristics of a regulatory (or regulated) environment is not entirely straightforward because, whilst some environments are regulated in a top-down fashion (with regulators clearly distinguishable from regulatees), others are more bottom-up (in the sense that they are self-regulatory). Whereas, in top-down regulatory environments, there is likely to be a significant

[2] Black (2005), pp. 1–11.

[3] Brownsword and Somsen (2009).

formal legal presence, in bottom-up self-regulatory environments, this is less likely to be the case. Moreover, while some regulatory environments are reasonably stable and well formed, others are unstable, overlapping, conflictual, and so on.

Despite this complexity, we need to be careful—and, above all, it is lawyers who need to be careful—to avoid two serious misunderstandings about the characteristics of the regulatory environment. The first misunderstanding, *the mistake of legal exclusivity*, is to assume that the only signals in the regulatory environment are formal legal signals, and, the second misunderstanding, *the mistake of normative exclusivity*, is to assume that the only signals in the regulatory environment are normative (that is, signals that prescribe what ought, or ought not, to be done). It is easy enough to appreciate why lawyers might be tempted to jump to these conclusions, but why precisely are they in error?

First, there is the mistake of legal exclusivity. One of the key points about the regulatory environment is that we may find regulators employing a range of mechanisms or modalities that are designed to channel the conduct of their regulatees. Some of these modalities may well be legal. It is not that regulatory environments never feature legal signals, and, in many instances, it will be the legal signals that have the highest profile. Nevertheless, the regulatory repertoire goes well beyond legal signals. Seminally, Lawrence Lessig has identified the following four regulatory modalities: namely, the law, social norms, the market, and architecture (or code).[4] So, for example: "The government may want citizens to wear seatbelts more often. It could pass a law to require the wearing of seatbelts (law regulating behavior directly). Or it could fund public education campaigns to create a stigma against those who do not wear seatbelts (law regulating social norms as a means to regulating behavior). Or it could subsidise insurance companies to offer reduced rates to seatbelt wearers (law regulating the market as a way of regulating behavior). Finally, the law could mandate automatic seatbelts, or ignition-locking systems (changing the code of the automobile as a means of regulating belting behavior). Each action might be said to have some effect on seatbelt use; each has some cost. The question for the government is how to get the most seatbelt use for the least cost".[5]

Once the modality moves away from law and social norms, to market, architecture, and code, the signal to regulatees can take on a different, non-normative, character; and this leads to the second misunderstanding, the mistake of normative exclusivity.

Laws are normative, as, of course, are social norms. Market signals might also speak to what ought (or ought not) to be done, not so much as a matter of respect for others but simply what ought (or ought not) to be done in one's own interest. For example, where a "green" tax is added to the price of larger cars or to fuel, we might reason that we ought to drive a smaller car because larger cars are expensive and put a strain on our personal finances. However, if the price of larger cars is increased

[4] Lessig (1999a), Chap. 7; Lessig (1999b), pp. 113, 501, 507–514.

[5] *Code*, at 93–94.

beyond our means, our reasoning shifts from the normative mode to the non-normative mode of practicability; it is not so much that, as a matter of self-interest, we ought not to buy a large car but that we simply cannot (afford to) do so. When the regulatory modality is that of architecture or code, or the like, we might well find that the signal is one of (non-normative) practicability or possibility. However, as with market signals, there might be elements of both normativity and non-normativity—witness, for example, Mireille Hildebrandt's important distinction between "regulative" (normative) and "constitutive" (non-normative) technological features.[6] Therefore, for example, if a car is equipped with sensors that can detect alcohol in the driver, it might be designed to respond normatively (by advising that it is not safe for the driver to proceed) or non-normatively (by immobilising the car).

Why is it important, even for lawyers, to avoid making these mistakes? Why is it important to be clear about the character of the regulatory environment? Essentially, it is important because the regulatory environment sets the context for the operation of the law. It follows that if we are to make informed choices about the right kind of legal intervention, especially about the legitimacy and effectiveness of the intervention, we need to know what other signals are in play in the regulatory environment. Moreover, as the non-normative elements of the regulatory environment gain in importance, we need to address the values of legality (and the Rule of Law) that we take to be central to civilised social ordering.[7]

In the light of these remarks, what kind of regulatory environment do we find for biobanking, particularly for UK Biobank? Whilst the regulatory framework for some biobanks has been set out in legislation, with others, the regulatory environment is much less formal.[8] In the case of UK Biobank, it falls to the Ethics and Governance Council (the EGC) to set the framework for, inter alia, UK Biobank's relationship with participants, as well as to supervise the way in which the Biobank operates. The question is whether the practical effect of this lack of formality, coupled with the EGC's lack of sanctioning powers, leaves the regulatory environment unfit for purpose.

Addressing this question (and implicit criticism),[9] the EGC says: "The EGC is an advisory committee and as such has no formal power of veto over UK Biobank's actions. It can, however, make public statements of concern about the project [. . .] The Council normally communicates its reflections informally to UK Biobank and a Memorandum of Understanding is in place which lays out the respective obligations of both parties. These obligations require UK Biobank to respond to all reasonable requests from the EGC. If the Council were not satisfied with UK Biobank's response, it would make a formal statement of concern (e.g., to the UK Biobank Board of Directors or the funders) or, if necessary, it would make a public

[6] Hildebrandt (2008).

[7] Hildebrandt and Koops (2010).

[8] Gibbons (2007a and 2007b).

[9] Ibid, p. 132.

statement about UK Biobank's conduct and recommend that certain actions should or should not be taken".[10]

Yet, some might remain sceptical about the EGC's chances of playing an effective role as the keeper of UK Biobank's conscience. Anticipating such scepticism, the EGC continues: "The power and impact of a public statement from an independent body such as the EGC should not be underestimated. Such a statement would have the possibility to undermine the trust participants place in the project, possibly resulting in withdrawals from the project or a serious down-turn in recruitment. Given that the success of UK Biobank depends on long-term participation, it is in UK Biobank's interest to maintain and strengthen the trust relationship between it and the participants and for this relationship to remain healthy".[11]

This point is well made. If we isolate the EGC's lack of formal enforcement powers from the rest of the regulatory environment in which UK Biobank operates, we might well think that this represents a design weakness. However, once we reintroduce the key features of the regulatory environment, we will see that, in the background, there are a number of relevant legal provisions (particularly concerning the privacy, confidentiality, and data protection rights of participants) that reinforce the EGC's mandate to oversee the proper conduct of the facility. Moreover, as the EGC itself emphasises, so long as UK Biobank relies on the cooperation of participants, the regulatory environment presents both ethical and prudential reasons for going about the biobanking business in the right kind of way.

The jury is still out on whether the regulatory environment for the operation of UK Biobank is, as Susan Gibbons has argued, "a disorganised, fragmented, confusing array of overlapping, potentially relevant but also potentially inconsistent statutory and common law rules, decisions and non-binding guidelines"[12] or a clever instantiation of a trust model of governance. Whatever the final judgment on this matter, in a community of rights, the first priority is *not* to ensure that regulation is effective and it is fit for purpose; rather, in such a community, the first priority is to ensure that regulation is compatible with the community's constitutive rights commitments and the purposes pursued by regulators are fit. Accordingly, it is to such questions of compatibility that we now turn.

3.3 After Property, Privacy, and Consent: The Question of Feedback

In the early stages of biobanking, when participants are being enrolled, some of the key regulatory questions concern the voluntary and informed nature of participation, the resolution of proprietary interests, and the measures for protection of the

[10] UK Biobank Ethics and Governance Council, *Review* 2008, at 4.

[11] Ibid.

[12] Op cit, note 9, at 134.

participants' privacy interests. In the case of UK Biobank, broadly speaking, the Ethics and Governance Framework (EGF) document designs in provisions that are relatively strong on consent (albeit wide and unspecific in the sense that the authorisation is simply for health-related research purposes), weak on property (participants being informed of "the fact that UK Biobank will be the legal owner of the database and the sample collection, and that participants will have no property rights in the samples"[13]), and reasonably protective of participants' interests in privacy and confidentiality.[14] There is much that could be said about the balance of interests struck in the EGF, but the focus for debate is moving on and we can move with it.

At UK Biobank, there is now a debate about asking participants to undergo various kinds of scanning. While researchers would welcome having participants' scans to enrich the data collection, the EGC has identified a number of concerns about the use of scanning, particularly brain scans. First, the general policy at UK Biobank—a policy recently underlined by the Board of Directors[15]—is not to give clinical feedback to participants. While, at enrolment, participants are provided with some very basic information concerning their blood pressure, body mass index, estimated amount of fat, and the like, the EGF emphasises that the Biobank is a research resource and *only* a research resource. Is there any reason why the use of scanning should create an exception to this general rule? Secondly, even if an exception were to be created, on what basis would feedback be given? As the EGC puts it: "What feedback, if any, ought participants to receive as a result of their MRI scans? What information, if any, ought participants [to] receive if the MRI shows an unexpected finding (e.g., a lesion on the brain)? When performing an MRI scan, what is the likelihood of making a false positive finding (i.e., a scan that is erroneously showing a problem when a situation is normal) or making a false negative finding (i.e., a scan that appears to show no problem when in fact there is a problem)?"[16] Thirdly, if scanning is adopted, how would this be articulated in the process of asking participants to consent?

How we answer these questions will depend on the particular ethical approach that we employ. In a community of rights, the governing approach will be rights-based. But, what would follow from that? What would a community of rights hold in relation to the questions of (i) clinical feedback, (ii) false positives, and (iii) consent? And, how might this differ from the positions taken by the utilitarian and dignitarian approaches that are the main rivals of rights-driven approaches? This is quite a clutch of questions and to do justice to them would take a number of papers. In the

[13] *UK Biobank Ethics and Governance Framework* (version 2.0, July 2006) p. 6, para. I.B.1.

[14] Thus, ibid. at p. 12, para. I.C.1, we read: "UK Biobank will maintain strict measures to protect confidentiality, and will ensure that data and samples are (reversibly) anonymised, linked and stored to very high standards of security. The same protection will be extended under contract for any handling or analysis of data or samples by third parties engaged to provide services necessary for developing the resource".

[15] UK Biobank Ethics and Governance Council, *Annual Review* 2009, at 9.

[16] UK Biobank Ethics and Governance Council, *Annual Review* 2008, p. 13.

present context, a comprehensive review is not possible. Accordingly, it should be understood that the review that follows is no more than an indicative sketch of the way in which these questions would be approached in a community of rights.

3.3.1 Clinical Feedback

If a community qualifies as a community of rights simply by treating a rights-based ethic as governing, then there will be many such qualifying communities with many articulations of the constitutive rights commitments. For example, a hard-line negative rights approach might insist that UK Biobank's policy against clinical feedback is justifiable provided that it causes no direct and tangible harm to participants. However, it is equally arguable (as, indeed, I have argued elsewhere)[17] that, in a rights-respecting community, it will be recognised that there is a *prima facie* positive responsibility to give clinical feedback where a four-stage test is satisfied. How does this argument work?

If we assume that a community of rights will not reject the very idea of background positive requirements, then the real question concerns the conditions that the community would set for the recognition of background positive obligations. I suggest that the conditions set would reflect the community's understanding and application of three guiding considerations. *First*, there are considerations of rational prescription. In any community that accepts the basic canons of rational prescription, an agent will only be required to assist another where "ought implies can" is satisfied. It follows that no agent will be burdened with a positive obligation unless they are capable of rendering assistance. If we are to prescribe that A ought to assist B, then the demands that we make of A should at least be within A's capabilities. *Secondly*, there are considerations of reasonableness. How much can we reasonably demand of A? We can imagine a hypothetical in which it would seem to be little more than a minor inconvenience for A to assist B. However, the circumstances might be very different. For example, if A would put his own life at risk by assisting B, would we *require* such a heroic act (or would this be a case of supererogation)? *Thirdly*, there are considerations of fairness. Even in a community that recognises positive rights, the default position is represented by "can implies ought"—that is to say, the default expectation is that those who are capable of helping themselves should do so.

Drawing on these considerations, a four-stage test along the following lines might be formulated for the recognition of particular background *prima facie* positive rights and responsibilities[18]:

[17] Brownsword (2009), p. 99; Brownsword (2010), p. 81.

[18] It should be emphasized that this test only takes the community as far as recognizing *prima facie* responsibilities. Even if A is judged to have a *prima facie* positive obligation in relation to B, there might yet be competing or conflicting rights-based claims to be arbitrated.

(i) Is A in a position to assist B?
(ii) Does A have the capability to assist B in any material respect?
(iii) Even though A is in a position to assist B and has the relevant capability, would the burden of responsibility on A be unreasonable relative to A's own essential interests?
(iv) Even though A is in a position to assist B, has the relevant capability, and the imposition of responsibility on A would not be unreasonable (relative to A's essential interests), would B be taking unfair advantage of A if A were required to assist B?

Quite clearly, there is still a great deal of interpretive work to be done on these general principles, particularly in relation to the pivotal notions of "unreasonable imposition", "essential interests", and "unfair advantage taking". Let us suppose that the community, recognising that these are slippery notions, tries to stabilise the four-stage test by focusing on the common needs of all agents, irrespective of their particular purposes, plans or projects—for example, the need of all agents for life and a level of basic physical and psychological well-being. With this focus, the community can say that A is not required to attempt to rescue B where this would jeopardise A's own life (this would be an unreasonable imposition) and, similarly, that A is not required to assist B where B is in no danger but simply wants A to assist him in relation to the fulfilment of some non-essential purpose (this would be an unreasonable demand that amounts to an example of unfair advantage taking).

Even with the test stabilised in this way, the community will also be mindful of a troubling pair of puzzles that threaten to undermine the practicability of any regime of positive rights. Stated shortly, one puzzle arises where A is not the only eligible rescuer. The question then is why we should single out A as the person responsible for assisting B. The converse puzzle arises where it is not just B, but B, C, and D who are in difficulty and A simply cannot assist all three. Here, the question is why we should single out, say, B as the agent to be assisted. For sure, the lesson to be taken from these puzzles is not that A is released from his positive obligation to assist (because, in the first case, others are also able to assist or because, in the second case, he cannot assist all three distressed agents). Rather, the lesson is that the community needs to articulate some principles of relative priority in relation to the bearers of positive duties (for the first kind of case) as well as those who are positive rights-holders (for the second kind of case).

In the light of these framework principles, does UK Biobank have a positive obligation to feed back health information to participants? In response to the first question, UK Biobank is plainly in a position to assist one of its volunteer participants; and, with regard to the second question, we are assuming that it is holding information that is material to the health and well-being of a participant. It has the capability to disclose that information; the question is whether it is required to do so.

The next step, the third stage, is to consider whether the demand made of UK Biobank is unreasonable relative to its own essential interests. Left to a subjective account of its essential interests, UK Biobank (conceived as an aggregate of agents)

might well argue that it is in the business of research and that the reasonableness of any obligation to feed back clinical information should be judged relative to this fundamental mission. However, this is just the kind of special pleading that the community has neutralised by tying the notion of essential interests to those basic interests shared by all agents. No doubt, the burden of having research-quality scans interpreted by an expert and then of contacting and informing participants is more than trivial, but the imposition on responsible agents falls a long way short of being unreasonable.

Where, as we are assuming, the information relates to a potentially serious medical condition, then the essential interests of participants are implicated. Hence, at the fourth stage, the demand to be informed is entirely reasonable and there is no hint of unfair advantage taking.

Seemingly, then, UK Biobank has a *prima facie* background obligation to feed back to participants important personal medical information where it happens to have it. This is not to suggest that researchers should actively seek out such information for all participants or offer treatment to them; and nor does this discount the possibility that UK Biobank might face competing or conflicting rights claims advanced by the potential beneficiaries of its research activities. Nevertheless, relative to the four-stage test, a participant's claimed right to be informed where UK Biobank knowingly holds (and withholds) potentially important personal medical information surely gets to first base.[19]

If this is the basic approach in a community of rights, what might we expect in the two principal rival ethical communities, that is, in the utilitarian and the dignitarian communities?

Utilitarianism is a broad church. However, if we take our lead from the rule-utilitarians, it seems likely that we would judge that UK Biobank is justified in focusing narrowly on its research objectives. For, the purpose of the research is to find ways of reducing the distress caused by major human diseases and disorders. Accordingly, the general rule that there is no duty to offer clinical feedback would seem to be, by utilitarian standards, the right rule. That said, we can imagine exceptional cases in which act-utilitarians, seeing significant utilitarian gain in giving feedback in the particular circumstances, would be tempted to defect from the general rule—a familiar problem for utilitarians.[20]

As for the dignitarians, while it seems unlikely that such communities would have strong views about the ethics of clinical feedback (in general, they might be expected to argue that we owe communitarian or solidarity duties to inform others

[19] Compare UK Biobank Ethics and Governance Council, *Annual Review* 2009, at 9, where the EGC reports that UK Biobank intends "to develop a protocol that incorporates a limited feedback loop for those incidental findings considered to be potentially 'serious' (defined in this context as likely to threaten life span, quality of life or major body functions) and which are observed during the imaging visit".

[20] Hodgson (1967).

where we have information that concerns their basic well-being),[21] the prior question is whether they would view the biobanking research enterprise itself as contrary to human dignity. In some places, dignitarians will judge that such a research inquiry into the mechanics of life, disease, and death is not compatible with human dignity; and, where this is the case, they will be opposed to the whole biobanking business—indeed, if dignitarians perceive biobanking as a "business", they will straightforwardly oppose such commodification and commercialisation of the human body.

It follows that, on the specific question of clinical feedback, the battlelines are likely to be drawn between, on the one side, the utilitarians (arguing against feedback) and, on the other, the rights theorists (probably with some duty theorists) (arguing in favour of feedback).

3.3.2 False Positives

Let us assume that the opening position taken up by the community of rights is that participants have a *prima facie* right to receive clinical feedback. But, of course, this is no more than a *prima facie* right. If feedback impinges on the promotion of more compelling rights; this *prima facie* right might be overridden. However, the question now is whether the possibility of feeding back anxiety-inducing false positive information cuts against the right. I do not think that it does.

In principle, a rights-holder may waive the benefit of the right by authorising acts that would otherwise be an infringement of the right. Accordingly, the practical resolution of the difficulty arising from the possibility of false positive feedback is to invite the right-holder to authorise the disclosure or the non-disclosure of the information that is to be fed back. Clearly, it is not satisfactory to do this after the scanning has been carried out. It needs to be done either at enrolment or before the scan is undertaken. This being so, the issue becomes one of informed consent for rights theorists.

3.3.3 Consent

Consent is central and integral to rights ethics,[22] and, as we have seen, it is critical that consent is properly handled if we are to deal with the risk of false positive

[21] Compare UK Biobank Ethics and Governance Council (2009), at 9: "We discussed the proposal for a strict policy of no feedback whatsoever and found this to be ethically problematic in relation not only to the participant but also the radiographer who might happen to notice an abnormality that they felt morally and professionally compelled to mention to the participant".

[22] Beyleveld and Brownsword (2007).

feedback. At enrolment, participants should be invited to agree to imaging (as one of the elements of their participation) and, if they agree, they should then be informed about the risk of false positives (and false negatives) and asked whether they wish there to be feedback of results. It might be possible to make the range of options more subtle than a yes/no to feedback, but if that is not possible, then the simple choice is the best that can be done.

What about the possible lapse of time between the election made at enrolment and the later time when feedback might be an issue? This is akin to the standard question that is raised about the durability of advanced directives. However, the practical solution looks straightforward: if the initial election was for feedback, the Biobank can ask for confirmation that this is still the preferred choice immediately before the scan is undertaken; on the other hand, if the initial election was for no feedback, that too can be reconfirmed at the time of the scan.

However, what if a scan very clearly shows a life-threatening and treatable condition in respect of a participant who has elected for no feedback? This would be a hard case for the Biobank. From the rights perspective, the fact that the participant has exercised the right not to know militates against giving feedback unless the election is in very general terms and without anticipating that this might be to forsake life-saving information.[23] However, this rider suggests that the range of options given to participants needs to be, and could be, more sophisticated. Ideally, from the rights perspective, we want the participant to have addressed this possibility very explicitly and to have made a focused choice. Where the choice is targeted and is for no feedback, which is then confirmed on scanning, rights theory would indicate that the participant's choice should be respected—there is a right not to know and this hypothetical participant has so elected.

Taking stock: rule-utilitarians will argue against feedback; but rights theorists and some duty theorists will argue for feedback and then will need to think carefully about the consenting of participants to deal with the risk of false positives; and, while dignitarians might not detect dignity-compromising issues in relation to feedback, some are likely to reject the whole idea of biobanking as dignity-compromising.

3.3.4 The Right to Know and the Right Not to Know

Arising from the above analysis, there is one further matter to consider. I have suggested that the approach to feedback that is taken in a community of rights will hinge on two rights: first, a positive right to know and, secondly, for those who do not want to take the risk of receiving distressing false positive information (or who do not want to have feedback about untreatable conditions), a right not to know. However, it might be objected that the co-existence of a right to know with a right

[23] Compare UK Biobank Ethics and Governance Council, *Annual Review* 2009, Annex A.

not to know is incoherent; and that the supposed right not to know is just another way of describing the position where a right-holder consents to "no feedback". Before we move on, we should put this objection to rest.

First, contrary to the objection, there is no incoherence in A having, in relation to B, both (i) a right to know x and (ii) a right not to know x (where, in both cases, x is an item of clinical information that relates to A). What would be incoherent here would be if A expressed the wish both to know and not to know x. In those circumstances, it would not be possible for B to respond in a way that satisfied A's contradictory wishes. However, this is not what the co-existence of the rights implies. Rather, given the right to know x, A is entitled to have feedback from B about x. B might prefer not to give this feedback; but, in the face of A's right to know, B has a responsibility to give feedback about x to A. In other words, A's right to know protects A against B's preference for no feedback. Alongside this right, A's right not to know protects A against B having the opposite preference, that is, a preference to give feedback. Whereas A's right to know gives A no protection against B's preference to give feedback, the right not to know so protects A. Conversely, whereas A's right not to know gives A no assistance where B prefers not to feedback, the right to know so assists A. The net effect is that, irrespective of B's preferences or wishes with regard to feedback, A is fully in control of whether feedback relating to x is given.

This leaves the question of whether A's right not to know equates to A consenting to "no feedback". Such an equation is misleading, both conceptually and in practice. Conceptually, as we have seen, the rights (to know and not to know) are distinct. Where A consents to "no feedback", A releases B from his correlative responsibility (and authorises an act that would otherwise infringe his right to know); where A stands on his right not to know, A holds B to his responsibility. Moreover, the equation does not hold in practice. The typical context of A consenting to "no feedback" is one in which B prefers to give no feedback and in which it is (to say the least) unlikely that B will disclose x to A. By contrast, the typical context of A needing the right not to know is one in which B prefers to give feedback; and, where this is B's preference, we simply cannot be confident that B will respect A's right.

3.4 Stewardship and the Agency Commons

For a community of rights, biobanking raises many issues about the relationship between the researchers and their participants. The first of the regulatory bottom lines, as we have said, is that regulators should strive to ensure that such interactions are compatible with respect for rights. However, the second of the larger bottom lines for the regulatory environment goes deeper. The transactions and interactions between stakeholders at the biobank presuppose a supportive infrastructure, an agency commons. Accordingly, the second bottom line is that this agency commons is properly protected and maintained.

The regulatory environment is one of signals and steering mechanisms, that are intended to direct the actions, transactions, and interactions of regulatees. However, this already presupposes a space in which such activities are viable; it presupposes an infrastructure. The general idea of an infrastructure as the underlying foundation for a system is reasonably settled; and the conventional wisdom is that infrastructures in this sense are found in transportation and communication systems, as well as being constituted by basic public services such as sewers, water, and energy.[24] By way of illustration, consider the regulatory environment for a railway system. That environment regulates the movement of rolling stock on the tracks and the conduct of passengers who are carried on the trains. It is an environment that is, literally, thick with regulatory signals. It is also an environment where we find non-normative design replacing (largely for reasons of safety but also to inhibit free-riding) traditional normative signals. However, none of this is viable without a supportive infrastructure, without a track.

Now, we can draw a distinction between those infrastructural features that are generic and, thus, essential for any human activity and those that are specific to particular activities. While the railway infrastructure is necessary for a railway transport system, it is not generic. It is not even generic in the context of transport systems because road traffic, for example, can function perfectly well in the absence of a railway infrastructure; and it is certainly not generic in the broader sense of being essential for any kind of activity to be viable. What, then, might be candidates for the generic infrastructure in this broader and most fundamental sense?

One thing that humans must have before they are capable of acting, transacting or interacting in the purposive (goal-directed) way that we associate with agency is a minimal level of health and well-being. For humans whose basic health and well-being is under threat, there is little prospect of actualising their agency—it is akin to the train system being paralysed by threats to the tracks. Immediately, this gives rise to two difficult questions. First, what are the elements that are relevant to an agent's basic health and well-being? And, secondly, where do we draw the line between the generic infrastructure, specific infrastructures, and activities on these infrastructures? Once we have made some headway with these questions, we can begin to see how this relates to biobanking and to regulatory environments.

Turning to the first of the difficult questions, let us suppose that we have a rough sense of what it means to say that a human enjoys basic health and well-being. Rather than asking what factors are conducive to such a condition, we can readily identify the kind of factors that are antithetical to such a condition. For example, we can point to problems with food security and clean water, to environmental pollution, and to the prevalence of disease. Sadly, chronic conditions of this kind can be found in many parts of the world and, following a natural disaster, we will often see some of these conditions in an acute form. In these cases, we can say that the infrastructure is deficient or, in the case of an emergency, that it has collapsed.

[24] Frischmann (2005), p. 923.

This leads to the second question. How do we draw the line between the generic infrastructure, specific infrastructures, and activities on these infrastructures? In the light of what we have already said, I suggest that it is not too difficult to distinguish between generic and specific infrastructures. To return to railway systems, their specific infrastructures are important and valued; they enhance agency but they are not essential to it. Human agency does not presuppose railway tracks, roads, or any other kind of transport infrastructure. These are not part of the *generic* infrastructure. We might say much the same about the infrastructural elements of a modern information technology system. Cybercrime is particularly serious when it strikes at these infrastructural elements; and, for those communities that increasingly transact and interact on-line, this is an extremely serious matter. Nevertheless, this is not part of the *generic* infrastructure. Having said that, it is much less clear how we should distinguish between infrastructures and activities that take place on those infrastructures. An agent's basic health and well-being can be damaged by the act of another human just as much as by deficient living conditions. What makes a feature generically infrastructural is that it strikes at the general possibility of agency, irrespective of the agent and of an agent's particular purposes, rather than the particular occurrent prospects of the agent. Or, to put this another way, there first has to be infrastructure and then there can be activity; while there can be infrastructure without activity, there can be no activity without infrastructure.

If we think about the regulatory environment in this kind of way, we can distinguish between those parts of the environment that are designed to secure the infrastructural conditions and those parts that are intended to direct the conduct of regulatees as they act, transact, and interact on the infrastructure. Arguably, three major regulatory implications follow from this.

First, while the former part of the regulatory environment should apply to securing the generic infrastructure for agency itself (and this implies arrangements for international stewardship), the latter can be more tuned to local cultural commitments and preferences. To put this in cosmopolitan terms, while there need to be universal standards that secure the essential infrastructure, each community of rights can regulate its activities in its own way.

Secondly, a form of pure precautionary reasoning might be acceptable in defence of the infrastructure.[25] According to such reasoning, where the regulatory stewards cannot rule out the possibility that some activity threatens the infrastructure, then they may in good faith apply protective measures even though such measures involve some sacrifice of a valued activity. This reasoning, it should be emphasised, assumes an active employment of precaution. It is not simply that a lack of full scientific certainty is no reason (or excuse) for inaction which puts one reason for inaction out of play but still has no tilt towards action. Rather, where the harm concerns the infrastructure, there is a need to initiate preventive and protective action.[26]

[25] Beyleveld and Brownsword (2009), p. 175.

[26] Fisher et al. (2006) and Fisher (2007).

Thirdly, as we will see in the final part of the paper, for communities that have moral aspirations or that value their individual autonomy, it is important that the regulatory environment does not design out the opportunities for acting freely or doing the right thing. Nevertheless, where the regulatory stewards are acting to protect the infrastructure, a resort to designed-in solutions may be more readily justified.

Finally, where does biobanking fit into this picture? Quite simply, the aim of projects such as UK Biobank is to improve our understanding of the interactions between genetic profiles, physical environments, and lifestyles, and their impact on the health of individuals (as well as the health of larger populations). The question is whether we see any resulting improvement in our understanding as relating to the generic infrastructure or simply to agents' activities on an already secured infrastructure. Do we understand more about how to set the *stage* (the infrastructure), or is it the *performance* (the activity) that we understand how to improve? For, to the extent that it is infrastructural, the stewardship jurisdiction may be invoked with all that this entails for the character of the regulatory environment. However, we need to be careful. In a community of rights, agents value the opportunity to choose their own lifestyle.[27] Even if there is a public health concern about, let us say, obesity, as Inez de Beaufort provocatively asked in a recent lecture, why shouldn't those who have a sweet tooth carry on eating "queen of puddings, sticky toffee puddings, and knickerbocker glories"?[28]

In the light of these remarks, imagine that, 50 years from now, biobank research has yielded important findings about the causes of major diseases. Equipped with this understanding, the State is in a position to make effective interventions that will reduce the incidence of disease. What would the community make of the following kinds of public-health directed measures that are proposed by the State? First, with a range of key genetic markers now identified, and with techniques such as PGD now wholly reliable and sophisticated, what if the State proposes that any embryos that carry a relevant marker should not be used? We should recall that such screening already takes place for markers associated with a predisposition to cancer, so why not also for markers associated with, say, obesity or addiction? Or, what if a similar approach is taken to pre-natal testing so that a foetus with the relevant marker is recommended for (or required to be) aborted? Secondly, what if products (such as tobacco and alcohol) that are judged to be contrary to public health are prohibited? Or, again, what if certain life-styles are treated in the same way? Thirdly, what if the physical environment is designed in ways that are not simply conducive to health but that presents agents with no option other than the healthy one? What if the only way to get from A to B is to walk or to use the stairs? In short, how far, in a community of rights, will it be accepted that the State as steward for public health cannot only set the stage in the right (health-promoting)

[27] Brownsword (2006a), p. 201; Brownsword (2006b), p. 42.

[28] "Whose Potbelly is it Anyway?" public lecture, hosted by the Nuffield Council on Bioethics, delivered at the Royal Society, London, April 26, 2010.

way but may also act as gatekeeper for who is admitted to the community and then as a monitor of individual lifestyles?[29]

These are difficult questions. However, we should not despair. If a community of rights can (and should) debate questions concerning the regulation of activities (of acts, interactions, and transactions), so it can (and should) debate its best understanding of the distinction between infrastructure and activity—and, concomitantly, its understanding of the regulatory competence that follows from this distinction.

3.5 Moral Community

Finally, we come to the third of the regulatory bottom lines, which concerns the need that agents have for a degree of freedom. In some communities, it might be freedom simpliciter that matters. However, in a community of rights, freedom will be understood in moral terms—in other words, one of the necessary conditions for treating an act as "free" or "autonomous" will be that it is compatible with rights' commitments.[30] To see how this ties in to the general picture, we need to return to the idea of a regulatory environment.

We said earlier that, in a regulatory environment, we might find a mix of normative and non-normative signals. In all cases, regulators seek to engage with the practical reason of their regulatees; and, in so doing, regulators employ three key registers:

(i) The moral register: here, the coding signals (normatively) that some act, x, categorically ought or ought not to be done relative to standards of right action—regulators thus signal to regulatees that x is, or is not, the right thing to do; or,
(ii) The prudential register: here, the coding signals (still normatively) that some act, x, ought or ought not to be done relative to the prudential interests of regulatees—regulators thus signal to regulatees that x is, or is not, in their (regulatees') self-interest; or
(iii) The register of practicability/possibility: here, the signalling is no longer normative, the environment being designed in such a way that it is either not reasonably practicable or even impossible to do some act, x—in which case, regulatees reason, not that x ought not to be done, but that x cannot be done.

In an exclusively moral environment, the primary normative signal (in the sense of the reason for the norm) is always moral, but the secondary signal, depending upon the nature of the sanction, might be more prudential. In traditional criminal law environments, the signals are more complex. Whilst the primary normative signal to regulatees can be either moral (the particular act should not be done

[29] Thaler and Sunstein (2008).
[30] Gewirth (1978, 1996).

because this would be immoral) or paternalistically prudential (the act should not be done because it is contrary to the interests of the regulatee), the secondary signal represented by the deterrent threat of punishment is prudential.[31] As the regulatory environment relies more on technological management (using CCTV, DNA profiling, RFID, and the like), the strength and significance of the moral signal fades. Initially, the signals to regulatees accentuate that the doing of a particular act is contrary to their interests (the likelihood of detection becomes more pronounced), and this is taken a step further when the technology is embedded in such a way that an act is either not reasonably practicable or simply not possible (for example, think about the regulatory environment at a modern security-sensitive airport).[32] Where the signal is that a particular act is no longer a possible option, regulatee compliance is, so to speak, fully determined; in all other cases, and especially so in the normative range, the conduct of regulatees is under-determined.

The movement away from normative signals can be tracked through three ideal-typical generations of regulatory environment. In a first-generation regulatory environment, regulators would rely exclusively on normative signals. In a second-generation regulatory environment, regulators would rely on both (first generation) normative signals and second-generation design of products and places (architecture). Where regulators rely on such a design strategy, the signal is no longer normative. Instead, the design features signal what is practicable or possible. Finally, in a third-generation regulatory environment, regulators would go beyond traditional normative signals and design of products and places by incorporating the regulatory design within regulatees themselves (for example, by means of pharmacological intervention, or neurosurgery, or by controlling their genetic coding). Where design is embedded in regulatees in such a way that it channels their behaviour, it is likely to be much less apparent to regulatees that they are being regulated—if the design is reliable, regulatees will simply behave (like products) in accordance with their specification.

Once again, we might ask, what have such developments got to do with biobanking? To answer this question, we must place biobanking in the context of two interacting general modern developments, one, the tendency towards medicalisation, the other, the tendency towards technocratic thinking.

First, we can observe the way in which anti-social behaviour gets to be classified as a health problem. Reasoning that "there must be something wrong with people who act this way", we medicalise their conditions. Conduct is increasingly explained in terms of underlying biology and this ushers in a treatment regime with its own ground rules. Regulation (via treatment) now operates in the register of what is practicable or possible. And, the more that biobanking uncovers the links between genetic and environmental factors, the more opportunities there will be for medicalisation, for treatment, and for a shift away from the normative regulatory registers.

[31] Norrie (2009), p. 1; Zedner (2009), p. 35.

[32] Koops (2009), p. 93.

The diagnosis of ADHD in children and the administration of Ritalin is a case in point. Once, children so diagnosed were viewed as simply boisterous or unruly. Now, they need to be treated. Having medicalised the condition, we respond by administering methylphenidate (Ritalin) and amphetamine (Adderall) to children whose conduct is outside the range of acceptability. Should we do this? In its report, *Beyond Therapy*,[33] the President's Council on Bioethics expresses its concern in the following terms: "Behavior-modifying agents circumvent that process [i.e. the process of self-control and progressive moral education], and act directly on the brain to affect the child's behavior without the intervening learning process. If what matters is only the child's outward behavior, then this is simply a more effective and efficient means of achieving the desired result. But because moral education is typically more about the shaping of the agent's character than about the outward act, the process of learning to behave appropriately matters most of all. If the development of character depends on effort to choose and act appropriately, often in the face of resisting desires and impulses, then the more direct pharmacological approach bypasses a crucial element. . ..By treating the restlessness of youth as a medical, rather than a moral, challenge, those resorting to behavior-modifying drugs might not only deprive [the] child of an essential part of this education. They might also encourage him to change his self-understanding as governed largely by chemical impulses and not by moral decisions grounded in some sense of what is right and appropriate".[34]

In other words, once we rely on design or architecture, or take an interventionist biotechnological or neurotechnological approach, to respond to (or manage) our social problems, there is a danger that, as the President's Council puts it, "we may weaken our sense of responsibility and agency".[35] If so, are we leaving sufficient space for regulatees to exercise moral choice and moral responsibility?

The other tendency is to place all problems, regardless of type or source, in a risk prevention and risk management paradigm.[36] This is modern technocratic thinking. However, for a community with moral aspirations, technocratic control is not necessarily unproblematic. As David Smith has pointed out in an insightful paper, technology "may have a moralising or alternatively a demoralising effect".[37] Thus: "A system which delivers a strong and consistent symbolic message. . .may have the effect of creating or reinforcing norms, strengthening belief in them, and making it harder for people to disengage their self-controls from these norms. By contrast, a system which removes all personal choice may tend to weaken self-controls, for a variety of reasons. If people are denied any autonomy, then they perceive that the moral responsibility lies entirely with the system, and they no

[33] President's Council on Bioethics, *Beyond Therapy* (Washington: Dana Press, 2003).

[34] Ibid., at pp. 105–106.

[35] Ibid., at 106.

[36] Bowling et al. (2008), p. 51; Koops (2009).

[37] Smith (2000), pp. 147–170.

longer retain any obligations themselves".[38] More generally, if we design out undesirable options, using the register of the (im)possible, the moral signal is left in the background.

Constructing a regulatory environment that is designed to channel regulatees away from unhealthy acts might seem to be some way away from steering regulatees away from harmful or anti-social conduct, but a mentality of risk prevention and risk management is common to both regulatory regimes.[39] Once a technological strategy is used to fix health problems, once the regulatory culture is centred on the prevention and management of risks, it is not so far to copying this strategy for purposes of social control. Having put such a premium on the need for participants freely to agree to enrol for UK Biobank, it would be ironic if, in the longer run, biobanking contributed to a culture of risk management in which there was a loss of individual choice and responsibility.

3.6 Conclusion

In a community of rights, the various transactions and interactions associated with biobanking give rise to many, so to speak, routine concerns all of which need to be debated and carefully regulated. Over and above the concerns about such matters as privacy, informed consent, feedback, and the like, there are two towering issues. One relates to the way in which biobanking might aid our efforts to protect the agency commons; the other relates to the way in which biobanking might chime in with other forces that threaten to erode the conditions for moral community. In this paper, I have highlighted a number of the questions that are provoked by reflections on these larger questions. In particular, can we draw a coherent and defensible distinction between infrastructures and activities? Can we draw and then hold a line between ill health and anti-social behaviour? Can we keep the risk paradigm at bay? Can we determine where it is legitimate to make use of emerging technologies to design in the desired regulatory outcome?[40] For a community of rights, as is the case with most modern technologies, biobanking is both a challenge and an opportunity.

3.6.1 Coda

In January 2011, not long after writing this paper, I was appointed as Chair of UK Biobank's Ethics and Governance Council (EGC). In view of this appointment, and

[38] Ibid. Smith is making this important point in the context of automatic ticketing systems that are designed to reduce fare evasion by users of public transport.

[39] Brownsword (2008), Chap. 8.

[40] Yeung (2008).

in order to maintain a clear separation between my current role as Chair of the EGC and my (pre-appointment) role as author of this paper, I have not updated the paper to take account of either developments at UK Biobank since January 2011 or my experience from that time as Chair of the EGC. Finally, to avoid any misunderstanding, let me emphasise that the views expressed in this paper are mine alone (as I saw things at the time of writing) and that, in no sense, am I speaking for the EGC.

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Chapter 4
Health Insurance, Employment, and the Human Genome: Genetic Discrimination and Biobanks in the United States

Eric A. Feldman and Chelsea Darnell

Abstract Does genetic information warrant special legal protection, and if so how should it be protected? (See Feldman (2012), for a discussion of the implications of GINA for primary care providers). This question has taken on greater urgency in the United States as genetic testing has become more common and biobanks have developed repositories for large amounts of genetic information. One central concern raised by the collection and storage of genetic and biomedical information is that individuals will increasingly experience privacy violations and discrimination (Kaufman (2009), pp. 643–644). Biomedical researchers worry that public fear of discrimination and privacy violations will limit their ability to collect and analyze genetic information in biobanks. As genetic testing advances and biobanks grow, such concerns will be amplified. The possibility that fear of genetic discrimination would cause people to refrain from genetic testing, which would in turn inhibit scientific research and the discovery of potentially life-saving medical interventions, was in large part responsible for the passage of legislation that addresses the potential threat of genetic discrimination in the USA.

This essay examines the most recent (and indeed only) significant effort by the US government to prohibit genetic discrimination, the Genetic Information Nondiscrimination Act (GINA). Advocates worked for more than a decade to secure GINA's passage. In the end, we argue that the legislation is unlikely to have the positive impact sought by advocates of genetic privacy. In part, GINA disappoints because it does too little. Hailed by its promoters as "the first civil rights act of the 21st century," GINA's reach is in fact quite modest and its grasp even more so. But GINA also fails by trying to do too much, tying the hands of insurers and employers in ways that may fail to serve the interests of individuals or society more generally. In short, if genetic discrimination is a problem that needs to be solved, GINA is not the solution. Instead, the Act creates a number of new and possibly intractable problems that may be more troublesome than what it originally set out to resolve.

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4.1 History of the Bill

GINA was signed into law on 21 May 2008, thirteen years after it was originally introduced in the House of Representatives. For a bill that floundered for over a decade, the vote in Congress was overwhelmingly positive, 94-0 in the Senate and 414-1 in the House. The lone dissenter was Ron Paul, the maverick Texas Republican who opposes all legislation that he sees as expanding the federal government. The first version of GINA was introduced in 1995 by Representative Louise Slaughter, a Democrat from New York with a background in microbiology and public health. Despite bipartisan support, a series of efforts by Representative Slaughter and Senator Olympia Snowe (R-ME), and broad public support for the bill,[1] GINA encountered various impediments. On the brink of passage in 2007, for example, GINA was stalled by Senator Tom Coburn (R-OK), an obstetrician who was concerned that it would encourage frivolous suits.[2] In March 2008, he and ten Senators signed a letter to the White House requesting amendments. The lawmakers then agreed to create a "firewall" between employment and insurance sector regulation (so that a person could not sue both a group health plan and the employer for the same violation) and insert a clarification that insurers can continue to base decisions on an existing/expressed disease".[3] With those amendments, GINA finally became law.

4.1.1 GINA: Content of the Act

The Genetic Information Nondiscrimination Act (GINA) is divided into two sections. The first, Title I, prohibits insurers from discriminating on the basis of genetic information, while the second, Title II, does the same for employers. Title I of GINA applies to insurers in three basic ways: (1) group health insurers are prohibited from using genetic information about an individual to adjust group premium plans, and insurers offering individual plans are prohibited from using genetic information to deny coverage, adjust premiums, or impose preexisting condition exclusion; (2) health insurers are not allowed to require or request genetic testing; and (3) health insurers are prohibited from requesting, requiring, or purchasing genetic information for underwriting purposes. Nothing in GINA, however, prevents group or individual insurers from considering manifested conditions for underwriting purposes. Insurers

[1] "Besides the more than 200 health advocacy and business organizations that support this bill, recent surveys show 93 percent of Americans believe that employers and insurers should not be able to use genetic information to discriminate". 153 Cong. Rec. H 4083, 4096 (April 25, 2007) [statement of Judy Biggert (R-IL13)].

[2] Ironically, Senator Coburn's official website press room reproduces a story critical of his hold-out period. *See* http://coburn.senate.gov/public/index.cfm?FuseAction=LatestNews.NewsStories&ContentRecord_id=9180ab87-802a-23ad-4e03-b65e171db230&Issue_id=.

[3] MacKenna (2008).

that do not comply with GINA are fined $100 per day for each violation; the minimum penalty is $2,500 (escalated to $15,000 if the violation is more than *de minimis*).

Title II of GINA contains provisions related to employers with 15 or more employees. GINA aims only to isolate the treatment of genetic information by employers and does nothing to alter pre-existing regulations on the eligibility and use of health information by employers in federal and state laws. Title II of GINA makes it illegal for an employer with more than 15 employees to discriminate with respect to hiring, compensation, terms, conditions, or other privileges of employment because of genetic information. Employers are not allowed to "request, require, or purchase genetic information with respect to an employee or family member". Title II is enforced under Title VII of the Civil Rights Act of 1964, which allows employees to recover up to $300,000 in compensatory and punitive damages. If an employer intentionally violates GINA, a court can enjoin the employer from engaging in the practice and order affirmative action, such as the reinstatement or hiring of employees.

GINA's broad definitions of the terms "family member", "genetic information", and "genetic test" mean that the Act prohibits insurers and employers from engaging in a wide array of activities. Genetic information is defined as "information about [an] individual's genetic tests, the genetic tests of family members of [the] individual, and the manifestation of a disease or disorder in the family member of [the] individual". Family member is also defined broadly to encompass any dependent or relative up to the fourth degree. These broad definitions mean that there is a significant amount of information that employers and insurers are prohibited from using. The term genetic test is defined in both Titles I and II as "an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes". There is, however, a slight difference between the definitions of genetic test in Title I and Title II. Title I includes an exception for tests that are directly related to a "manifested disease, disorder, or pathological condition". In making this distinction, lawmakers recognised that, "there are important and necessary uses for non-genetic health information in the health insurance setting that are not applicable in the employment context".[4]

4.2 The Case for GINA

Given the existence of both federal and state anti-discrimination laws, and the thin evidence that genetic discrimination is currently practiced, proponents of GINA struggled to justify the need for new legislation targeting genetic discrimination.[5]

[4] S. Rep. No. 110-48, at 28.

[5] Existing legislation includes, for example, the Health Insurance Portability and Accountability Act, the Americans with Disabilities Act, Title VII of the Civil Rights Act, and a large number of state statues that prohibit genetic discrimination by insurers and employers in at least some contexts.

In building their case, they largely relied on the historical case of discrimination against carriers of sickle cell anemia and anecdotal evidence of isolated instances of genetic discrimination as proof that GINA was needed. Sickle cell was their most powerful example. During the 1970s state governments began to screen and identify carriers of sickle cell anemia, a disease that afflicts African-Americans. The goal was to identify not only individuals suffering from the disease but also healthy carriers. Genetic testing for sickle cell was justified by claims that those with the sickle cell gene might be hyper-susceptible to certain workplace toxins, even though such claims lacked empirical support.[6] The discrimination (by both insurers and employers) that resulted from screening for sickle cell anemia was exacerbated when "state legislatures began to take steps in the area, and in the early 1970s began mandating genetic screening of all African-Americans for sickle cell anemia, leading to further fear and discrimination".[7] In response, "Congress in 1972 passed the National Sickle Cell Anemia Control Act, which withholds Federal funding from States unless sickle cell testing is voluntary".[8]

In addition to the case of discrimination against carriers of sickle cell anemia, proponents of GINA presented anecdotal evidence of more recent instances of genetic discrimination. Representative Slaughter recounted the tale of Heidi Williams, who in 2004 testified that a large health insurance company had denied coverage for her two children because they were carriers of the gene for alpha-1 antitrypsin deficiency. Slaughter argued that, "GINA will make these discriminatory practices illegal by prohibiting health insurers from denying coverage or charging higher premiums to a healthy individual because of a genetic predisposition, which means [they] may never get the disease".[9] Isolated anecdotal instances of alleged genetic discrimination and a historical case of genetic discrimination that has already been addressed by Congress were the bedrock of the argument for GINA. But they offered only weak evidence that genetic discrimination is occurring or that government action is necessary.

To justify Title II of GINA, proponents relied primarily on surveys indicating that genetic discrimination may be occurring in the workplace. The American Management Association conducted a "Workplace Testing Survey" in 2000 and found there were several instances in which members used what they understood to be genetic information in hiring and firing decisions.[10] Of 2,133 employers included in another survey, seven indicated that their companies performed what they thought was genetic testing of employees (that number was up from three in 1999). Of the seven, three reported performing genetic testing of job applicants and six reported performing genetic testing of employees. The Office of Technology Assessment conducted a similar survey in 1989 of Fortune 500 companies; of the

[6] S. Rep. No. 110-48, at 8 (citing Kaufmann 1999).

[7] S. Rep. No. 110-48, at 9 (citing 42 U.S.C. § 300(b)).

[8] Ibid.

[9] Id. at 4095.

[10] S. Rep. No. 110-48, at 6.

330 companies that responded, 12 admitted to conducting genetic tests of employees.[11]

Given the scant evidence of genetic discrimination, proponents had little choice but to emphasise the possibility of future discrimination rather than actual instances of discrimination. They pointed to the large number of genetic disorders and the millions of people affected to conclude that genetic discrimination *could* affect everyone. In arguing for passage of GINA, Representative Slaughter stated that, "Already, over 15,500 recognised genetic disorders affect 13 million Americans, and . . . each and every one of us is in that category of carrying between 5 and 50 bad genes, or predicted genes".[12] Moreover, supporters of GINA argued that regardless of whether there is currently widespread genetic discrimination, fear of discrimination could dampen research efforts and inhibit scientific progress. This was emphasised by the Senate Committee on Health, Education, Labor, and Pensions (HELP), which published a report on genetic discrimination in 2007 finding that fear of discrimination is the most common reason for not participating in research on potentially lifesaving genetic testing for breast cancer and colon cancer. According to the report, more than one third of those who were eligible declined to participate in a genetic testing program; those who declined cited fears about the potential effect of test results on their health insurance coverage as the primary reason for their refusal.[13] In the end, given the lack of evidence that genetic discrimination is currently a significant problem, GINA's primary target appears to be the fear that genetic discrimination could become a serious issue in the future.

4.3 The Case Against GINA

4.3.1 Criticisms of Title I

No one advocates genetic discrimination, and no politician wants to be seen as favoring the mistreatment of the genetically vulnerable. But Congress' overwhelming support of GINA should not mask the various deficiencies of the legislation. Most significantly, GINA is a response to an imaginary need—there is little evidence of genetic discrimination in the United States, and similarly little evidence that GINA will lead to increased participation in clinical research or a greater willingness among patients to pursue genetic testing. Proponents of the Act pointed to anecdotal evidence of discrimination and recounted discrimination against carriers of sickle cell anemia in the 1970s. Beyond that, there is scant evidence of actual genetic discrimination occurring in the United States. According to the

[11] Id. at 7.

[12] 153 Cong. Rec. H 4083, 4095 (April 25, 2007) [statement of Louise Slaughter (D-NY28)].

[13] S. Rep. No. 110-48, at 5. See also Rothenberg (2007).

Senate HELP Committee, for example, "[a]lthough surveys and polls demonstrate a fairly widespread fear of discrimination, there is little evidence or documentation of actual discrimination in health insurance. For instance, the American Academy of Actuaries notes that private insurers do not require applicants for insurance to undergo genetic testing or use genetic tests to limit coverage for preexisting conditions".[14] Noting "the apparent conflict between actual discrimination versus the fear or perception of discrimination", the Senate HELP Committee nevertheless found the Act necessary to assuage (irrationally) worried consumers.[15]

In addition to prohibiting a type of discrimination that rarely if ever occurs, GINA represents an incomplete and flawed solution to the hypothetical problems it addresses. The Act prohibits discrimination only by a limited class of insurers, health insurers. It does not prohibit discrimination in other insurance contexts, notably life insurance, disability insurance, and long-term care insurance. The implication of such a limitation is that it is appropriate for insurers to use genetic information when writing insurance policies that do not fall within the scope of the Act. If the use of genetic information by the insurance industry is discriminatory in the health insurance area, so too would it be discriminatory *vis-à-vis* life insurance, and GINA should prohibit all insurers from using genetic information, not only a narrow subset of insurers.[16]

Even with regard to health insurance, GINA's applicability is relatively limited. Most Americans with health insurance are covered by a group plan provided by their employer, with only 9 % of Americans purchasing health insurance privately.[17] When insurance companies price group plans, they evaluate the overall health characteristics (and claims history) of the group and set uniform premiums. Individual members of the group all pay the same amount for their health insurance.[18] Consequently, at least when it comes to group health plans, there is little opportunity for discrimination against individuals on the basis of genetic information. In the absence of GINA, insurers could raise rates for an entire group as the result of an individual's genetic information, thus raising the possibility of discrimination against all members of the group. But such actions do not appear to have

[14] S. Rep. No. 110-48, at 7. "Another study of insurance practices found there are almost no well-documented cases of health insurers either asking for or using presymptomatic genetic test results in their underwriting decisions. The same study found that 'some insurers clearly do use family history information for important disease categories such as heart disease, cancer, and diabetes, but they do so only to look for or evaluate other signs of existing or prior disease, not to predict the onset of future health problems.'" *Id.* at 8.

[15] *Id.* at 8.

[16] It is not clear why GINA did not prohibit all insurers from using genetic information. One possibility is that the politically powerful life insurance industry would have effectively opposed such legislation.

[17] DeNavas-Walt et al. (2008).

[18] Because the insurance industry is heavily regulated by state governments, there is significant variation in how companies engage in community rating and experience rating when setting health insurance premiums.

occurred in the past, and are highly unlikely to happen in the future, given the extremely ambiguous link between genetic information and increased health care costs. Thus, even in the field of health insurance, where GINA appears to boldly prohibit genetic discrimination, the applicability of the Act is limited by the fact that the insurers through which most Americans obtain their health insurance are unlikely to be in a position to use genetic information in a discriminatory manner.

The most challenging question raised by GINA is whether the use of genetic information by insurers should be condemned as inappropriately discriminatory. Determining what constitutes discrimination is always contentious, but within the insurance industry that job has been made easier by the National Association of Insurance Commissioners (NAIC). NAIC's Model Unfair Trade Practices Act prohibits "making or permitting any unfair discrimination between individuals of the same class and of essentially the same hazard in the amount of premium, policy fees or rates charged..." Under this definition, for example, it is clear that it would be unfairly discriminatory to price health insurance differently for two people if they both presented identical risk profiles. It would not, however, be unfairly discriminatory to price one of their insurance policies higher if one of them had suffered two heart attacks and the other had a healthy heart. It would also be unfairly discriminatory to price insurance differently for two people if they both tested positive for a gene connected to breast cancer and were the same in all other respects, but not unfairly discriminatory to price insurance differently if one of the individuals tested positive for the gene and the other did not. As long as there is a reasonable basis for believing that testing positive for a particular gene can have an impact on someone's long term health profile and corresponding health care costs, then under the insurance industry's definition of discrimination, it does not appear as though pricing insurance plans differently based on genetic information would be unfairly discriminatory.[19]

Since its inception, classifying risk and making distinctions between individuals based on their risk profiles has been the lifeblood of the insurance industry. Evaluating individuals based on the risks they present, and distinguishing between individuals based upon their different risk profiles, should be considered discriminatory only when the basis of such distinctions is inappropriate. Insurers have long taken into account gender, medical history, weight, alcohol consumption, and smoking, for example, when evaluating an individual's future health trajectory. Such information may be useful for determining different health risks and potential costs of providing health care treatment. If fine grained genetic tests provided accurate information about individual proclivities to certain medical conditions,

[19] See Baker (2008), section re: "Topics in Substantive Insurance Regulation", subsection "Insurance Risk Classification", for a discussion of risk classification and fair discrimination: "As understood by many people in the insurance business, classifying people according to their risk is fair and gives them an incentive to arrange their affairs so that they pose a lower risk" (p. 748?). In other words, insurers believe that it is fair for people to pay more for insurance if they present higher risks, but unfair to charge people different premiums if they are of the same class and represent the same hazards.

then using that information in insurance coverage decisions may not run afoul of the notion of unfair discrimination in the insurance industry, or perhaps of broader societal views of discrimination. Higher risk individuals end up consuming more insurance than lower risk individuals; when insurers are able to determine which individuals pose a higher risk then they will charge those individuals a higher premium to compensate for the fact that they are likely to use more insurance in the future. Indeed, some European nations that enacted genetic discrimination legislation earlier than the USA have found that legal prohibitions on genetic discrimination have increased the degree to which insurers factor 'lifestyle' risks into their underwriting practices. The result is that people who smoke, or are obese, or present other types of lifestyle risks, face greater levels of discrimination (which are generally manifested by higher insurance premiums) than before the passage of legislation prohibiting genetic discrimination.[20]

If insurers cannot collect the information necessary to evaluate individual risk profiles, then they will raise all premiums and lower risk individuals will end up subsidising higher risk individuals. According to the prevailing values of the US insurance industry and its embrace of experience rating, the greatest injustice occurs when insurers do not use all available information (including genetic information if it is a reliably predictive indicator of an individual's risk potential) to distinguish between the insured population, and lower risk individuals are charged the same amount as higher risk individuals. Such an approach to insurance runs the risk of adverse selection, making it less likely for low risk than high risk individuals to buy insurance, and increasing the average risk of those in the pool.[21]

If one were to object to experience rating and challenge the usual insurance industry practice of treating individuals differently on the basis of the future risks that they pose, then the distinction that GINA draws between genetic information and manifested diseases becomes suspect. Korobkin and Rajkumar argue in *The New England Journal of Medicine* that a person whose colonoscopy finds an actual disease (a manifested condition not protected by GINA) bears "no more responsibility" for their increased risk of future treatment than those whose genes predispose them to illness (a genetic predisposition protected by GINA).[22] GINA further complicates the problem: "Because insurance companies may no longer make use of clearly relevant information such as family history in their risk assessment, they will rely even more heavily on current health status when setting rates, even when it has only slight value in predicting future illness. In a post-GINA world, not only will the very sick have even more trouble obtaining affordable insurance, but so will the mostly well. Additionally, while those who get bad news from genetic tests will rely on GINA to obtain health insurance at a subsidised rate, those whose genes put them at lower risk can opt out entirely or, more likely,

[20] Van Hoyweghen and Horstman (2008).

[21] As the Patient Protection and Affordable Care Act of 2010 is implemented, some of these issues will lose their salience.

[22] Korobkin and Rajkumar (2008).

purchase insurance with higher deductibles, greater cost sharing, and more exclusions. If the lower-risk portion of the population segregates itself into what is essentially a separate insurance pool, the goal of spreading the cost of genetic risk cannot be satisfied".[23]

One response to this challenge is to abandon the regulatory efforts of GINA and leave health insurance to market forces. Given the recent passage of the Patient Protection and Affordable Care Act, however, it appears that the US health insurance industry is likely to be more heavily regulated in the future, not less, Another response, embraced by Korobkin and Rajkumar, is to admit that the distinction between genetic information and other immutable characteristics is arbitrary and to move toward a system that prohibits insurance companies from taking into account any health information, not just genetic information for underwriting policies. This would create one large community rate, with the only difference in premiums being driven by those circumstances within a person's reasonable control.[24]

In addition to the conceptual challenges of collecting and evaluating individual genetic information, there is also a practical concern. As of 2011, genetic information is not usefully predictive of health outcomes. Testing can reveal the existence of specific genes in an individual's DNA, but scientists are not able to make useful predictions about the increased likelihood that a particular individual will end up manifesting a particular condition. Moreover, genetic testing is only available for a limited number of the many diseases that affect humankind. Since the use of genetic information is not usefully predictive of future health outcomes, companies that rely on genetic information are at a competitive disadvantage. For that reason, at least currently, health insurers have little practical use for genetic information. Even if a company chose to ignore the economic irrationality of collecting and using genetic information in underwriting decisions, individuals who believed they had suffered from genetic discrimination would be able to pursue their claims under one of several already-existing federal or state laws. GINA provides few if any new useful legal tools to potential plaintiffs.

4.3.2 Criticisms of Title II

Although employment discrimination is intolerable, matching people's skills, abilities, and qualifications to particular jobs is the lifeblood of human resources departments throughout the nation. For a commercial airline hiring pilots, for example, it is critical that potential employees not only have technical knowledge about how to fly a plane, but also have good reflexes, react well under pressure, and be in good physical condition. It would certainly be undesirable to have pilots who were particularly susceptible to sudden and unpredictable seizures or who suffered

[23] *Id.* at 336.

[24] *Id.* at 337.

from narcolepsy. A recent study by Japanese researchers raises challenging questions about the use of genetic information in the employment setting. According to that study, there is a genetic variant that is linked to a much higher than average risk of narcolepsy.[25] In addition, scientists have identified at least 12 forms of epilepsy with a genetic basis.[26] If science progresses to the point that genetic tests can provide scientifically reliable information about whether a given individual has the gene for narcolepsy or epilepsy, and can accurately predict the likelihood that the condition would manifest within a given amount of time, should airlines ignore that information when they hire pilots? Should they use it to screen out particular employees?

These are challenging questions, ethically and legally. But at least in contexts like commercial aviation, erring on the side of caution is the most appropriate response. When boarding a plane, people should know that the airline has examined all relevant, reliable, and available information to ensure that the pilot is not likely to have a seizure or a narcoleptic attack during the flight. That includes ambiguous but suggestive information from genetic tests, as well as information about an applicant's family history. GINA prohibits airlines from gathering and using both types of information in their hiring decisions. Of course, if science has not progressed to the point of being able to identify a relevant genetic variant, or provide useful information about the likelihood of that variant leading to the manifestation of the disease, then genetic information cannot and should not be used in the employment setting. And there will always be disagreement about how to interpret the science, how to evaluate particular data, and how to understand the relative risks associated with particular genes. But under GINA's broad definition of genetic information, employers are prohibited from collecting and using information that is at least arguably relevant to an individual's fitness for a particular position. GINA puts an end to an important conversation about genetic information, when society should be engaging with the meaning of that information and evaluating if, how, and when it should be used.

4.3.3 Litigating Genetic Discrimination

The paucity of litigation over genetic discrimination further supports the view that such discrimination is extremely rare, and that GINA is likely to provide potential plaintiffs with few new legal tools in those rare circumstances in which they chose to litigate. There are only two regularly cited cases related to genetic discrimination. In the first, *Norman-Bloodsaw v. Lawrence Berkeley Laboratory,* 135 F.3d 1260 (9th Cir. 1998), Lawrence Berkeley Laboratory, a research institution

[25] Miyagawa (2008).

[26] National Center for Biotechnology Information, "Genes and Disease", http://www.ncbi.nlm.nih.gov/books/NBK22237/.

operated jointly by State and Federal agencies, tested unknowing employees for syphilis, sickle cell trait, and pregnancy. In its opinion, the court reiterated that, "[t]he constitutionally protected privacy interest in avoiding disclosure of personal matters clearly encompasses medical information and its confidentiality".[27] The court acknowledged that, "cases defining the privacy interest in medical information have typically involved its disclosure to "third" parties, rather than the collection of information by illicit means".[28] However, the court ultimately held that, "it goes without saying that the *most basic* violation possible involves the performance of unauthorised tests–that is, the non-consensual retrieval of previously unrevealed medical information that may be unknown even to plaintiffs".[29] The tests done by Berkeley labs were found to violate the Fourth Amendment search and seizure rights as well as the Due Process Clause of the Fifth or Fourteenth Amendments.[30] Without GINA, in other words, the *Norman-Bloodsaw* court was able to remedy an instance of genetic discrimination.

The second case involving genetic discrimination, *Burlington Northern Santa Fe Railroad Company v. EEOC*, was filed on 9 February 2001 by the EEOC; it was the first lawsuit filed by the EEOC alleging genetic discrimination under the American's with Disabilities Act (ADA).[31] Many commentators claim that the Railroad, in its search for a gene it believed contributed to its employees' carpal tunnel syndrome, conducted tests on asymptomatic employees without their knowledge or consent. In reality, the EEOC never claimed that the railroad tested asymptomatic employees. Instead, the EEOC's claim involved employees who said that they had developed work-related carpal tunnel syndrome and that the railroad had asked them to undergo a 34 part medical evaluation, which included a blood test looking for a genetic marker. Employees refusing the test claimed that the railroad engaged in retaliatory behavior. One employee, for example, claimed to have been threatened with termination for failing to submit to the blood test.

The EEOC alleged that the Railroad's genetic testing was a violation of the ADA, but that theory was never tested because the case was settled. As part of the settlement agreement, Burlington Northern Santa Fe Railroad Company paid the EEOC and the Claimants $2.2 million and agreed not to conduct genetic testing. The Railroad did not admit fault, and the settlement contained a clause stipulating that, "The parties agree that this Agreement does not constitute an admission by BNSF of any violation

[27] Norman-Bloodsaw v. Lawrence Berkeley Laboratory, 135 F.3d 1260, 1269 (9th Cir. 1998).

[28] *Id.*

[29] *Id.* at 1269.

[30] *Id.* Of course, the Constitution only protects persons from state action. The use of genetic information by health insurance companies, plans, researchers and private employers does not raise constitutional problems and was what prompted genetic information nondiscrimination legislation. S. Rep. No. 110-48, at 7.

[31] EEOC v Burlington N. Santa Fe Railway Company, **Civ No 01-4013 MWB** (N.D. Iowa, 8 February 2001). *See* Press Release, EEOC Settles ADA Suit against BNSF for Genetic Bias, http://www.eeoc.gov/eeoc/newsroom/release/4-18-01.cfm (last visited 20 February 2010) (announcing settlement).

of the ADA, or any other anti-discrimination or other laws".[32] Although the EEOC's theory that genetic testing was a violation of the ADA was not tested, there is at least a possibility that the ADA can be used to protect Americans from genetic discrimination, making additional legislation to prevent genetic discrimination (GINA) superfluous.

Even cases that directly reference GINA provide little evidence that GINA is a valuable legal tool. Although the legislation is still quite new, only eight reported cases have mentioned GINA since its enactment in 2008. Six of them were brought under Title II of GINA, while the remaining two only tangentially reference the Act. None of the cases were at all dependent upon GINA; in the absence of the Act, plaintiffs could (and did) assert their discrimination claims by referencing other legal standards. And the six GINA-related claims have not fared well in the courts. Three were dismissed for failure to state a claim; one for both failure to state a claim and failure to exhaust administrative remedies.[33] One was filed against the Department of Education in Guam and was dismissed on jurisdictional grounds. The remaining claim brought under GINA was dropped by the plaintiff.[34] Over time, the situation could change. But at least so far, GINA has not served as a useful legal tool for those who believe they have been victims of genetic discrimination.

4.4 Conclusion

In the absence of evidence that genetic discrimination by insurance companies or employers is occurring in the USA, it is difficult to justify federal legislation preventing such discrimination. Even if genetic discrimination were occurring, it is not clear that GINA is the appropriate response. If discrimination based on genetic information at the hands of insurers were a problem, then the prohibition on discrimination should apply to *all* insurers, not only health insurers. GINA also falls short in the workplace; although employment discrimination is clearly undesirable, there are some circumstances in which we might want employers to use genetic information to ensure that candidates are, and are likely to remain, physically qualified for particular positions. In both the insurance and employment settings, it is critical to appreciate the difference between unfair discrimination

[32] EEOC and BNSF Settle Genetic Testing Case under Americans with Disabilities Act, http://www.eeoc.gov/eeoc/newsroom/release/5-8-02.cfm (last visited February 20, 2010) (elaborating on settlement conditions).

[33] See Bullock v. Spherion, No. 3:10-cv-465, 2011 WL 1869933 (W.D.N.C. May 16, 2011); Robinson v. Starplex/CMS Event Security, No. CV-10-723-HU, 2011 WL 1541290 (D. Or. March 15, 2011); Citron v. Niche Media/Ocean Drive Magazine, No. 10-24014-CIV, 2011 WL 381939 (S.D. Fla. February 2, 2011); Benoit v. Pennsylvania Board of Probation and Parole-West Division, No. 094047, 2010 WL 481021 (E.D. Pa. February 9, 2010); Capulong v. Dep't of Education of Guam, No. 10-00005, 2011 WL 1134986 (D. Guam March 24, 2011).

[34] Armes v. CSX Transportation, Inc., No. CCB-11-112, 2011 WL 2471476 (D. Md. June 20, 2011).

and appropriate distinction. The former bespeaks prejudice, bias, and ignorance, the latter a rational response to the different inherent qualities of individuals. The border between discrimination and distinction is often blurry, but in the context of genetic information it is a line that society must critically engage. As biobanks continue to grow and more genetic information is collected, the threat of genetic discrimination in the USA will only increase and it will become even more important for society to engage these issues. GINA might temporarily serve to assuage fears that people have related to the collection and storage of their genetic information by biobanks; however, if genetic discrimination truly becomes a problem, GINA will not adequately address it. Ultimately, GINA is a solution in search of a problem; it is an unnecessary piece of legislation that creates more problems than it solves.

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Chapter 5
Ownership of Biomedical Information in Biobanks

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Abstract Translational research will increasingly rely on large collections of genomic and biomedical information held in biobanks and cohort studies. Those who are involved in the research process or who curate biobanks often use the concept of 'ownership' when they refer to the custodianship that they have over information in the biobank. There is also a widely accepted belief that individuals 'own' their personal information, particularly in the case of genetic information. However, information is incapable of being owned as a matter of law in the UK. The purpose of this paper is to demonstrate that ownership of genetic or medical information is not a reliable legal basis for protecting rights in relation to the information held in a biobank. Although ownership rights on information might seem intuitively appropriate or desirable, persisting with references to property and ownership may be misleading and any attempt to enforce such rights on the basis of ownership in law is unlikely to be successful. In this paper, we outline the rights that apply to personal information held in a biobank from the perspective of the donors of information to the biobank and from the perspective of the researchers who are the custodians of this information.

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5.1 Introduction

Translational research will increasingly rely on large collections of genomic and biomedical information to develop research outcomes, and biobanks provide an invaluable resource in this regard. Without the contribution of such information by participants, the research would be impossible. Often, the argument is made for participants in genomics research to have greater rights in relation to the project in which they are participating, with correlative duties of researchers towards participants or third parties framed in terms of participant 'ownership'.[1]

Property rights and ownership are important and significant rights, both in a legal and a symbolic sense. However, 'information' cannot be owned in English law.[2] Despite the intuitive appeal in applying common understandings of property and ownership to information, this concept is both confusing and misleading for those involved in research as it can foster unrealistic expectations about the legal protection of information and its use in research.

This paper considers the legal status of information in biobank research—genomic or genetic information, as well as the associated phenotypic information. We argue that ownership of genetic or medical information is not a reliable legal basis on which to ground rights for participants in research and hence not helpful when clarifying the rights of researchers, their employers, or their funders towards such information. To talk about the rights, obligations, and responsibilities that attach to information in terms of ownership can be misleading. Furthermore, any attempt to enforce rights based on ownership in law is unlikely to be successful and could have grave implications for future research.

5.2 Genomics Research

Biobank research depends upon a continuing willingness on the part of participants to take part in research by donating samples and providing personal information. Samples from individuals form a core element of a biobank or project, and collections made over many years are greatly valued as a research resource in many translational research projects. Although samples are often stored in the hope that improved techniques in the future will allow further analysis to be carried out,

[1] A small number of recent studies discuss the views of research participants and researchers on ownership of samples and data in research, e.g. Cadigan et al. (2011) and Capron et al. (2009). These studies concentrate on people's views about physical samples and have found uncertainty and lack of consensus about ownership. They also include some findings about data (information), which reveal confusion amongst participants and researchers regarding the legal protection of samples and data. A recent study in the UK has found that lack of knowledge on how samples and data are protected differently in law can cause uncertainty amongst biobanking researchers over how these entities can be protected effectively (Whitley et al. 2012).

[2] Also as summarised in Curren (2010).

samples are only the first step—it is the information derived from samples that is important for researchers, and it is this information that tends to be shared widely.[3] Samples tend to be shared more rarely, and on a much more restricted basis. Unless further analysis is performed on the sample, the physical DNA molecules are subsidiary to the information that can be derived from the sample, such as the sequence of bases. In practice, scientists may not make a distinction between the physical sample and the information extracted from it. However, as a matter of law, a physical sample is treated differently to the information extracted from it. Although it may be possible for researchers or their institutions to own a physical sample if certain conditions are met,[4] we argue that it is not possible to own the genomic information that is derived from that sample.

In this paper, we leave to one side questions of ownership of physical samples.[5] Instead, we focus on the question of ownership of the information, the clarification of which is so crucial to research. We first address some general comments on the nature of property rights in this context and then consider the questions of ownership of an individual's genomic sequence and phenotypic information, collections of information, and finally, inventions developed from research.

5.3 What Is Property, and Why Does Property Matter?

Whether property rights exist or not does matter and whether something is property is not merely a technical legal distinction relevant only to lawyers. Property rights have significance for those involved in biobanking—for researchers, managers, and participants—because they assign rights, duties, and responsibilities that are legally enforceable and shape the way that a biobank is constructed and managed.

As a matter of law, property rights matter largely because the remedies available for interference with property rights are broader than for interference with weaker rights. Such rights become important if a biobank is dissolved, as in the case of bankruptcy, where assets owned by the biobank will be sold to satisfy outstanding debts. In such a case, whether the information is property, and if so, who is the owner, is likely to be crucial.[6]

Leaving aside the strict legal view, there are other more symbolic reasons why the characterisation of something as property is important. Participants in research have a well-developed practical sense of the meaning of property in an everyday sense—people know what it means to own personal property such as their physical goods. For example, ownership implies a certain set of generally understood rights and level of control. If participants are led to believe that they have ownership rights

[3] Kaye et al. (2009).

[4] Hardcastle (2009).

[5] Milanovic et al. (2007) and Lemke et al. (2010).

[6] Janger (2005), Maschke (2005), Winickoff and Winickoff (2003) and Stanley (2008).

in relation to their information, then they are likely to be disillusioned if they attempt to enforce their rights in the same way that they can in relation to goods. Even if the language of property is used as convenient shorthand by researchers in communication with participants, it is likely to lead participants to conclude that they do have such property rights, which may have the effect of misleading participants. To do so may lead to a loss of trust in the biomedical research process, which may affect the sustainability of research in the future.

Box 1. What Is Property?

Property concerns goods (usually material goods) and the rules governing who can control and access these goods. Private property is only one kind of property—property can also be publicly owned, held in common for all, or held collectively by a group. Property rights are governed and enforced by social rules that regulate how we can share and make use of resources, especially limited resources. Commonly, property rights do not in fact give absolute rights of control but are limited in some respects by rules governing use, for instance, rules concerning planning permission for buildings and rules governing use of land. These rules may be quite different for different sorts of property. For instance, there will typically be more rules governing the use of historically significant buildings; public rights of way may cross private land.

There is no simple notion of what it is to have property rights in an object. Property rights are a bundle of rights that vary considerably in different cases. Societal enforcement of property rights also takes various forms. For instance, there may be rights of redress against theft, but control over property may be limited by lack of redress against borrowing for a limited time without permission or rules on trespass.

Many philosophers have grappled with questions about the nature and justification of property. One of the most influential of these has been John Locke, whose account has been historically particularly attractive to those considering the position of people arriving in a ‘new’ land. Starting from a premise that everything in the world is given to humans in common, Locke argued that each person starts out with a right to the ‘Labour of his Body, and the Work of his Hands’; by removing something from nature and mixing his labour with it, it thereby becomes his property.

Such philosophical notions lead to the commonly used legal notions of property based upon the concept of ‘work and skill’ as a justifying ground of property ownership, which have grounded judgments in some significant legal cases and inform the basis of much relevant legal regulation.

However, claims about property rights are enormously contested in political philosophy, with wildly different views about the basis, extent, and legitimacy of property rights. Very many philosophers with widely divergent views on political issues have all entered the debate about property rights,

from Hegel, who saw property as essential to the development of the self, to Marx, greatly critical of the notion of private property, to conservative thinkers such as Robert Nozick who argues that private property rights in a market economy should take precedence over considerations of distribution. It can immediately be appreciated how widely theories about property differ, from views that give private property rights very high prominence, to views that property rights should be restricted or even, following the anarchist thinker Proudhon, that 'property is theft'.

5.4 Ownership of Information in Relation to a Single Individual

In the past, questions over the ownership of medical information have not tended to arise in the same way they do in the digital era. Where information is held in paper records, the ownership of those physical records tends to work as an effective proxy for ownership of the information. However, where records are held digitally rather than on paper, the information is more readily copied, which makes the question of ownership and control of the information, as opposed to the storage medium, more relevant.

Bare data or information, in contrast to the expression of that information, its interpretation or an invention derived from it, cannot properly be regarded as a form of property in law.[7] Despite some older cases which appear to recognise proprietary rights in information,[8] English law now seems relatively settled that information is not property.[9] It follows therefore that individuals do not 'own' their own genomic sequence information, despite claims such as that of Navigenics that 'we believe you own your own genome' (http://www.navigenics.com/visitor/what_we_offer/our_policies/gene_patents/). Similarly, participants have no ownership rights over the phenotype information about them which is used in genomic research.

This is not to say that individuals have no rights whatsoever in relation to their health or genetic information. There are other legal and equitable causes of action that protect individuals from negative consequences of disclosure of information, such as the duty of confidence and the rights under European data protection legislation. Although they may appear analogous, these causes of action do not however protect a proprietary interest in the information.[10]

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[7] Hardcastle (2009); Fairstar Heavy Transport NV v Adkins [2012] EWHC 2952 (TCC) at [69]; *Phillips v Mulcaire* [2012] UKSC 28 at [20]; *Douglas & Ors v Hello! Ltd & Ors* [2007] UKHL 21 at [275]; *Douglas & Ors v Hello Ltd. & Ors* [2005] EWCA Civ 595; *Oxford v Moss* (1979) 68 Cr App R 183; *Boardman v Phipps* [1967] 2 AC 46.

[8] *Rolls Royce v Jeffrey* [1962] 1 All ER 801; *Herbert Morris v Saxelby* [1916] 1 AC 688.

[9] Stanley (2008) and Palmer and McKendrick (1998); Law Commission of Great Britain *Breach of Confidence: Report on a Reference Under Section 3(1)(e) of the Law Commissions Act 1965*. (H.M.S.O., London, 1981).

[10] Stuckey (1981).

Intellectual property law also does not provide any legal basis for a participant's ownership of biomedical information. If the information exists in the form of a medical record, then copyright protection may apply. However, the copyright relates to the expression of the information, not the information itself.[11] The distinction is of relevance; it is possible therefore to extract the information from the medical record without infringing copyright, provided that it is the information, rather than the expression of the information which is copied. As a result, participants have no property rights in relation to their individual medical or genomic information.

5.5 Ownership of a Collection of Information

While the question of the ownership of information relating to an individual may be of some interest to that individual, scientists typically work with large collections of information about many people. This raises the question as to whether such large collections, or databases, of information can be owned.

Previous disputes about ownership and control over research databases have tended to focus on the question of ownership of the physical samples of tissue; that is, the ownership of physical things.[12] In such cases, the permitted uses and ownership of the collection as a whole are likely to depend on the terms of the original consent from donors, the contractual arrangements for collection, storage and research use, as well as statutory schemes such as the Human Tissue Act UK.

While the information about an individual cannot be owned, when the information from many individuals is compiled in the form of a database, intellectual property rights may arise for the creators of the database. Copyright may subsist in the database as a compilation.[13] Additionally, in Europe, a collection of genomic information may be covered by a *sui generis* database right.[14] In such a case, those who compile a database that require some skill in the selection and compilation of the information, may have a right to prevent others from copying that database. However, another person may compile the database again from first principles.

Again, intellectual property law will not aid a participant's assertion of ownership of information. Neither copyright nor the database right will be of assistance to a participant who wishes to exercise control over their individual data, as the rights subsist only in the collection of information. However, the ownership of the collection of information is of vital importance to those who compile it, whether

[11] And in any case, the patient would not be the owner of the copyright—copyright would vest in the creator of the information (i.e. the doctor who wrote the record) or their employer.

[12] *Washington University v Catalona* 490 F 3d 667 (2007) (United States Court of Appeals, Eighth Circuit); Dickenson (2008).

[13] D'Agostino et al. (2008); Copyright, Designs and Patents Act 1988 s 3(1)(d).

[14] Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the Legal Protection of Databases.

a researcher or their institution. Such resources can be extremely valuable, and those who are able to control the use of the resources may be able to produce many publications, or develop inventions. However, it is important to note that while intellectual property rights may arise in the way the database is constructed, the information held within the database cannot be owned, by either researchers or participants.

5.6 Ownership of the Outcomes of Research

There are two major ways in which the outcomes of research may be owned. The first of these is academic publications that result from the research. Copyright will arise in these publications, and the ownership of such right will vest originally in the author(s) of that work who, depending on the terms of the journal which publishes the research article, may assign or licence the copyright to the journal. With an increasing tendency toward open access publishing, many journals allow the authors to retain their copyright in the research paper (see for example http://www.nature.com/authors/editorial_policies/license.html).

The major area in which there may be ownership of the outcomes of research is in the context of inventions. Should an invention arise from the research, then the invention could potentially be patented, provided that it satisfied the requirements for patentability. Whilst inventions arising from genetics and genomics research may be owned, participants traditionally have not shared in this ownership, in the absence of pre-existing contractual arrangements.[15] The USA cases of Moore[16] and Greenberg[17] demonstrate that participants do not have any proprietary interest in relation to the inventions made on the basis of their samples and information. In the USA, property based on contractual arrangements can arise in the form of joint inventorship of genetic tests developed through successful collaboration between patient groups and researchers, but its standing in a court of law could be uncertain.[18]

Box 2. Property in Information? Influences on Ethical, Legal and Regulatory Debates in Genetics and Genomics

Much of the literature that debates and discusses rights over genetic information implicitly or explicitly draws upon the idea that individuals have property rights in their own biomedical information. This potentially causes

(continued)

[15] Terry et al. (2007).

[16] *Moore v Regents of the University of California* 793 P 2d 479 (Cal SC 1990).

[17] *Greenberg v Miami Children's Hospital Research Institute* 208 F. Supp.2d 918 (2002).

[18] Kanellopoulou (2009).

greater difficulty when it is implicit rather than articulated, because it can create problematic assumptions that are not directly addressed or questioned.

A difficulty that should by now be apparent (Box 1) is that the claim to property rights can be extremely vague: the nature of any such rights, and their basis, are both contested. Moreover, since property rights are bundles of rights, and since they vary greatly in different instances, even individuals were to have property rights in data or in samples, this leaves open a large arena of uncertainty and may well not give a great deal of guidance.

Often the notion of ownership is used as little more than a rhetorical device—assuming that the information belongs to the person from whom it is derived—but often without any clear legal grounding. If the question is asked 'to whom does this information belong?' it may seem as if it must belong to the individual in question. But the way such a question is posed actually presumes that the system of private property is in operation in this instance. And even then, exactly what property rights an individual might have over their data and samples remains to be seen.

The notion that information belongs to participants also underscores some of the arguments in favour of feeding back results of research to participants, on the basis that it is really 'their' information. But the 'work and skill' of researchers needed to generate even raw data might equally be used to argue that if anyone has property rights in the information, actually it is the researchers. Yet the debate about feedback of results, which is a greatly complex and current thorny question, can proceed entirely without reference to notions of property. For example, an arguably far more promising approach would be to base questions of feedback around weighing up potential benefits and costs.

5.7 Conclusions

The notion of ownership of information in the context of translational research in genomics is legally meaningless. There is no such thing as ownership of information as a matter of law, and to discuss such matters using the language of property does not benefit any of the parties involved in research, whether they are participants, researchers, research institutions or research funders.

First and foremost, we should not talk about the ownership of information because to do so is likely to be misleading and potentially harmful towards participants. Participants should not be led to believe that they have property rights when such rights do not exist in law. Consent forms should not use the language of property, even as convenient shorthand. Any attempt to enforce property rights by participants would lead to disillusionment, and, potentially, loss of public trust.

Such loss of trust can be hugely damaging in genomic research, as was demonstrated when the breakdown of the researcher–participant relationship led to highly publicised problems and litigation, between Arizona State University and various members of the Havasupai tribe.[19] Such loss of trust may damage the sustainability of research into the future.

Moreover, governance structures for genomic research projects should not be based on a belief that ownership of the information is possible. Whilst lawyers are likely to be aware of such limitations, researchers who are developing the broad arrangements for large projects should also have an awareness of the limitations of the property model insofar as information is concerned. It is important that governance structures are based on a correct understanding of the law because legal uncertainty in this area could result in significant difficulties should disputes arise during the course of a research project.

We do not consider ownership of information to be necessary. In fact, we consider that ownership and property rights in information are likely to be unworkable since one of the main incidents of ownership, the exclusivity of a property right, is missing as the transferors retains the information that they transmit.[20] Other areas of law provide myriad mechanisms for the organisation of large research consortia. In particular, appropriate contractual arrangements setting out obligations that will ensure that information is properly used and controlled are vital in biomedical research.

Participants may in some cases argue in favour of their property rights, largely because they may see such property rights as providing robust protection of their rights. However, such property rights are neither feasible as a matter of law, nor necessary, since there exist other, more efficient means of protecting the interests of participants. Participants may have their interests protected through regimes such as data protection, and legal and equitable principles relating to confidential information or tort. Whilst it may be important to consider whether these other legal mechanisms do indeed appropriately serve the interests of participants, it is unhelpful to turn to a rhetoric of property rights, when there exists no clear basis for such rights in law.

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[19] Harmon (2010).

[20] Bridge (2002).

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Chapter 6
Human Tissues in the "Public Space": Beyond the Property/Privacy Dichotomy

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Abstract During the past 20 years, human biological materials (HBMs) have become increasingly important for research as well as for therapeutic uses and related commercial exploitation. The scientific and regulatory conditions for their procurement, testing, processing, preservation, storage, and distribution have been reflected upon widely and developed in both the civil law and the common law domains.

In the normative puzzle taking place around the biobanking of HBMs and information, the basic legal perspectives underlying most normative analyses remain anchored to the concepts of autonomy—also conceived of as privacy—and property. The former has been primarily developed in Europe, the latter in the US. Both are showing some failures, while the normative picture as a whole appears inadequate.

This contribution explores the main existing legal frameworks for biological materials, both in the US and EU contexts, and the potential for reconciling individual and collective dimensions in biobanking through a participatory approach.

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The legal fate of bodily materials is somewhat similar to that of the environment. In both instances, the notions of subject of rights (the rights holder) and of object of property (the object held) have failed to fully represent the potential for collective sharing. And in both cases, the procedural participatory turn has allowed a more adequate legal imagination to address different needs and goals.

6.1 HBMs: A Normative Puzzle

The different pegs composing the regulatory framework on the uses of cells and tissues came about in different stages, while several problems were emerging.[1] The first question concerns the separation/overlap of bodily materials and information; the second theme was that of informed consent to secondary uses of biological materials; the third problematic area was tied to procedures of anonymisation, which is conceived as a possible solution to secondary uses.

The principles and norms regulating cells and tissues as materials, and as source of information, have distinct origins and aimed at protecting different values. Protection of personal data and the right to privacy represented the main concern for regulating information (personal and in families, clinical, biological, and genetic); the needs to frame donation as a free form of solidarity and to protect safety were the major tenets in dealing with biological materials.

However, the similarities between the two distinct topics soon became evident, and pushed towards a unified regulatory approach. The very same issues of informed consent, confidentiality, and rights of access were at stake in both cases. Notwithstanding, it took a long time for the regulatory frameworks to be made coherent and connected, and still, several issues are surrounded by normative uncertainty both in Europe and the US.[2]

A critical point concerns the consent to "secondary uses", the use of cells and tissues originally collected for diagnostic or therapeutic reasons, and subsequently destined for research uses that are often unforeseeable. The unpredictability of the uses of research on biological materials has made informed consent ambiguous because what donors are asked to consent to cannot be specified. Potential solutions highlighted by scholarly analysis range from restricted to wide, and even to blanket and blank forms of consent.[3] In the US context, a general agreement exists about specific or multi-layered consent to secondary uses.[4] The Code of Federal

[1] Karlsen et al. (2009).

[2] Cambon-Thomsen et al. (2007), Andrews (2006), Charo (2006), Rao (2007), and Glantz et al. (2008).

[3] Harrison (2002), Tutton et al. (2004), Wright Clayton (2005), Lipworth et al. (2006), MRC (2006), da Rocha and Seoane (2008), Salvaterra et al. (2008) and Hofmann (2009).

[4] NBAC (1999) and Greely (1999, 2007); for a different position, see Caulfield (2007).

Regulations (45 CFR 46.116) banned all forms of "blanket consent" (OHRP 2008).[5] In Europe, if existing documents still endorse specific consent (COE 2006), scholarly literature increasingly lines up for open consent.[6]

6.2 Legal Strategies: The Myth of Privacy, the Denial of the Body

The history of the layered and unfinished regulation of bodily materials has been determined by several factors. In this normative puzzle, however, the fundamental unresolved issue remains the dichotomy between the subjects giving up their own biological materials and the materials themselves. The legal destiny of biological materials depends on how this interface is framed. Other issues, such as informed consent, are a consequence of this relationship.

Two different strategies have been followed in the US and in the European institutions to frame the dichotomy seemingly inscribed in the body. The United States has addressed the question of bodily property—or, more broadly, proprietary interests—in an explicit and direct way. In fact, though evoking privacy—mostly interpreted as a synonym for autonomy, namely, as a domain for private decisions—the US courts have primarily defined the question in terms of property. The two main legal frameworks have either compared the weak proprietary interests on raw biological materials with the well-established intellectual property rights or have presumed that tissues are donated or abandoned by individuals, and then they are acquired for free as *res nullius* by researchers who are entitled to put them in the market.

The European normative framework has avoided dealing directly with the body—traditionally framed as a *res extra commercium* that as such cannot give rise to financial gain—and has symbolically subsumed it within the concepts of individual dignity, autonomy, and privacy. At the same time, however, the denial of the marketability of bodily materials has gone hand in hand with the construction of a European market for tissues. Both perspectives have led to some unsatisfactory outcomes, the primary source of which is the dichotomy between the body as a person and the body as an object.

[5] "No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence". 45 CFR 46.116, http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116 (Accessed July 2012).

[6] Cambon-Thomsen et al. (2007) and Hansson (2005).

6.3 The US Normative Framework: Privacy vs. Property and the Abandoned Gift

In the US, where the first leading legal cases about biological materials emerged, although privacy was evoked, it did not really represent the main legal concept addressed by courts and legal scholars. Privacy was kept on being mentioned in the US judicial history of tissues, but in a non-problematic way. The proprietary discourse appeared since the official beginning (in *Moore*) as the core issue. The very same construction of different forms of anonymisation, apparently aimed at protecting privacy, was explicitly directed towards the legal reshaping of subjects as objects (namely data). Also, in order to make property rights more flexible, several legal ontologies have been constructed: material and intellectual, strong or weak, property rights and proprietary interests.

The first US judicial case to gain international renown was *Moore v. Regents of University of California*, dealing with the personal and economic aspects of HBMs.[7] Depicting secondary uses as the dichotomy between privacy and property, in 1990, the California Supreme Court established a very successful conceptual distinction.

The famous formula, according to which it is not necessary "to force the round pegs of 'privacy' and 'dignity' into the square hole of 'property'", determined the ambiguous destiny of HBMs. These belong to the sphere of "private autonomy" as far as they remain in the body. The body-subject is only legally entitled either to abandon or to donate them. When detached, they become abandoned things (*res derelictae*) that some legally entitled subject or entity (research institutions, corporations) may acquire as *res nullius* (things that nobody owns). At this point, biological materials become potential subject matters for intellectual property rights.

In a straightforward way, the Court acknowledged that the legally constructed dichotomy between privacy and property entirely depended on the need not to damage pharmaceutical corporations by limiting their access to "necessary raw materials".

In 1987, the Office of Technology Assessment (OTA)—the agency advising the US Congress at that time—helped the *Moore* decision. The OTA reinforced the idea that biological materials could be seen as *res derelictae* and *res nullius* by offering an unheard metaphor between the biological materials detached from the body and wild animals: "It could be argued the patient and his tissues stand in a relationship similar to that between a landowner and wild animals on his land... Not having exercised dominion or control over the tissues, the patient's rights therein would be like those of a landowner who had made no attempt to capture wild animals passing over his land".[8]

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[7] *Moore v. Regents of University of California*, Cal. App. 2 Dist. 1988; *Regents of University of California v. Moore* 51 Cal. 3d 1990.

[8] OTA (1987), 82.

In 1999, the National Bioethics Advisory Committee (NBAC) went even further in legitimising the *Moore* decision, stating that, "the biological materials are available not to anyone, but in general are restricted to those who have legitimate research interests in their use and presumably possess the capability to perform sophisticated scientific studies that can reveal biological information about the samples or even health-related information about the persons from whom they came".[9]

The theory of abandonment of tissues in the name of the social utility of research uses (and commercialisation) is theoretically strengthened by patentability. If no real property rights exist on raw materials, intellectual property rights may originate from their artificialisation, an invention created from, but "factually and legally"[10] distinct from, bodily materials.

However, the issue of HBMs availability has been constantly debated since *Moore* in several major courts' decisions. In 2003, the *Greenberg v. Miami Children's Hospital* case was decided (264 F. Supp. 2d 1064 S.D. Fla. 2003). It dealt with the donation of samples for the study of Canavan disease, made by Mr. and Mrs. Greenberg to Dr. Reuben Matalon, a researcher at Miami Children's Hospital. The Court argued that the relationship between researcher and tissue donor is not comparable to the doctor–patient relationship. In particular, the researchers are not subject to the same financial obligations, even the one involving communication of possible economic interests. On the other hand, having acquired a patent on Canavan disease, Dr. Matalon was the undisputed owner of materials involved in the invention.

Greenberg was innovative compared to *Moore*, where lack of economic disclosure was recognised as violating Moore's rights. The *Greenberg* court introduced different duties for researchers and physicians. While the latter is obliged to full disclosure, the former is allowed to be more entrepreneurial. But the cases are similar in that they both point to the unsurpassable legitimate ground for property in patenting. Once patented, biological materials have their legal ontology changed, from non-appropriable "natural" entities to artefacts.

In *Greenberg*, also, the Court introduced an additional factor to make biological materials freely available to industry, establishing that the already limited property rights existing on tissues "evanish" when tissues are donated.

In 2006, *Washington University v. Catalona* (437 F. Supp. 2d 985 E.D. Missouri 2006) added a further piece to this legal picture, as the trial dealt with biological materials owned in their "natural state", and not as a patented invention.

The prostate samples, received by Dr. William Catalona from his patients while he was working at Washington University, and that he and his patients wanted to transfer to Northwestern University in Chicago, were declared by the Court of Appeals of Missouri to belong to Washington University. Washington University,

[9] NBAC (1999), 59.

[10] *Regents of University of California v. Moore*, cit.

according to the court, received the HBMs through an "unconditional donation". The US Supreme Court declined to accept the case in 2007.

Catalona strongly divided the US legal doctrine. In general, the prevailing interpretation was favourable to the market and to innovation in the US judicial system, while only a few courts adopted a different attitude.

Also, among the US legal scholarship there is an extensive convergence in accepting "proprietary interests" on tissues, and in believing that these interests must find clear recognition.

Lori Andrews, in favour of individual rights on tissues, emphasised that several court decisions, though still a minority, affirmed proprietary interests for tissue donors.[11] Patients who donated their tissues for altruistic aims should not see their expectations disregarded.

Glantz, Annas and others,[12] on the contrary, while welcoming the *Catalona* decision, claimed that legal certainty would call for a clear recognition of property rights on biological materials in favour of research institutions. The present situation would hypocritically leave human tissues in a judicial no-man's land, where researchers' needs require a uniform and stable legal framework.

In this perspective, Glantz and Annas have also argued against the misleading analogy between "research on human subjects" and "research on human materials". This analogy, according to which the patient's right to revoke consent similarly applies to experimentation both on human subjects and on biological materials, is completely inadequate. The two topics are by now radically different and they bring about a conceptual clarification that definitively separates their destinies.

6.4 The European Normative Framework: Heteronomous Autonomy and the "Right to Destroy" the Donated Body

In the European context—for several reasons, also including the unresolved economic/political identity of the EU—[13] the regulation of biological materials has been primarily discussed within the two "mantras" of individual autonomy and the prohibition of gaining profit from the body and its parts.

Facing the new prospective uses of human tissues, both the European Union (EU) and the Council of Europe (COE) have produced two separate legal and policy

[11] Andrews (2006) cites on this matter *York v. Jones, 717 F. Supp. 421, 426 (E.D. Va. 1989)*, where "proprietary interest" was recognised for a couple on their own pre-embryos, which limits the powers of the clinic where they were deposited; *Hecht v. Superior Court of Los Angeles County, 16 Cal. App. 4th 836, 850 (Cal. Ct. App. 1993)*, which recognised heirs' property of the seminal liquid of the deceased; *Whaley v. County of Tuscola, 58 F. 3d 1111 (6th Cir. 1991)*, relative to the proprietary interests of a relative on the body of the deceased.

[12] Glantz et al. (2008).

[13] Tallacchini (2009).

frameworks; respectively, the EU for cells and tissues donated for therapeutic purposes, and the COE, for materials conferred to scientific research.

6.4.1 The EU Institutions

The European institutions have designed biological materials donated for therapeutic purposes and those given to scientific research as separate regulatory issues, notwithstanding their initial orientation seemed to lean toward a unitary perspective. In 1998, the European Group for Ethics (EGE) of the European Commission, affirming the "moral imperative" to regulate tissues, did not make any distinction between forms of donation and uses (diagnostic, therapeutic and research)—even when tied to commercial implications—and declared that informed consent should always be conceived as revocable. [14]

The EGE's main concern was to connect the individual dimension of tissue donation with public trust towards potential collective research and therapeutic benefits. This meant creating the premise for the construction of a unitary public policy for tissues. The EGE was in fact well aware of the substantial difference that existed between organ donation and cell and tissue donation, as, while the former are utilised in their natural state, the latter represent the base for "therapeutic products", usually patentable and certainly destined for the marketplace. For several reasons (marketability, safety reasons, storage methods, etc.), research and therapeutic uses of cells and tissues have more in common than tissues and organ in the therapeutic domain.

However, the unity of the normative perspective disappeared during the legislative process. A notable distance was introduced between therapy and research: also a consequence of the (then) exclusive COE's jurisdiction in the domain of human rights and biomedicine. The EU could only intervene in regulating research experimentation in an indirect way.

In 2004, Directive 2004/23/CE on donation, supply and storage of all cells and tissues (with the exclusion of organs and blood) was approved. Aimed at defining the safety and quality requirements for HBMs destined for therapeutic human applications, the directive stated the principles of free, unpaid donation, informed by solidarity, thus, introducing an explicit "European philosophy" on donation.

[14] EGE (1998), 8: "The information provided to the donor should concern:

- the procurement arrangements, in particular concerning the free nature of the donation, and the extent of its anonymity.
- possible tissue storage time and conditions, and conditions of registration of data in databases, in conformity with requirements of privacy protection and medical confidentiality;
- foreseeable use of the tissues (diagnostic, allograft or autograft, pharmaceutical products, research, production of cellular lines for various uses, etc.). The donor may at any time withdraw her/his consent".

The regulatory framework was completed in 2007 with Regulation 1394/2007/CE.[15]

This document aimed at establishing a centralised authorisation for all "products" derived from tissues and cells (cell therapies, gene therapies, and tissue engineering products), defined as "advanced therapies" (ATMP, Advanced Therapy Medicinal Products).

Together, the directive and the regulation constructed and accurately separated the two domains of voluntary, unpaid tissue donation by European citizens, and the reality of the European tissue market. In other words, European ˝citizen-donors"[16] are asked to freely provide their biological materials for solidarity reasons; the pharmaceutical industry can get the raw materials to create new therapeutic products; European patients–consumers will purchase these products in the marketplace.

During the consultative process prior to approval of Regulation 1394/2007, the question of who owns biological materials was raised by some commentators highlighting the need for clarification.[17] The Regulation has not addressed the issue, but has only stated that, at least in principle, "cells or human tissues contained in medicines for advanced therapies should come from voluntary and free donation" (Article 15). However, although not explicitly stated, it is clear that materials involved in the production of advanced therapies are owned by those using them and putting them on the market, after exploiting them also for research and experimentation.

The proprietary discourse, therefore, is not foreign to the EU legislation, even when it seems to disappear. Advanced therapies were not framed like organs or blood, instead they were intentionally thought of as commercial pharmaceutical products.

To provide stability to the economy of tissue products, Directive 23/2004 does not allow donors to revoke their donation. Donors must be reassured regarding the confidentiality of the present and future use of their information, but cannot take back what has been contributed.

Moreover, in the policy of advanced therapies, the same rights to privacy, even when called upon and guaranteed, do not appear as stringent as in the case of research. Reasons of safety and security here prevail over privacy. Tissues and related information are completely traceable—from the donor to the product to the recipient (Article 8); and a complete traceability of advanced therapies is made mandatory (Article 15). Traceability of tissues and anonymity of the donor and recipient then coexist in different "public spaces": donors and recipients are reciprocally anonymous, but they are all traced by institutions and industries involved in storage and use of biological materials.

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[15] Regulation 1394/2007 of the European Parliament and of the Recommendation of 13 November 2007 on medicine for recanted advanced therapies modification of the Directive 2001/83/CE and of Directive (CE) n. 726/2004.

[16] Tallacchini (2009).

[17] DG Enterprise (2004), 6: "Ownership of the cells and tissues after donation: as legislation differs from one Member State to another, it is recommended that the regulation should provide clarity on this issue".

In this respect, during the approval of Directive 45/2010 on the safety of organs for transplantation, it has become clear that traceability and privacy are incompatible goals, and that citizens should be aware of this. As the European Data Protection Supervisor[18] noted, "the term anonymity is actually used to stress the need for enhanced *confidentiality* of the donors' and recipients' data, meaning that information is accessible only to those authorised to have access. [. . .] anonymity is not the correct term to be used".

6.4.2 The Council of Europe

In 2006, almost in parallel with the work of the EU institutions, the Council of Europe, exerting its powers in the area of human rights, approved Recommendation 4(2006) dedicated to research on biological materials. The non-binding document conferred more control to individuals over scientific research using their materials and data.

The analogy motivating the Recommendation, and reflecting a widespread tendency,[19] is that research on HBMs and research on human beings are comparable and need similar regulations. "Biomedical research", the Explanatory Report on the Recommendation stated, "can be carried out not only on human subjects, but also on materials of human origin".[20]

The Recommendation is very rigorous in asking for explicit (and detailed) consent to the use of biological materials for research and in indicating different forms of de-identification of materials. Furthermore, it established that, similarly to the rule in clinical trials, donors of biological materials have the right to revoke their consent. Moreover, when withdrawing consent, they are entitled to have their materials destroyed or anonymised.[21] Donors may ask for the destruction of their donation.

It is not clear if destruction and anonymisation of materials are meant as equivalent options, and who has the right to make the choice.

What clearly emerges is the fracture in the discipline of donation, which can be or cannot be revoked in relation to its different purpose.

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[18] European Data Protection Supervisor (2009).

[19] UNESCO (2008).

[20] CDBI (2005).

[21] Rec(2006)4, "Article 15 – Right to change the scope of, or to withdraw, consent or authorization – (. . .) When identifiable biological materials are stored for research purposes only, the person who has withdrawn consent should have the right to have, in the manner foreseen by national law, the materials either destroyed or rendered unlinked anonymised". And at 73: "The individual has the right to withdraw from the research and the right to destruction of his/her biological materials and data. In the case where a person withdraws and the research has already generated findings, these findings ought to be rendered unlinked anonymised, unless they already have been published or it is otherwise impossible to withdraw them from the research".

Anonymisation of biological samples—namely techniques for preventing identifiability of involved individuals—has been the most common techno-legal tool to neutralise issues of consent.[22] In fact, the mechanism has a double effect: while rhetorically presenting institutions and corporations as accountable and trustworthy, it de facto limits the necessity to reiterate consent.

The de-identified subject-donor—made anonymous—is supposed to have lost all personal interests in his/her materials and information, as they have become "impersonal".[23] Also, anonymisation is further associated with the loss of control of biological materials and information, or with the willingness to abandon them. Finally, abandonment implies that third parties (operating in research and the market) may freely acquire biological materials as *res nullius* (things not belonging to anybody).[24] The result is that a subtle but clear connection is established between the identifiability of materials and the right to control them.[25]

This process reflects the ideology that James Boyle has called the "informational" reduction of the body[26] According to Boyle, the body has been de-materialised both by science and the law, and has been re-constructed in terms of information. In this paradigm of information—also involving other relevant products of technological innovation—"the tendency is toward the economic and conceptual separation of the informational message from the medium—cells, diskettes telephone directories, or whatever—and the progressive devaluation (literally, the diminishing marginal cost) of the medium as compared with the message".[27]

Noticing that Rec 4(2006) does not meet the need of researchers, most European ethicists have argued in favour of a broad informed consent unconditionally legitimising all future unforeseeable research. Different strategies have been adopted

[22] Tallacchini (2005).

[23] Lowrance (2002).

[24] Tallacchini (2005).

[25] At the end of the 1990s the National Bioethics Advisory Committee (NBAC 1999) clarified that only originally unidentified samples can be properly called anonymous; all samples identified at the moment they were taken, even if later coded or anonymised, can be re-identified. The US Department of Health and Human Services (DHHS), in its 2004 guideline—mentioning section 45 of the Code of Federal Regulations (CFR, at 46.102(f))—further reinforced the point, affirming that, "to gain private identifiable information or biological samples identifiable for research purposes integrates the extremes of research on human subjects". The most recent proposals of standardisation of practices, like that of the International Conference for Harmonisation between the United States, Europe and Japan (ICH 2007) introduced the category of *double coded* samples—where the codes are entrusted to different subjects.

[26] Boyle (1996).

[27] Ibidem, 7.

to make autonomy and privacy compatible with less stringent consent requirements. Some authors, such as Hansson, have reinterpreted the Kantian concept of autonomy in terms of solidarity—autonomy as the duty of solidarity towards others and as a duty to "give back" what individuals have received from society.[28] What is taken for granted here is the assumption that everything is performed in the name of science and research is *per se* good and legitimate, and that there is no need for citizens to discuss public health policies and allocations, as they can be unproblematically decided by scientists and policy makers.

In reality, the Kantian idea of autonomy, though socially embedded with solidarity, has little to offer to the current debate on science and democracy. It only helps to describe heteronomy as autonomy.[29] However, does it still make sense, or is it misleading to maintain the language of autonomy where the dimensions at stake concern the public sphere, socially shared goals, investments in health, transparency and the democratic functioning of institutions?

It is difficult to resist the impression that the ethical idea of autonomy, when reframed as heteronomy, is instrumental to rapidly achieve legitimacy for resource allocations that should instead go through legal and democratic procedures.

Other scholars, such as Lunshof et al.,[30] have more realistically displayed the contemporary limits and even non-sense of autonomy and privacy, which simply can no longer be granted. The open recognition of the impracticability of privacy should thus open towards protecting a different value: veracity. For researchers, to be veracious would mean to disclose their inability to protect privacy. And the reward for their sincerity should be their being legitimated to violate privacy.

This further perspective lay behind and was evoked as theoretical background to legitimise innovative experiences such as the Personal Genome Project (PGP).[31] The PGP is an ongoing public genomics research study which aims to improve the understanding of genetic and environmental contributions to human traits. It enrols volunteers who are willing to share their genome sequence, their biological samples, and other personal information with the scientific community and the general public on the web.

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[28] Cambon-Thomsen et al. (2007).

[29] Hansson (2009), 9: "Making autonomous decisions in accordance with the Kantian tradition thus involves taking into account the well-being of others through a judgment of how one's own decisions affect other people's ability to act in a morally responsible way and to attain their own goals. Autonomy in the Kantian tradition is inherently social, with the implication that the working out of legal protections for self-determination and privacy in association with biobank research must simultaneously do justice to both the research subject's independence and to this individuals' dependence on others for fulfilling mutual interests such as new biomedical knowledge and new treatment opportunities".

[30] Lunshof et al. (2008).

[31] The PGP is based at Harvard Medical School and is lead by Prof. George Church, who is also a participant to the research. See http://www.personalgenomes.org/ (Accessed July 2012).

6.5 Beyond Privacy and Property: The Participatory Turn

It has been observed that the proprietary language is so pervasive that it influenced the legal framing of bodily materials, even when formally avoided.[32] As illustrated before, human tissues are basically treated as property also within the paradigm of privacy and autonomy.[33]

However, though the prevailing Western philosophical and legal perspectives have conveyed the body through the dichotomy between subject and object, the body is not necessarily confined within these boundaries. Other visions are available that have the potential for reconnecting the subjective and objective dimensions.

Classic Roman jurisprudence framed the legal representation of the world according to three different ontologies: *personae, res*, and *actiones*. [34] The human body has been constructed both as *persona* and *res*.[35] However, in the aftermath of the multiple uses of biological materials, a procedural legal representation becomes necessary—and here perhaps the notion of *actiones* is the closest available traditional metaphor.

A procedural, participatory turn may help reconcile the human subject with the human body through the recognition of citizens' participatory rights to public decision-making concerning their biological materials.

In this respect, the legal fate of the body is similar to that of the environment. Both the body and the natural environment, the internal and external loci of human experience, represent two special entities that are difficult to be framed within a radical dichotomy between the subject or object.

In fact, environmental philosophy has dealt with similar issues in framing the relationships between humans and nature in constructing the concept of shared (common) environmental goods.

First of all, both the environment and the body have been disputed objects for the marketplace. Jasanoff has compared the legal destinies of the natural environment and of live nature—including the human body—arguing that the steps specifically required to reframe natural objects as social entities involves "two kinds of moves that are tacitly, though not explicitly, granted controlling status in the law: specificity and circulation. Put differently, the property claim has to involve *both* taking a specific, characterisable and reproducible bite (and, today, perhaps as much byte as

[32] Rao (2007), 380.

[33] According to Rao (2007), the idea of property as stewardship, taking care, and administration is susceptible to apply to the body. And that conception is not at all new—for example, it was present in John Locke. According to the author, one can speak of proprietary right with respect to the body forging these "dormant properties" around the idea of stewardship.

[34] See Karlsen (2011).

[35] Honoré (1962).

bite) out of nature *and* the ability to make the excised element circulate widely in commerce".[36]

Jasanoff revisited in constructivist terms what the legal doctrine characterised as the necessary elements for an object to become a legal good: quantification and economic value. This is why so called *res communes omnium*, namely water, air, and most natural entities cannot be owned: their unlimited abundance implies their lacking economic value.

However, the similarities between the environment and the body are even stronger.

According to scholarly work on the history of the idea of nature, the philosophical roots that have led to the environmental crisis are to be found in the "epistemology of the human dominion over nature", namely the culture of the humankind owning and controlling nature, perceived as a mere object of property.[37] This dominion was first justified in the name of a divine mandate (in Genesis), and later performed through science and technology.

In an essay on the environmental crisis, the French legal scholar Martine Rèmond-Guilloud argued that the most powerful expression of ownership, as defined by Article 544 of the Code Napoléon of 1804, does not consist in donating for free or in selling the object of property, but in the self-referential, irreversible act of destroying it. This is "le droit de détruire", the right to destroy.[38]

The destruction of the environment performed in the name of the human dominion on nature recalls the powers of biological materials' donors who ask for their destruction. The desire to destroy biological materials previously donated, with all their potential for generating new knowledge and benefits, re-proposes in a different context the same perspective of the destruction of environmental goods, namely, what Garrett Hardin called, the "tragedy of the commons".[39]

Finally, also the environment has gone through legal attempts to portray it as a subject of rights. Different attitudes towards nature have been proposed other than the prevailing Western vision of dominion. The cultures of administration and conservation, for instance, involve relationships of stewardship and partnership towards environmental goods. These visions have insisted more on showing nature as a place where human activities may take place in compatible and respectful forms, than on property.

In his famous essay *Should Trees Have Standings?*, written in 1972 to support the Sierra Club's claim to represent the rights of nature, Christopher Stone argued in favour of subjective rights for natural objects as the only way to directly act for the benefit of nature.[40]

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[36] Jasanoff (2010).

[37] Passmore (1974).

[38] Rèmond-Gouilloud (1989).

[39] Hardin (1968).

[40] Stone (1972). see also Edelman and Hermitte (1988)

However, in environmental philosophy and law, after the attempts to endow nature with subjective rights or to establish fixed objective boundaries to ecosystems as to other ordinary things, the most successful theoretical move has taken place when the legal perspective was shifted from substantial rights to procedural, participatory rights. More than a subject of rights or a mere object of property, the environment has been finally and more adequately seen and inhabited as a space for participation and shared decisions.[41]

Participatory approaches are now widely performed in most science-based decisions both in the US and the EU, as they migrated from the environment to risk assessment and technology assessment, both for safety/precautionary and democratic reasons.

This participatory lesson has been transferred to the legal framing of bodily materials—the most direct and intimate human environment. In this direction, several attempts have been made (both theoretically and in practice) to introduce shared decisions and powers for participants in the domain of biological materials.

Already in 2003, Winickoff and Winickoff argued for the model of bio-trust, an innovative version of the charitable trust—a common law legal construct. They suggested that "proprietary interests" on tissues could be transferred to a custodian or trustee who, together with proprietary powers, also receives fiduciary duties. The trustee has to use the donation in favour of a third party (the public, current and future patients) according to certain determined uses. Also, while the trustee has duties of transparency towards the public, the donor maintains participatory and consultative rights, as well as powers of controls.[42]

In a more explicit way, Gottweis and Lauss have argued for a "participatory turn" in the governance of biobanking. "There is a need for new strategies to regulate the relationships between individual citizens, society and biobanks, and to find new solutions for dealing with the core issues of consent, privacy, ownership, access and benefit sharing in the linking of society, citizens and biobanks. . . .Participatory arrangements that are responsive to the views of patients and "lay people", and also operate on a transnational level, will be key to such novel arrangements".[43]

Moreover, the tendency of involving citizens in scientific research projects has increased both in no profit and for profit sectors,[44] becoming a valuable requirement in several epidemiological and genetic research activities, as it enhances trust between participants and researchers, and thus improves the quality and effectiveness of research.[45]

[41] The major international legal documents in this respect are the UN Ksentini Report of 1994 and the Aarhus Convention of 1998.

[42] Winickoff and Winickoff (2003).

[43] Gottweis and Lauss (2010), 187.

[44] See Check Hayden (2012). A harsh discussion has surrounded direct-to-consumer gene-testing companies such as PatientLikeMe and 23andMe.

[45] Such as community-based participatory research, an approach to studying human populations that emphasises extensive partnerships between researchers and community members. See Horowitz et al. (2009) and Resnik and Kennedy (2010).

However, currently the major obstacle to these initiatives is the obsolete and static legal vision of individuals. In fact, it is becoming clear that citizens tended more towards solidarity than the normative picture, and sometimes also the theoretic reflection, are able to recognise and allow. The way legal anthropology and legal concepts are still representing human attachment to a private sphere narrowly conceived cannot be justified any longer as realistic: currently, this vision is primarily a shallow way to legitimise vested interests.

Real citizens seem to be concerned not as much with privacy or attached to owning their bodies in order to feel protected and respected, but are instead more interested in the meaning and the goals of research.[46] "Respect for persons", it has been noted, should "entail a respect for the ability, willingness and right of participants to share in imagining the futures to which research aspires. If human subjects are asked to give material from their bodies for research, they should also be treated as competent to govern the material's future uses".[47]

The next open frontier is the vision that goes beyond two of the major tenets in legal systems, namely, the current boundaries between what is private and what is public in our lives, and some narrow versions of private property. These perspectives for reframing rights[48] require major changes not only in the regulatory approach, but also in some fundamental assumptions about legal anthropology. The construction of a trusted and shared public space for civic participation may contribute to a more robust normative framework for biological materials.

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[46] Wynne et al. (2007). See also the perspectives described in interviews with patients: Chandros Hull et al. (2008), O'Doherty and Burgess (2009) and Check Hayden (2012).

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[48] Jasanoff (2011).

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Chapter 7
Should Privacy Be Abolished in Genetics and Biobanking?

Amedeo Santosuosso

Abstract In this paper, after a short outline of current main features of biobanking, first the disenchantment on privacy and informed consent in the field is presented and discussed as a reaction to the recognition of full (individual) rights even to each piece of biological materials and/or genetic information. Secondly, the real interests at stake (when biological materials and genetic information are involved) are clarified: is human genome really/exclusively human? What are the boundaries of human family and those of biological group? What does biological group encompass in scientific terms and legal terms? Under what conditions and to what extent does the individual compass interact with those of other family members and with the biological group as a whole? Finally, both the human individual and the biological group compass are conceptualized as legal artefacts, whose definitions are the responsibility of lawmakers and individuals and not of scientists, even if lawmakers and individuals should act being fully aware of the latest scientific findings and views.

7.1 Individual Privacy and Family Ties in Genetics and Biobanking

The concept of privacy has expanded as innovations in technology have made public what was previously out of the public view. Initially, it was photographs and newspapers that "invaded the sacred precincts of private and domestic life" (Warren and Brandeis 1890). In recent decades, other developments have further enriched the concept of privacy. Indeed, because of the extraordinary development of biological sciences and medicine, the right to privacy has taken the shape of right

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to self-determination in choices regarding individual life and medical treatments (such as the use of contraceptives, abortion, and end-of-life decisions). On the other hand, informational privacy has stemmed from information technologies, which have made it possible to collect, store, and access huge quantities of data (including medical and health data) on individuals. Since human genetic information is often viewed as a type of personal information that needs special protection,[1] questions on informational privacy include whether people have any right of ownership over their stored (genetic) information and whether they have a right to view, verify, and challenge that information.

In general terms, the individual's legal endowment has widened and gained new ground, as new aspects of a person's sensitivity, personality, ideas, and interests are perceived to be under threat and require legal protection.[2] A very recent EU document refers to the connected issue of personal data and states that, according to the current EU legislation, "the definition of 'personal data' aims at covering all information relating to an identified or identifiable person, either directly or indirectly".[3]

This individualistic approach has worked well in fields where the individual can be considered as an isolated entity, clearly distinct and independent from society. However, this approach leads to paradoxical consequences when mechanically applied to genetics. Assuming that biobanking is a fundamental tool in genetic research,[4] there are two main reasons that make the individualistic way of dealing with the issue unworkable: on one side, genetic data endure for the entire length of an individual's life and beyond; on the other, genetics is the domain of familiarity of heritable characteristics, and the individual is considered in all his/her biological connections with the other members of his/her family.

In this paper, after a short outline of current main features of biobanking, firstly, the disenchantment on privacy and informed consent in the field is presented and discussed as a reaction to the recognition of full (individual) rights even to each piece of biological materials and/or genetic information. Secondly, the real interests at stake (when biological materials and genetic information are involved) are clarified: is human genome really/exclusively human? What are the boundaries of human family and those of biological group? What does biological group

[1] See Study on the Economic Benefits of Privacy Enhancing Technologies (PETs). Final Report to the European Commission (2010) and also UNESCO International Bioethics Committee. DRAFT International Declaration on human genetic data, Addendum 2, 8.10. 2003: "Human genetic data have a special status. Due consideration should be given and where appropriate special protection should be afforded to human genetic data and to biological samples".

[2] Among many others, a list of definitions is available at http://www.privileged.group.shef.ac.uk/. See also Article 29 Data Protection Working Party (2009).

[3] European Commission, Brussels, 4.11.2010, com(2010) 609 final, Communication from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions, A comprehensive approach on personal data protection in the European Union.

[4] "Human biobanks and genetic research databases, which bring together and allow the sharing of human biological material and information derived from its analysis, are a key element of the scientific infrastructure underpinning such research" (OECD 2009).

encompass in scientific terms and legal terms? Under what conditions and to what extent does the individual compass interact with those of other family members and with the biological group as a whole? Finally, both the human individual and the biological group compass are conceptualised as legal artefacts, whose definitions are the responsibility of lawmakers and individuals and not of scientists, because even lawmakers and individuals must be fully aware of the latest scientific findings and views.

7.2 Current Main Features in Biobanking and Privacy

It is well known that the term biobank is relatively new, as "it appeared in PubMed for the first time in 1996 (Loft and Poulsen 1996) but was not used with any frequency until 2000. Although the term is used to describe various biological repositories, it originally referred to large population banks of human tissue and related data".[5]

Thus, it is clear that when talking of biobanks, a crucial point is that of how to define them, what items to include in their compass, and what kind of response to give to crucial issues such as confidentiality and access.

7.2.1 Definitions

A study funded by the European Union has listed about twenty-six definitions, while contributions are still open.[6] In very general terms, we can say that each definition depends on the aspect that he/she who gives the definition wants to stress. To give some examples, *human* biobanks emphasise that human materials are collected, rather than materials of vegetal or animal origin; a *gene* bank means "a database established and maintained by the chief processor consisting of tissue samples, descriptions of DNA, descriptions of state of health, genealogies, genetic data and data enabling the identification of gene donors"[7]; in the use of the word *repository* (instead of *bank*), there is a clear intention to escape the financial metaphor of bank towards a more neutral word/concept.

[5] Elger and Caplan (2006).

[6] The Project (2007–2009) was coordinated by Mark Taylor (Sheffield Institute of Biotechnological Law and Ethics, School of Law, University of Sheffield) and David Townend (Faculty of Health, Medicine and Life Sciences, Department of Health, Ethics & Society, Maastricht University) and was looking to determine the ethical and legal interests in privacy and data protection for research involving the use of genetic databases and biobanks. Please find the list at http://www.privileged.group.shef.ac.uk/. Accessed 30 October 2010.

[7] According to the Estonian Human Genes Research Act, 2000, as reported at http://www.privileged.group.shef.ac.uk/. Accessed 30 October 2010.

Currently, there is enormous variation in the definitions used in regulatory literature: "Some literature refers explicitly to biobanks, such as the Norwegian law in which the definition includes samples without explicit reference to data, i.e. a biobank is a collection of biological samples which are permanently preserved. Others include a gene bank (Estonia), a database of gene donors (Latvia) or several kinds of biobanks (diagnostic/research)".[8]

Although the word biobank frequently refers to "any collection of human biological material—organs, tissue, blood, cells and other body fluids—that contains at least traces of DNA or RNA that would allow genetic analysis",[9] it is well known that biobanks have a twofold character, as they can collect samples or data or both samples and data. However, it is becoming increasingly necessary to distinguish between *data* biobanks as opposed to *sample*/*tissue* biobanks, according to what they store (biological materials or—simply—data originating from some biological material). [10]

Of course, in this way, further material-centred kinds of *samples*/*tissue* biobanks can be listed, such as *Umbilical Cord* biobanks, *Cancer Human* biobanks,[11] *Stem Cell* biobanks, *Synthetic Biology* biobanks, and so on. A study conducted in the EU shows that, "most biobanks store DNA combined with serum, whole blood and/or different types of tissue, whereas only 12 % store DNA alone. Other tissues stored (as specified by the respondents) include, for example, stem cells and RNA, urine, dried blood and red blood cells".[12]

Further distinctions are based on the purpose of the repository: *diagnostic* biobanks, *disease-oriented* biobanks, *research* biobanks, *police* biobanks and more.

Of course, each of the above-listed definitions does not necessarily exclude the others, as, for instance, a research biobank may also be, at the same time, a sample biobank and a disease biobank and a stem cell biobank and more. Nevertheless, some distinctions have a greater importance as they are linked to socially sensitive points. A clear example is the distinction between *police* biobanks, whose materials are collected independently of the consent of involved people (being such biobanks established for criminal investigation purposes), and *research* biobanks, whose

[8] Cambon-Thomsen et al. (2007).

[9] Elger and Caplan (2006).

[10] Nationaler Ethikrat defines biobanks as collections of samples of human body substances (e.g. tissue, blood, DNA), which are electronically linked to personal data and in particular to health information on the donors (Nationaler Ethikrat 2004).

[11] "In response to a critical and growing shortage of high-quality, well-documented human biospecimens for cancer research, the National Cancer Institute is developing a national, standardized human biospecimen resource called the cancer Human Biobank (caHUB). Currently, no centralized, standardized infrastructure of this type exists in the United States. caHUB will serve as a continuous and reliable source of high-quality human biospecimens and associated data for the broader cancer community, including basic and clinical researchers and the biotechnology and pharmaceutical industries that rely on human biospecimens for cancer diagnostics and drug development". http://biospecimens.cancer.gov/cahub/default.asp. Accessed 30 October 2010.

[12] Zika et al. (2010).

materials are fundamentally collected on a confidential basis and with the consent of involved people.

7.2.2 *Interconnection of Biobanks, Confidentiality and Access*

Needless to say that confidentiality is a critical point and is likely to become even more critical if we consider the move towards interconnection between biobanks and the possibility of multiple accesses to them. A study promoted by the EU Commission exactly focuses on harmonisation and interconnection of existing biobanks: "While biobanks are increasingly recognised as a crucial infrastructure for research, at the same time the widely varied practices in biobanking regarding for example collection, storage and consent procedures may also pose a barrier to cross-border research and collaboration by limiting access to samples and data. In this context, a recent study indicates that the limited sharing and linkage of samples is a key barrier for research, such as pharmacogenetics. Wide variation is observed in the implementation of relevant existing regulation, which may add further burden to harnessing the public health benefit of these collections. Therefore, it has been suggested that there is a strong need for a harmonised approach on biobanking practices and improved networking of existing and new collections".[13]

What is worth noting is that, if the need that "research must respect the participants and be conducted in ways that uphold human dignity, fundamental freedoms and human rights" is universally shared,[14] the passage move from isolated biobanks to networked biobanks implies a scale shift of old (still unresolved) problems. For instance, even traditional distinctions (such as that between *police* and *research* biobanks) that were supposed to be strong because of the kind of stored materials and the rules of collection (voluntariness, previous information) and access, seems to become uncertain. Indeed, even bio samples and DNA profiles collected in police laboratories, repositories and databases might be an interesting source of information for scientific research, e.g. research on responsibility, behavioural genetics, psychiatry, neuroscience and more. On the other hand (and most significantly), even research biobanks can be searched by police and the more connected they are, the more appealing they might be for investigative purposes.

The problem with the interconnection between databases for criminal investigation purposes and research biobanks is the possibility of multiple accesses by the police with or without a Court order. As said above, the word biobank encompasses many different realities and entities and differs according to the kind of materials

[13] The Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre, in collaboration with the European Science and Technology Observatory (ESTO), launched the following study: Zika et al. (2010). See also Scaffardi (2008).

[14] See, e.g., *Guidelines for human biobanks, genetic research databases and associated data*, prepared by the Office of Population Health Genomics Public Health Division, Government of West Australia, February 2010.

and information they collect. With the exception of police biobanks, all others collect materials on a confidential and voluntary basis and give guarantees of respect of informed consent as to the limits of use of the material and information.

The problem is whether the police could be interested in searching other biobanks. No case of this kind is currently reported, but we cannot exclude such an interest, either theoretically or practically. Otherwise, what might be the reason why the UK research database in 2005 inserted in its rules of access the possibility of police access, even if with a court order?[15] We also have to wonder why in 2004 the *Nationaler Ethikrat* of the Federal Republic of Germany (National Ethics Council, NER) and the French *Comité consultatif national d'éthique* (CCNE), in a jointly delivered opinion, stress the following point: "biobanks not only promise benefits, but also arouse anxiety and distrust within the community. These reactions are due to concern that the data and bodily substances might be used for purposes other than those to which donors have consented. For this reason, the samples and information accruing from a medical research project should not be made available to the police, the judicial authorities, employers or insurance companies".[16]

More recently, the OECD Guidelines on Human Biobanks and Genetic Research Databases (2009) states at point 7.F that, except when required by law, the operators of HBGRD should not make accessible or disclose participants' human biological materials or data to third parties (e.g. law enforcement agencies, employers, insurance providers for non-research purposes).

The issue is not considered at all in some relevant international[17] and national[18] documents, while in other more recent guidelines, it is carefully scrutinised. The Australian Office of Population Health Genomics, Public Health Division, published in February 2010 the *Guidelines for human biobanks, genetic research databases and associated data* that shows a high level of attention on the issue: "It is clear that wide access to such data for biomedical advances must be balanced by consideration of the interests of research participants. The ability to establish biobanks and genetic research databases will depend in part on research participants' willingness to contribute. Research must respect the participants and

[15] UK Biobank (2005). The drafters take some precautions on this very crucial point and say: "It is likely that UK Biobank will take steps to resist access for police or forensic use, in particular by seeking to be represented in all court applications for access in order to defend participants' trust and public confidence in UK Biobank" (p. 5). The problem is if sample givers are informed about this possibility. In its latest version, the policy seems to be less restrictive "Access to the resource by the police or other law enforcement agencies will be acceded to only under court order, and UK Biobank will resist such access vigorously in all circumstances", UK Biobank (2007).

[16] The opinion *Biobanks for research* was published in 2004 by the German National Ethics Council (chair: Prof. Spiros Simitis), www.ethikrat.org, pp. 98–99.

[17] Such as International Declaration on Human Genetic Data (16 October 2003) and Recommendation of the Council of Europe Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin (adopted 15 March 2006).

[18] See Italian National Bioethics Committee (2006). Opinion of the NBC on a Recommendation of the Council of Europe and on a document of the National Committee for Biosecurity and Biotechnology (2006).

be conducted in ways that uphold human dignity, fundamental freedoms and human rights".[19]

At Chap. 7, the AU document is very detailed and recalls that, according to Australian legislation, law enforcement agencies may obtain access "if the Coroner reasonably believes it necessary for the investigation" and thus authorises a police officer "to enter a specific place, to inspect a specified place and anything in it, take a copy of specified documents or classes of documents and seize specified things or classes of things. It is an offence for the Department to delay, obstruct or otherwise hinder the exercise of the power to take documents with written authority". More specifically the Criminal Investigation Act 2006 (WA) states that, "if an individual dies as part of any offence under written law, then a search warrant, sought by a police officer (who is also a Coroner's investigator) or a public officer may be used to seek biological material and related information".

The Australian document has the merit of going into details of what could be considered evident in general terms, in any country. It is clear that the problem cannot be denied and any barrier erected in the name of confidentiality of the collection of samples is unfortunately extremely weak once criminal investigation needs are at stake. We have to realistically admit that, even without any specific legal provision allowing the police to have access, no judge or court would refuse to sign an order once police officers have given a reasonable demonstration of the utility of questioning a research biobank in a serious crime investigation. Also, an explicit legal prohibition of such access could probably be questioned from a constitutional point of view or in principle. Moreover, if this is true for investigation needs in serious crimes, there is no reason to exclude a similar access for severe public health reasons.

The most exhaustive discussion of the issue is presently in the Opinion on *Human Biobanks for Research* prepared by the *Deutscher Ethikrat* in 2010, pp. 33–34. They state that, "not only the research institutions which have established biobanks, but also third parties may be interested in using biobanks. This applies, for example, to insurance companies and employers, but also to state agencies, for example in connection with warding off danger and criminal prosecution and to identify victims of catastrophes or to establish identity in connection with litigation in the civil courts".[20]

The opinion surveys foreign experiences and recalls that such a use of biobanks has already occurred in Sweden, where the nationwide PKU biobank, which since 1975 has collected DNA from every newborn in order to research the metabolic disease phenylketonuria (PKU), was used in 2003 in order to convict the murderer of the Swedish foreign minister Anna Lindh, and later to identify victims of the

[19] Office of Population Health Genomics, Public Health Division, Guidelines for human biobanks, genetic research databases and associated data (February 2010), p. iii, at http://www.genomics.health.wa.gov.au/publications/docs/guidelines_for_human_biobanks.pdf.

[20] German Ethics Council (2010).

December 2004 tsunami.[21] Then they clearly recognise (showing a more realistic approach than in the previous 2004 Opinion) that, "in Germany too, it is in principle possible for the security services to access biobank samples and data. It may be assumed that the interest of private and state agencies in using systematically designed and informative biobanks will increase. Such access raises central questions as to rights of personality and data protection (p. 14)".

Dealing with biobank secrecy and the need for protection, they note that, although there are "no specific provisions for biobanks", there are "models for this in current law" that can be used, and suggest that, "there must also be provisions defining the right to refuse to give evidence for persons with a duty of professional discretion [comparable to section 53 of the *Strafprozessordnung* (Code of Criminal Procedure)] which prevents these persons from having to testify as witnesses and thus break their duty of professional discretion to a state agency" (p. 28).

The main points are as follows (pp. 28–34):

- "Donors who provide samples and data disclose extensive and sometimes sensitive information on their person and therefore deserve particular protection of their rights of personality";
- "at the same time, the constitutionally guaranteed freedom of research under Article 5(3) of the Basic Law suggests that data traffic within the domain of research should be given particular privileges and should be separated from other (non-academic) domains. [. . .] all persons who have de facto access to data keys and identifying data should be included in the group of persons with a duty of biobank secrecy";
- "biobank secrecy should include a right to refuse to give evidence and a prohibition of seizure";
- thus, "if the legislature created a right to refuse to give evidence for persons who deal with biobank materials and data, it would also be complying with its particular mandate of protection of personal data. [. . .] The right to refuse to give evidence is justified for the protection of the general right of personality and the right to informational self-determination under Article 1 in conjunction with Article 2 of the Basic Law"; and
- From a practical point of view, "at present, there is little likelihood of the sample or record of a criminal offender being stored in a biobank" (the DNA patterns stored in scientific databases are different in structure from the DNA profiles which are prepared in forensic investigations). However, it is possible that in a near future each stored sample is identified by extracting a specific DNA pattern, "in a similar way as this is done with the use of forensic DNA examinations". In such a case, it would then be possible for the same pattern to be extracted from traces at the scene of the crime and to be compared with the patterns of samples in a biobank with the help of an automatic search procedure.

[21] There are discussions at present as to whether the Swedish Biobank Act should be amended and the possibilities of access for criminal investigations by the police should be extended. Swedish Kommittédirektiv (2008).

Finally, the Opinion suggests that a legal Biobank secrecy should be introduced by a statute, in accordance with EC Data Protection Directives.

7.2.3 Privacy Without Boundaries

The above-considered documents and opinions are extremely interesting for their new and more realistic approach to the issue of access.

In general terms, the need for protection of data that are collected on a confidential basis is reaffirmed, even if it is not clear why some documents do not distinguish between public authorities and private entities and interests (such as insurance companies). I think that when interests at stake have to be balanced, we must weigh them carefully. The state should not be intrusive in private lives (unless it is strictly necessary), but the public need for criminal investigation of serious crimes has an incomparable higher value than the economic interests of a private company.

The proposal of establishing a "biobank secrecy" and the related right to refuse to give information to public and private entities is interesting. But it is surprising how the considered documents and opinions seem to follow the way of unlimited extension of the privacy pattern to each piece of information, even the smallest and the furthest.

Finally, no interest seems to be reserved to familiarity of heritable characteristics and the implications that it has on the interests and the balance between rights and interests.

Familiarity of genetic data and low stringency searches, on the one side, and the interconnection between biobanks, on the other, and envisioned further connections and searches in huge research biobanks—all those aspects, together, weaken national legal guarantees, cross-national borders and seem to make our informational privacy a dream.

7.2.4 Disenchantment on Privacy and Informed Consent

We live in an era marked by many controversial attitudes towards issues like privacy and intrusions in our lives. On the one side, the feeling that we have entered the post-privacy society, where we have lost track of how many entities are tracking us and our behaviours (behavioural tracking), seems to be a matter of common sense, "not to mention what they are doing with our personal information, how they are storing it, whom they might be selling our dossiers to and, yes, how much money they are making from them". [22] As for science and technology, the latest

[22] Singer (2010).

Eurobarometer survey on the Life Sciences and Biotechnology, based on representative samples from 32 European countries and conducted in February 2010, points to a new era in the relations between science and society.[23] The drafters of the Report stress that among European citizens "the crisis of confidence in technology and regulation that characterised the 1990s is no longer the dominant perspective. In 2010 we see a greater focus on technologies themselves: are they safe? Are they useful?"

One the other side, legal regulations draw a picture of the situation that seems to belong to a completely different world. The Council of Europe adopted on March 2006 a Recommendation "on research on biological materials of human origin" which, dealing with obtaining biological material for research, states that, "information and consent [. . .] should be as specific as possible with regard to any foreseen research uses and the choices available in that respect" (Article 10).[24] They seem to adopt a perspective that implies that each piece of biological material is recognised full (individual) rights and full control for an undetermined period of time.

In such a general scattered landscape, it is not surprising to see what is happening in the field of ethics of biobanking. In a provocative article in *Nature Reviews Genetics,* Lunshof et al. suggest abandoning the illusion of genetic privacy and adopting a more solidaristic approach. They start considering that recent advances in high-throughput genomic technologies are showing concrete results in the form of an increasing number of genome-wide association studies and in the publication of comprehensive individual genome–phenome data sets. As a consequence of this flood of information, the established concepts of research ethics are stretched to their limits, and issues of privacy, confidentiality, and consent for research are being re-examined. Thus, they try to demonstrate "the feasibility of the co-development of scientific innovation and ethics, using the open-consent framework that was implemented in the Personal Genome Project as an example".[25]

The crucial point is "the applicability of confidentiality to large-scale genomic research" as "developments in both medical informatics and bioinformatics show that the guarantee of absolute privacy and confidentiality is not a promise that medical and scientific researchers can deliver any longer". Despite the amount of

[23] Europeans and biotechnology in 2010. Winds of change? A report to the European Commission's Directorate-General for Research by Gaskell et al. (October 2010), available at http://ec.europa.eu/research/science-society/document_library/pdf_06/europeans-biotechnology-in-2010_en.pdf. Special attention is reserved to Biobanks. However, the results seem to be not so significant given that only 17 % of interviewed people had a minimum idea of what biobanks are (p. 60).

[24] Council of Europe. Committee of Ministers, Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin (Adopted by the Committee of Ministers on 15 March 2006), at https://wcd.coe.int/ViewDoc.jsp?id=977859 (last visited 22 November 2010). Recently, the Italian legislator introduced a new restrictive regulation that forbids *any* use of *any* "human material" without a previous specific authorisation (Art. 170 ter, D.Lgs. n. 131/2010, containing integrations to the Codice della Proprietà Industriale, C.P.I., Gazzetta Ufficiale n. 192, 18 August 2010).

[25] Lunshof et al. (2008).

effort made to improve data safety, some studies have shown that re-identification of individuals is possible through genotype–phenotype inference and through methods such as genealogical information, trail re-identification or so-called dictionary attacks. Thus, the idea of genetic privacy (i.e. an individual's right to protection from non-voluntary disclosure of genetic information) is an illusion.

Consent, which is a fundamental tool of genetic privacy, ends in a *cul-de-sac*, as it is clear by simply considering that even "including the option of re-contacting and obtaining re-consent", which is usually considered a high-level protection of privacy "implies, by definition, maintaining identifiability and traceability of research participants" and, thus, puts participants' privacy at risk.

The authors suggest the following realistic approach:

- The building of any comprehensive genotype–phenotype data collection requires that the individuals from whom these data are derived be fully aware that the data can be and likely will be accessed, shared and linked to other sets of information, and that the full purpose and the extent of further usage cannot be foreseen.
- Individuals should realize that they are potentially identifiable and that their privacy cannot be guaranteed.
- Open consent means that volunteers consent to the unrestricted re-disclosure of data originating from a confidential relationship, namely their health records, and to the unrestricted disclosure of information that emerges from any future research on their genotype–phenotype data set, the information content of which cannot be predicted.
- No promises of anonymity, privacy or confidentiality are made. The leading moral principle is veracity—telling the truth—which should precede autonomy.

At first sight, the approach described above brings a fresh air of realism into a debate which sometimes seemed to be more attentive to a sort of bioethical correctness on autonomy and privacy of individuals than to the understanding of what is really happening in society and how to regulate it. Having said that, I find that the approach taken by Lunshof et al. has the limitation of oscillating from individual rights to duty of solidarity, from the burden of information to researchers' veracity. In doing so, they miss the crucial question: why should any piece of biological materials and information receive the same kind of protection as an individual as a whole? In other words, they overlook legal reasoning and the related need to consider, when talking about rights, up to what extent these rights should be protected and in relation to what kind of interest. This is the point that I will discuss in next paragraphs.

7.3 The Real Interests at Stake

The real interests at stake, when biological materials and genetic information are involved, cannot be overlooked anymore and need to be carefully scrutinised. And thus, what is the real interest of individuals in their own genetic information that is

processed in a research biobank? Where does such an interest vanish? What about when information is genetic information about characteristics shared within their biological group? Should each member of the group be entitled to interfere with lives and choices of other group members? And how should the amplitude of the biological group be determined? Should it date back to some common ancestor? If not, where do we draw the boundary line and according to what criteria?

Drawing such a line is essential today if we want to avoid, on the one hand, abuse of personal information and, on the other, paralysis of scientific research because of a privacy overclaim attitude or policy.

7.3.1 *Family and Humanity: Is the Human Genome Really Human? What Family?*

"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", solemnly states the *Universal Declaration on the Human Genome and Human Rights*, endorsed by the General Assembly of the United Nations on 9 December 1998. Ten years later, the same idea was reaffirmed in the Preamble of the *Additional Protocol to the Oviedo Convention on Genetic Testing*,[26] that explicitly recalls the Universal Declaration and the idea that, "the human genome is shared by all human beings, thereby forming a mutual bond between them while slight variations contribute to the individuality of each human being" and, thus, "the particular bond that exists between members of the same family".

Such solemn statements seem to conceal a tautology: saying that *the human genome is shared by all human beings* does not increase our level of knowledge about what *human being* means and why his genome should be *human*. An example may clarify the point. Although it is well-known that human beings are mostly made of water, this does not imply that such water is *human water* and does not justify the statement *the human water is shared by all human beings*, as it is clear that the water of all (human and not-human) animals and non-animals is the same water.

In a very provocative way John Harris says, "we, humans are already *humanimals*. We know we are descended from apes, but we perhaps need to remind ourselves that this descent is seamless and means that our genetic constitution contains a mixture of the genes of all the creatures, all the other species, that are part of the origin of our transient and transitional species".[27] From a scientific point of view, it has been clarified that the main cause of phenotypic variation, on which natural selection acts, is the mutation of the developmental genes. In other words,

[26] Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. Strasbourg, 27 November 2008, at http://conventions.coe.int/Treaty/EN/Treaties/html/203.htm. Accessed 24 October 2010.

[27] Harris (2009). See also Saniotis (2007).

nearly the same 20–30,000 genes shared by all multicellular animals express themselves in a different ontological time and space to produce the wonderful animal variability we admire: it is their heterochronic and heterotopic expression that results in the construction of the different animal design and changes. In addition, other genetic forces contribute to the phenotypic variability increasing or decreasing the allelic frequency, e.g. genetic (other than developmental) mutations, genetic drift, modulation of *gene expression*, all of which could produce phenotypic variation, thus contributing to the evolution of new species.[28]

However, even if we would assume the complex issue of humanity to be resolved, another problem remains on the table: which family are we talking about?

When the Universal Declaration on the Human Genome and Human Rights uses the words "the fundamental unity of all members of the human family", it is clearly referring to *family* as a metaphor. Indeed, family does not literally denote humanity as a whole, but nowadays "a fundamental social group in society typically consisting of one or two parents and their children".[29]

The above-quoted Additional Protocol on GT (2008) uses in several parts the words "family" and "family members",[30] although it never explains what exactly family is according to their views, whether a social, biological or legal entity.

Two main attempts have to be reported in this field. A first draft of a new legal concept of family data or shared genetic data was outlined by the European Union Recommendation 1997(5), point *58* of the *Memorandum* to the Recommendation. The drafters approach the issue in the following way: "The collection and processing of genetic data involve the storage of data concerning third parties. These third parties may be constituted by members of the data subject's genetic line or collateral relatives or members of his/her social family. The drafters agreed to accord an intermediate status to members of the data subject's genetic line so as to distinguish them from third parties in the strict sense of the term and to grant them hybrid legal protection".

The statement looks quite original in legal terms. However, unfortunately the European Recommendation defines neither the concepts of *intermediate status* and of *hybrid legal protection*, nor the criteria according to which such a hybrid should be defined (and how to manage conflicts among *third parties* having an *intermediate status* is completely unclear).

A further step is taken by the EU *Working Document on Genetic Data*. With the premise that some well-known characteristics of genetic data such as the fact that genetic information is unique and distinguishes an individual from other individuals, but it may also at the same time reveal information about, and have implications for, that individual's blood relatives (*biological family*), and the fact

[28] De et al. (2009). I have the pleasure to thank Prof. Carlo Alberto Redi (University of Pavia, I) for helping me in giving an accurate description of this point.

[29] The American Heritage Dictionary of the English Language, Fourth Edition copyright 2000.

[30] In the Preamble, Articles 7, 8 and 18, and the all Chapter VI (articles 13–15) are dedicated to "Tests for the benefit of family members".

that genetic data can characterise a group of persons (e.g. *ethnic communities*), and reveal parentage and family links, and that genetic information is often unknown to the bearer and does not depend on the bearer's individual will since genetic data are non modifiable, they conclude as follows: "a new, legally relevant social group can be said to have come into existence – namely, the biological group, the group of kindred as opposed, technically speaking, to one's family. Indeed, such a group does not include family members such as one's spouse or foster children, whereas it also consists of entities outside the family circle – whether in law or factually – such as gamete donors or the woman who, at the time of childbirth, did not recognise her child and requested that her particulars should not be disclosed – this right being supported in certain legal systems".[31]

Although the situation looks clear enough from a descriptive point of view (even if the use of concepts is less clear and unambiguous[32]), again, no clear response is given to the questions of the amplitude of the biological group and how we should manage the conflicts arising within the biological group.

The precise legal consequences of this argument are not clear yet. At least two scenarios can be imagined. One is that other family members could also be considered as "data subjects" with all the rights that follow from this. Another option is that other family members would have a different kind of right of information, based on the fact that their personal interests may be directly affected.[33] We find ourselves thrown back full circle.

7.3.2 Where Should We Draw the Boundary Line? Biology

If we consider humanity as a whole, modern humans originated 100,000–200,000 years ago from pre-modern humans and represent a relatively homogenous species.[34] Two random human individuals on our planet are identical for about 99.9 % of their DNA. Each individual inherits from his or her parents a random set of 23 chromosomes (a chromosome is the single unit in which the nuclear DNA is packed and arranged within the nucleus) present in the gametes. These 23 chromosomes contain half of the genetic programme of the individual (and related genetic variation) and are formed from the complete kit of 46 chromosomes, which contain all the genetic information and are present in all other cells of the organism. Thus, we inherit from each of our parents and we transmit to our children just one of each of the two homologues and related genetic information. The number of

[31] Article 29 Data Protection Working Party (2004).

[32] Knoppers and Saginur (2005).

[33] Working Group, cit., p. 8.

[34] I am deeply in debt to Prof. Francesco Cucca (University of Sassari, I) who generously and kindly provided me accurate and precious information on the scientific grounds of the issues this paragraph deals with.

46 chromosomes typical of our species is then re-established with the formation of the zygote after the fecundation of one mature maternal gamete (or egg) by one mature paternal gamete (or spermatozoa) and the deriving fusion of the two kits of randomly assembled 23 chromosomes present in these paternal and maternal gametes. Since the two homologues derive from different individuals (the parents), their genetic content is not identical; that is, the genetic instructions contained in the two copies of the same gene are in some points different on the two chromosome homologues.

Stunningly, there are 8.4 million (2^{23}) possible theoretical combinations in the process leading to the generation of the half kit of 23 chromosomes in each parental gamete, which for this reason is always unique. Furthermore, in the randomly selected 23 chromosomes there is also some reshuffling between the chromosomes inherited from the previous parental generation by means of a process named recombination, which determines a further increase of variability and contributes to making each gamete unique. These processes explain why two individuals, even two siblings (with the special exception of monozygotic twins, who result from the fecundation of one egg by one spermatozoa) cannot be genetically identical. Furthermore, it is also evident that as a result of sexual reproduction, variation among contemporary individuals is the cumulative result of past processes before and after the appearance of our species.

It is also evident that, independently of the population of origin the DNA of related individuals is more similar than the DNA of unrelated individuals. For instance, the parents must transmit half of their entire DNA sequence to their children by force of circumstance. This means that parent and child share an extra 50 % of their DNA over and above the baseline value of 99.9 % that all individuals of our species share in any case. Also, two brothers tend to share 50 % of the variable portion of their genome. However, while the genetic relatedness of parent and child is always and exactly defined by a sharing value of 50 %, the relatedness between two brothers is 50 % on average. In fact, the stochastic nature of the chromosomal "lottery" leading to the formation of the half kit of chromosomes in the gametes makes it possible for two brothers to share more or fewer chromosomes, and thus, more or fewer genes, than the average value of 50 %. Child/grandparent pairs or child/uncle pairs tend to share 25 % of the variable portion of their genome. Likewise, first-degree cousins and child/great-grandparent pairs share 12.5 % and, going further in genetic relatedness, second-degree cousins only 3.1 % of the variable portion of their genome. Most importantly, two closely related individuals are not only genetically more similar to each other but they also have a higher probability of a concurrent appearance of genetic variants (including rare ones) than unrelated individuals.

In other words, there is a linear reduction in the co-inheritance of DNA variants with the increasing distance of relationships. Science presents life as a continuum of biological links with several nuances and distances, but no clear boundary and for all aspects.

7.3.3 Where Should We Draw the Boundary Line?

It is now worth turning to general legal regulations of family and verifying whether laws, when they use the word family, refer to the same social and/or biological entity (reserving special attention to its amplitude). Hereinafter, a short list of legal texts is presented.

- The Italian Civil Code (1942) deals with the "Limits of kinship" at Article 77 and states that, "the law does not recognize kinship beyond the *sixth* degree".
- The Italian Guidelines on Genetic Medicine (2004) considers at Article 7 the problem of relatives and information on genetic testing results and states that, "personal data should not be communicated to relatives unless the interested person has given his/her consent [. . .] the relatives to be informed are only those within the *third* degree".[35]
- The Statement on DNA Sampling: control and access (1998), HUGO Ethics Committee, states that, "special considerations should be made for access by *immediate relatives*. Where there is a high risk of having or transmitting a serious disorder and prevention or treatment is available, *immediate relatives* should have access to stored DNA".[36]
- The Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing of Health Purpose (2008), dealing with *Tests on person not able to consent* (Article 13), clarifies that, "the purpose of the test must be to enable family members, with whom the person concerned has a *biological link*, to obtain a preventive, diagnostic or therapeutic benefit that has been independently evaluated as important for their health, or to allow them to make an informed choice with respect to procreation".[37]
- The Universal Declaration on Human Genome and Human Rights, Article 1, solemnly declares that, "the human genome underlies the fundamental unity of *all members of the human family*".[38]

Although incomplete and includes texts of different legal value, this short list makes one point clear: there is no way to reach unanimity within existing legal texts about the boundary of what is called family. There is an astonishing shift from *third* degree, to *sixth* degree, to *immediate relatives*, to (any) *biological link* ending with the metaphor of *all members of the human family*. Even if we can find a reason for such a situation (each legal act and/or document reflects the idea the drafters had in mind in relation with what they aimed to regulate), the temptation to move back to the Francis Galton cosmology is strong: "Neither must we be misled by the word 'individuality', because [. . .] our personalities are not so independent as our self-consciousness leads

[35] Società Italiana di Genetica Umana (2010).

[36] http://www.hugo-international.org/img/dna_1998.pdf. Accessed 22 November 2010.

[37] http://conventions.coe.int/Treaty/EN/Reports/Html/203.htm. Accessed 22 November 2010.

[38] http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html. Accessed 22 November 2010.

us to believe. We may look upon each individual as something not wholly detached from its parent source. There is decidedly a solidarity as well as a separateness in all human, and probably in all lives whatsoever".[39]

However, as jurists, we should not be seduced by such an undetermined perspective and give up our job saying that because of the biological ties of all humans, there is no reason for distinguishing between individuals and their rights anymore.[40] In a situation where biology is unable to enlighten our path, looking for the degree of genetic distance where the individual interest at stake is still or is no longer worthy of legal protection, the legal approach should elaborate *legal* solutions, taking into account scientific evidence and technological reality (e.g. about the quantitative relevance of information at a certain distance), rather than waiting for prepackaged solutions coming from science.

7.4 Human Individual and Biological Group as Legal Artefacts

It is now worth trying to see whether a thread of legal consistency can be found within such a jumble of biology and law.

7.4.1 From Patriarchy to Bio-Archy?

The *Working Document* seems to suggest that a new general obligation is taking shape within the biological group: the specificity of genetic data makes it necessary to view some aspects of the regulations applying to them in a more than merely individualistic perspective—with particular regard to access to these data by kindred members inside the relevant biological group. Furthermore, issues related to the mechanisms for circulating genetic information within this group arise. These issues concern, in particular, a possible obligation of an individual to disclose his/her genetic data to his/her kindred where such data are relevant in safeguarding their health, and the exercise of the right not to know inside the group. In this context, questions arise as to whether or not genetic data belong exclusively to the single, specific individual from whom they are collected, and whether family members have the right to access such data even in the absence of the individual's consent. To the extent that genetic data has a family dimension, it can be argued that it is "shared" information, with family members having the right to information that may have implications to their own health and future life.[41]

[39] Galton (1869), p. 373.

[40] See Lunshof et al. (2008).

[41] Working Group, op. cit., p.8.

In short, each of us, while having a unique genetic make-up, belongs to a genetic line which is the common source of all the members of the biological group. This means that our power to exclude the other members in the name of personal ownership fails simply because we do not have any exclusive ownership on that part of inherited characteristics and data. The essential terms of the problem are as follows: if sharing data gives each "share-holder" a right of (non)disposal of data of the other "share-holders", we would no longer have any genetic privacy and the individual's sovereignty would hold out against the applications of genetics. On the other hand, we have an obligation to give a response to the share-holders who need to know more about the genetic data of other share-holders for health reasons. Hence, there is a strong need to balance opposing rights, which have to be carefully evaluated and mutually pondered.

It is important to note that the new obligation stems not from an authoritative relationship, as the relationship citizen-health institutions does. Although deeply involved, family shows in this case its facet made of blood relationship, the facet of biological group, without any (at least at first sight) hierarchical nuance. Or we can say more precisely that there is no stable hierarchy and that the scale of authority is strictly linked and varies according to the importance of the reasons the individual brings in support of his or her claim. It is clear that this hierarchy changes according to the different weights of the interests at stake.

Two different kinds of genealogical tree can be envisaged, the first one is a typical expression of *Patriarchy* (the old family trees of old noble families) and the second one is a family tree like those nowadays used in genetic clinical settings (and represents what can be called *Bio-Archy*). Although they look quite similar (in both ancestors and descendents are represented), the first hierarchy is stable, linear and vertical (from top to bottom), while in the latter the relations are horizontal and hierarchy (or, better, pre-eminence) is not established once and for all.

The above-outlined new obligation (see the passage above quoted from the *Working Document*), adds to the general obligation that everybody has towards public institutions, which are interested in taking advantage of familiarity for the public good, such as safety, crime control or public health reasons. Thus, we probably have to reshape the individual's sovereignty on himself and to imagine him as equipped with a multifaceted and ever-changing set of rights coexisting in his domain, depending on the specific interests that, case by case, he may have and on the nature (public or private) of other subjects possibly involved in the conflict.[42] This is common to all, even economic, rights. The novelty consists in having individual biological source and boundaries implied and the biological and the legal aspects strictly linked, in the sense that the individual domain is eventually enlarged or reduced and, in either case, interrelated with others in ever-changing relations and shapes.

[42] See above the conclusions of paragraph 4.6.

7.4.2 *Chickens, Lands and Genetic Distance (Talking of Rights and Interests)*

The relation between legal rights and underlying interests is a conceptual locus in legal theory and, of course, this chapter makes no claim to deal with the huge literature dedicated to the issue.[43]

Nevertheless, the regulation of property/estate rights and the extent to which owner's rights are recognised might be helpful in understanding the real question at stake. It might be likewise helpful in testing the conceptual patterns that we use when dealing with rights recognised and belonging to individuals, their detached parts or their biological materials, the related information and individual's control on information, as well as interference with other group members. Indeed, it is undeniable that the distance from the full person to partially shared information (from non-coding DNA) is very wide and the conceptual shift dramatic.

So let us consider the metaphor of land ownership and the limit to which the owner's interest is recognised by law.

According to both civil law tradition and an ancient doctrine of common law, the landowner's rights extend "from the depths to the heavens" as "to whomever the soil belongs, he owns also to the sky and the depths"[44] [*Cuius est solum, eius est usque ad caelum (ad sidera), et usque ad inferos*]. Such an unlimited claim was seriously hampered by the development of aviation, mining enterprises and other activities that modern technologies made possible in the nineteenth and twentieth centuries.

United States v. Causby is the leading case in the USA in the legal debate of whether property is taken (within the meaning of the Fifth Amendment) by frequent and regular flights of army and navy aircrafts over owner's land at low altitudes. The case was summarised by the Supreme Court as follows: "Respondents [Thomas Lee Causby et ux.] own 2.8 acres near an airport outside of Greensboro, North Carolina. It has on it a dwelling house, and also various outbuildings which were mainly used for raising chickens. The end of the airport's northwest-southeast runway is 2,220 feet from respondents' barn and 2,275 feet from their house. [...] Various aircraft of the United States use this: airport-bombers, transports and fighters. [...] Since the United States began operations in May 1942, its four-motored heavy bombers, other planes of the heavier type, and its fighter planes have frequently passed over respondents' land buildings in considerable numbers and rather close together. They come close enough at times to appear barely to miss the tops of the trees and at times so close to the tops of the trees as to blow the old leaves off. The noise is startling. And at night the glare from the planes brightly lights up the place. As a result of the noise, respondents had to give up their chicken business. As many as six to ten of their chickens were killed in one day by flying into the

[43] Macilotti (2008).

[44] Black's Law Dictionary (6th ed. 1990).

walls from fright. The total chickens lost in that manner was about 150. Production also fell off. The result was the destruction of the use of the property as a commercial chicken farm. Respondents are frequently deprived of their sleep and the family has become nervous and frightened. Although there have been no airplane accidents on respondents' property, there have been several accidents near the airport and close to respondents' place".[45]

By flying planes in this airspace, Causby argued, the government had confiscated his property without compensation, thus violating the Takings Clause of the Fifth Amendment.

The Court concluded that the ancient common law doctrine "has no place in the modern world" and Justice Douglas noted that, were the Court to accept the doctrine as valid, "every transcontinental flight would subject the operator to countless trespass suits. Common sense revolts at the idea". However, while the Court rejected the unlimited reach above and below the earth described in the common law doctrine, it also ruled that, "if the landowner is to have full enjoyment of the land, he must have exclusive control of the *immediate reaches* [italics mine] of the enveloping atmosphere". Although not defining any specific limit, the Court stated that flights over the land could be considered a violation of the Takings Clause if they led to "*a direct and immediate interference* [italics mine] with the enjoyment and use of the land". Given the damage caused by the particularly low, frequent flights over his farm, the Court determined that the government had violated Causby's rights, and he was entitled to compensation.[46]

Coming back to biobanking and genetic distance, the question is whether spatial concepts, like *immediate reaches* and *direct and immediate interference*, might work in order to establish the degree of genetic distance where the individual interest at stake is still or no longer worthy of legal protection.

A further step is made possible by the Italian legislation on land property. According to the Italian Civil Code (1942, Article 840), land property extends to the subsoil, and the landowner is permitted to excavate or build without causing damage to neighbours. The most interesting point is in the second part of the article where it is stated that, "the landowner is not entitled to oppose to third party's works extending into the deep subsoil or the space above the land, unless he has a specific interest". It is worth noting that in this legal provision, the interest seems to act as the external boundary of the right. In this light, we may say that the right encompasses normal uses of the land and not uses exceeding the interest of the landowner. Thus, landowner's interest is the limit to the right of land property so that if there is no interest there is no right.

In addition, in order to confirm the crucial importance of the interest (underlying rights) in Italian law, it might be recalled that even in Italian procedural law, whoever files a suit against another party before a judge should have an interest

[45] United States v. Causby, 328 U.S. 256 (1946).

[46] Among many, see http://www.oyez.org/cases/1940-1949/1945/1945_630.

in it, otherwise, their suit is not admissible and the court has no duty to decide the case (Article 100, Italian Civil Procedural Code).

7.4.3 Weighting Interests in Biobanking

If we move back to informed consent and genetic distance, the question is whether the shift from *persons*, whose protection is at the origin of informed consent doctrine,[47] to the smallest *piece of information,* makes any difference.

Of course, improper uses of my personal information by a third party may produce injury, but all this does not authorise us to skip questions like these: What is personal information? Does any kind of personal information have the same value? May we extend the individualistic pattern to all information related to my person, even the smallest or remote, eventually shared within a wider biological group as far as distant relatives and... the Common Ancestor of all humans?

Individual interest is not a general concept having the same extension and weight whatever the issue and context. We have to envisage a way of considering and weighing the interests at stake: individual interests, group interests, public interests, interests of scientific research, and so on.

Such a complex of interests and rights has two sides. The first one is made of full individuals with physical and psychological integrity[48]: they prevail in all cases, with the only limitation of not to harm others. The second one is public interest (assuming that there is a public interest even in scientific research) that prevails in all cases where individuals' rights are not involved. In the middle, there is a vast range of situations where interests at stake face each other in many different kinds of relations. In my opinion, there is no way to escape the duty of evaluating and weighing such interests, if not case-by-case, then at least kind of situation by kind of situation.

Situations should be categorised following clear criteria. Here are some examples:

- Definition of the interest:
  a) According to the kind of activity (research or other)
  b) According to the genetic distance
  c) According to the time that has passed from the collection of a sample and its use and to the kind of use
- Who has the burden of proving his/her interest?

[47] Nuremberg Code: "... [information on] the effects upon his health or person which may possibly come from his participation in the experiment. [...] The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury".

[48] Art. 3 Charter of Fundamental Rights of the European Union: http://www.europarl.europa.eu/charter/pdf/text_en.pdf.

- Who is entitled to oppose some kinds of use? Generally speaking, we may say that, at a certain genetic distance, the existence of a right (and its underlying interest) has to be demonstrated by whoever is claiming it.
- Public and private interests:

  a) Public interest in scientific research, and thus in biobanking as a powerful tool for genetic research (metaphor: biobanking as railways);
  b) Private interest in specific research, with potentially related economic interests (metaphor: researchers as private trains on public railways).

About the public–private divide, the metaphor of trains and railways may work. There is a clear public interest in railways, but not necessarily in train transportation. Private actors and companies can own trains and not railways.

In conclusion, we may say that rights and/or interests must be weighed taking into account the many facets of the issue and the homogeneity of the terms of comparison.

7.5 Combination of Individuals and Genetic Ties: Law and Science

We may say that our concept of the *individual* has changed in the last few decades. The individual, even if *dividual*, *divisible* or compartmentally constructed from a biological point of view and split in their psychological continuity, seems to have become the sovereign of their own self-defined biological, psychological and social boundaries.[49] Although, at first sight, all that can appear morally controversial or legally questionable, however, on a deeper level all these choices do not appear incongruous, or at least not *per se* incompatible, with the individualistic tradition of modern legal systems. All modern Bills of Rights, openly or implicitly, are based on these individualistic assumptions. Nowadays also, the Preamble of The Charter of Fundamental Rights of the European Union clearly states that the Union "places the individual at the heart of its activities, by establishing the citizenship of the Union and by creating an area of freedom, security and justice".[50] The only two main limits that the contemporary idea of individual liberty meets were clearly set by John Stuart Mill: not to harm others and not to sell oneself as a slave.

Modern genetics, and the extraordinary disrupting strength of the concept that we belong to a genetic line rather than own our genetic make-up, seem to challenge these ideas. Indeed, modern genetics disclose the 'invisible' part of heredity at the molecular level, "prior to which the information about hereditary traits was limited to what could, in principle, be known to others — such as individual and family

[49] Santosuosso et al. (2007) and Santosuosso and Bottalico (2009).

[50] See at http://www.europarl.europa.eu/charter/default_en.htm.

health history (even if certain diseases running in the family were kept as a family secret), pedigree information and obvious physical traits".[51] In addition, the biological description of our common source seems to supersede almost all traditional legal concepts and marks the triumph of Galton's prophecy on overvaluation of "individuality".

At this point, should we say that the sovereignty of the individual and Mill's dowry of liberty yield to the overwhelming power of genetic ties? In my opinion, an attitude like this would be conceptually wrong because it does not correctly discriminate between biology and law. In order to clarify this assertion, two points are crucial: Kelsen's concept of the juridical physical person as a creation of the law and Mill's idea of combination of individuals as one of the expressions of individual liberty.

According to Hans Kelsen, "to define the physical (natural) person as a human being is incorrect, because man and person are not only two different concepts but also the results of two entirely different kinds of consideration. Man is a concept of biology and physiology, in short, of the natural sciences. Person is a concept of jurisprudence, of the analysis of legal norms".[52]

The answer to the further facet of the question on what constitutes the kind of unity we call physical (natural) person is as follows: "the human being is not the physical (natural) person but, so to speak, only "the compass" of a physical (natural) person. The relation between a so-called physical (natural) person and the human being with whom the former is often erroneously identified consists in the fact that those duties and rights which are comprised in the concept of the person all refer to the behaviour of that human being".

Thus, according to Kelsen, "since the concept of the so-called physical (natural) 'person' is only a juristic construction and, as such, totally different from the concept of 'man', the so-called 'physical' (natural) person is, indeed, a 'juristic' person. If the so-called physical (natural) person is a juristic person, there can be no essential difference between the physical (natural) person and what is usually exclusively considered as a 'juristic' person".

In brief, the main points of Kelsen's concept of person can be summarised as follows: (a) the human being, as *biological entity*, is a different entity than the physical person in legal terms; (b) the human being is the basis of the physical person in legal terms as a *symbolic and linguistic unity*; (c) the *biological* human being is only the *enclosing line* (Kelsen uses the word compass, in double quotes) of a physical person in legal terms; (d) the human being exists in the law only for the limited extent to which rights and duties refer to him; and (e) the physical person in legal terms and the juristic person (i.e. corporation) are both legal creations having in common the character of artificiality.

On the other side, John Stuart Mill outlines very clearly the different aspects of individual liberty: "there is a sphere of action in which society, as distinguished

[51] Lunshof et al. (2008).

[52] Kelsen (1945), Part One, Chapter IX, A-B, pp. 93–95.

from the individual, has, if any, only an indirect interest; comprehending all that portion of a person's life and conduct which affects only himself, or, if it also affects others, only with their free, voluntary, and undeceived consent and participation. [...] This, then, is the appropriate region of human liberty. It comprises, first, the inward domain of consciousness; demanding liberty of conscience [...] Secondly, the principle requires liberty of tastes and pursuits; of framing the plan of our life to suit our own character; of doing as we like, subject to such consequences as may follow; without impediment from our fellow-creatures, so long as what we do does not harm them even though they should think our conduct foolish, perverse, or wrong. Thirdly, from this liberty of each individual, follows the liberty, within the same limits, of combination among individuals; freedom to unite, for any purpose not involving harm to others: the persons combining being supposed to be of full age, and not forced or deceived".[53]

At this point, the question is as follows: can the ideas of the physical person as a legal artefact and the combination of free individuals be of some help in one of the main critical points of biobanking, i.e. that of the extension of privacy beyond the individuals and genetic distance?

Kelsen's theory is one of the pillars of modern legal thinking and, even if not unquestioned in its general terms, is surely very productive and convincing in the issues where the law faces scientific applications. More complex is the reference to Mill's combination of individuals. Of course, when writing about such combination, Mill was thinking about everything but genetic ties and biological group. However, if we consider the new fragments of the law on shared genetic characteristics (e.g. *The Working Document*) and the prior place that autonomous individual choices still have and the importance (in case of litigation within the biological group members) of the basic rule *audiatur et altera pars* and the need to recognise the prevalence of a right or another according to the underlying interest, if we consider all these, the shape of the so-called biological group no longer looks like a *biological* entity thrown into the *legal* field and challenging its internal consistency. It rather looks like a *legal* entity (not dissimilarly than the physical person for the law), whose shape is the result of all individual choices that the members make, widening or narrowing the group compass. We may say that the biological group, if seen in its legal relevance, is a free combination of persons and, thus, an artificial legal entity.

One could object that in this field nothing is free, because of genetic ties and a strong common biological source. I do not think so. The position every member of the biological group takes may be considered as a party's will in a free contract. Of course, genetic ties exist. However, they are only the occasion for a stipulation within free individuals. In some sense, the decisions of persons (who bear a reasonable interest) "create" the genetic tie or, at least, make it relevant.[54]

[53] Mill (1859), Chapter I.

[54] Of course, this does not solve all the problems, because the condition of full age, and not forced or deceived person is not always possible and we have to decide how to deal with incompetent people. However, this is a not new problem and it is well known in all patient autonomy literature.

In more general terms, the conclusion could be that the human individual and the biological group compass are legal artefacts, whose definitions are under the responsibility of individuals and lawmakers, who should be aware of scientific findings and background.

7.6 Should Privacy Be Abolished in Genetics and Biobanking?

The answer to the main issue of this work (whether privacy should be abolished in genetics and biobanking) is twofold. The answer is yes, if privacy claims to extend biologically to any (even smaller and less significant) biological connection at any time.

The answer is no, if privacy refers to people directly involved, their free determination and, in a wider area, only to those who have, or are able to, demonstrate a concrete interest, provided that public interest to the "common genetic railway" is properly stewarded.

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Chapter 8
Biobanks and Electronic Health Records: Open Issues

Paolo Guarda

Abstract This paper provides the description of possible, desirable interactions between biobanks and the genetic data they process on the one side, and a regulatory concept that is becoming crucial in the European and Italian privacy law context, namely Electronic Health Records (EHR) on the other. The computerized processing of personal health data via digital platforms has received by the Italian Data Protection Authority a regulatory definition which appears to be quite narrowly constructed around the idea that this kind of data treatment will be authorized only if carried on for the purpose of providing a medical service for the therapeutic or diagnostic benefit of the patient.

The interactive treatment of genetic data combining health data providing a follow up of the health conditions of the original donor is crucial in the so called post-genomic era. Bioinformatics itself is characterized by a series of activities taking place at the informational level, like acquisition, storage, distribution, analysis and interpretation. Providing health services based also on individual genetic identities and on the knowledge of genomic risks of patients will enhance the efficacy of health care.

8.1 Introduction: A "Leap in the Dark"

The gradual spread of research biobanks within the health sector can lead to anticipated and favourable prospects for human health, but at the same time, can cause the emergence of new risks and, therefore, of interests that need to be protected.[1]

[1] For further information on research biobanks see: Kaye and Stranger (2009); Macilotti (2012); Id. (2009), p. 153; Id. (2008), p. 222; Barbareschi et al. (2008), p. 139; Macilotti et al. (2008), p. 86; Bregman-Eschete (2006).

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There are various types of biobanks, each of which is directed to at a specific function, whether for research, criminal investigation, therapeutic support, etc. All of these are unified by the fact that for their operation they need to process genetic data, which, as data regarding health status, are themselves a subcategory of so-called "sensitive data", but which differ, however, due to their peculiar nature[2]: they are inextricably linked to the individual from which they come, since they contain his genetic characteristics. They may, therefore, reveal present state of health, predisposition to develop a specific disease in the future, racial and ethnic origin, gender, and a range of information that could be precursors of possible discrimination in the life of each individual and social group. The research biobanks necessarily interact with genetic data, since they are at base "archives" of tissues and associated data.[3] Biological samples stored in a biobank are indeed characterised by a dual nature: the material and the purely informational, which, precisely, is represented by the genetic data contained therein and related thereto. Since the sample is to be consumed in its physical dimension, it is not inconceivable that someday biobanks will become guardians only of collected data concerning samples that have disappeared in the meantime.

The advent and widespread diffusion of computers has led to an upsurge of new problems and demand for protection. Digital technology has provided the extraordinary ability to access large amounts of aggregated data very quickly, but it has simultaneously made possible the creation of large databases to which more and more people—even if limited in number and specifically identified—may have access. This has greatly increased the risks associated with the treatment of these data, their unlawful circulation and dissemination, and the ability to affect the dignity and the fundamental freedoms and rights of the individual data subject.[4]

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[2] The European legislator—with the famous Directives 95/46/ECand 2002/58/EC—intervened, devoting to the problem of health data processing an *ad hoc* regulation, thus highlighting the specificity and the dangers that operations relating to this particular category of data may show. Regarding data protection regulation in general, see: Bygrave (2002); Guarda (2008), p. 65. At the national level, Italian legislator (at art. 4, co. 1, lett. d) of Legislative Decree 30 June 2003, n. 196 (Code for protection of personal data; hereinafter: Privacy Code) defines so-called "sensitive data" as follows: "personal data allowing the disclosure of racial or ethnic origin, religious, philosophical or other beliefs, political opinions, membership of parties, trade unions, associations or organizations of a religious, philosophical, political or trade-unionist character, as well as personal data disclosing health and sex life". In order to process this kind of information a stricter and more protective discipline has been provided, since their collection, communication and dissemination may present the data subject to which they pertain with several serious risks of discrimination. With respect to health data processing in the Italian legal system, see: Buttarelli (1997); Caggia (2007), p. 405; Finocchiaro (2008), p. 207; Palmerini (2007), p. 1303; Viciani (2007), p. 315. An old, but very interesting, essay on health data and privacy by an economic analysis perspective in Schwartz 1997, p. 1.

[3] For further information see a recent study on the relationship between genetic data and biolaw: Casonato et al. (2011).

[4] With respect to telemedicine issues, see: Izzo (2000), p. 807; Cangelosi (2007), p. 431; Sinha (2000).

The so-called "Electronic Health Record" (hereinafter, EHR) represents a pivotal moment in the digitalisation of health data processing. The definition of this new legal concept, which has encountered many difficulties, consists of two basic elements: the moment of storage, by means of the digital technologies, of all the data and information that until now had been collected and managed on paper, and the moment of sharing of data collected by all the parties involved in the system, entitled to their communication and processing.[5] Unlike the traditional electronic platforms of health data management, which privilege the role of health-service providers and give the patient a very marginal and limited role, the new approach underlying the concept of EHR is characterised by the patient becoming the crucial point of the information management system. From this point of view, any interaction between the patient and the new system involves the creation of new data. The first e-health data revolution—the introduction of information technology and EHRs—concerned the digitising and rationalisation of the flow of data. The second step is represented by the so-called Personal Health Record (PHR): patients will increasingly create health data (or links to other data) without the intermediation of any "qualified person".[6]

At the international level we found several documents pushing for the implementation of EHR. Above all, we must cite the "Working Document on the processing of personal data relating to health in electronic health records (EHR)" adopted on 15 February 2007 by the Working Group Party on the Protection of individuals with regard to the Processing of Personal Data. This document aims to provide guidance on the interpretation of the applicable legal framework of data protection for EHR systems and to establish some general principles. It also seeks to set the data protection preconditions for establishing a nationwide EHR system, as well as the applicable safeguards.[7]

In this context, the Italian *Garante per la protezione dei dati personali* (hereinafter, Privacy Authority) enacted, by a General Provision, some guidelines on the implementation of an EHR system (*Provvedimento a carattere generale del Garante per la protezione dei dati personali—Linee guida in tema di Fascicolo sanitario elettronico (Fse) e di dossier sanitario—16 luglio 2009*) (hereinafter, LG FSE).[8]

[5] See in general Guarda, *Fascicolo* (2011); Froomkin (2008a, b); Terry and Francis (2007); Hall (2009); Hoffman and Podgurski (2006); Jacobson (2002); Terry (2008). For a further analysis with respect to the incorporation of legal principles of privacy into digital architecture see: Guarda and Zannone (2009), p. 337.

[6] *See* Cushman (2008).

[7] This document proposes the following definition of this new instrument: "A comprehensive medical record or similar documentation of the past and present physical and mental state of health of an individual in electronic form, and providing ready availability of these data for medical treatment and other closely related purposes".

[8] It is also worth mentioning another General Provision that provides some guidelines on online medical reporting: Garante per la protezione dei dati personali (2009).

This paper attempts to describe a sort of "leap in the dark": the use of and simultaneous interaction between research biobanks and the EHR systems represents a near-future scenario, which only today we are able to foresee as likely to emerge soon. This allows us to "spotlight" the patient as both the person from whom tissue samples are collected and managed within the biobanks and also as a main character in the informational flow that must return to him as the result of the analysis undertaken by biobank research.[9]

8.2 Post-genomic Age and Bioinformatics: Biotechnology Back to the Clinics

The period in which we are living may be referred to as the "post-genomic age" and is characterised by the processing of huge amounts of individual genetic data.[10] There is, in some ways, the attempt to establish a close and secure relationship between so-called "genotypic" information, referring to the human genome, and so-called "phenotypic" information, which concerns the actual manifestation of that data in sensory reality.

A new branch of science stands out, called "bioinformatics", which is characterised by the use of digital technologies in the field of biomedical science in order to provide, in essence, two types of means: those designed to analyse and use genetic data to develop new therapies, medicines, and medical diagnostic methods, and those designed to provide information for analysing and using genomic data to achieve the objectives outlined above.[11]

The attention here is focused on the patient. There is an increasing trend towards personalised medicine, which takes back genetic studies and reports them directly to individuals. Diagnostics, and related therapies, are based, fundamentally, on two aspects: on the one hand, the identification of genetic identity and the knowledge of the so-called "genetic risk" (i.e. the possibility of the future occurrence of a specific disease) and, on the other, the predictive analysis derived from this information.

This new capacity provided by genetic testing allows us to trace possible interactions with the EHR. As we saw above, these systems are characterised by the processing of health data aimed at ensuring a better healing process for the patient. Italian guidelines on EHR state the following: "In order to guarantee the

[9] Digital technologies and, in particular, the so-called Web 2.0 encourage and, in some ways determine, this need-to-know that distinguishes the user of the network and, more generally, individuals of this beginning of the third millennium.

[10] See the interesting document of Comitato Nazionale per la biosicurezza e le biotecnologie 2005, see also Rodotà (2005), p. 571.

[11] See Monti (2006), p. 511; Den Besten (2003).

person concerned, the intended purposes must only be referred to the prevention, diagnosis, care and rehabilitation of that person".[12]

However, other possible ways of using data through an EHR system for research purposes are, however, not explicitly excluded by the Privacy Authority. The LG FSE on this point states: "Possible future, even if partial, use of the HER or of the dossier for further purposes of scientific research, epidemiology or statistics are not per se precluded, but they can only be done in compliance with sector regulations and be subject to prior and specific attention, even in cases where - as in the case for certain EHR examined projects - the keeping of the list of health events on a particular person involved is delegated to regional infrastructure".[13]

This step permits other reflections on the relationship between EHRs and research biobanks.

EHR systems guarantee the possible availability of the clinical history of a particular person; this significantly strengthens the prognostic ability of the healthcare professional committed to determining the proper healing process for patients who have submitted to his care. However, there is more: the ability to analyse the detailed, aggregated, clinical picture of a patient, updated and supplemented by information deriving from the analysis carried out on his genetic tissue samples, would result in an exponential growth of predictive ability with respect to his medical course.[14] Thus, the healthcare worker could put in place very effective diagnostic protocols and develop innovative predictive tests. This feature will have a positive effect on two main recipients of these revolutionary diagnostic techniques: in particular, individual patients who will benefit from adequate health care to their actual, present and future, clinical picture, and, more generally, the National Health Service (NHS), which will prepare medium- and long-term strategies that will be profiled on the needs of society in the near future (imagine the impact that this kind of scenario could have on investment plans at a national and local level with reference to one of the largest spending areas in the budgets of state agencies).

[12] LG FSE, p. 2.9.

[13] LG FSE, p. 2.11. On the use of information from EHR systems for purposes of medical research see Willison (2009).

[14] Roden et al. (2008), p. 362, with specific reference to the relationship between biobanks and Electronic Medical Records (EMR): "Coupling these biobanks to electronic medical record (EMR) systems has the potential to enable investigators in the field of genomics to search, record and analyze phenotypic information pertaining to large numbers of patients in a "real word" context". On the desirable return to the donor of the results of research conducted in biobank research see Skene (2009).

8.3 Keeping It Private

The framework we have outlined, however, has not only positive aspects. In the Anglo-Saxon context, the expression "keeping it private" is often used with reference to the management of genetic data established by research biobanks[15]: it once again underlines the fact that the privacy of individuals who undergo genetic testing must be protected in the most robust and efficient way, given the sensitivity of the results that these tests are capable of producing.[16]

There are several crucial results on which to focus.[17] Foremost, the aspect of the data subject's consciousness is pivotal: the patient must be adequately informed of the objectives related to undergone research, of the different ways which will characterise the treatment of data related to him and, where possible, of the probable future analysis that might concern them. Then, it the issue of *consent* is fundamental when we analyse the borders of an individual's privacy. This is not the time or place to examine a topic that has engaged commentators dealing with this matter for years.[18] However, it is important to remember and highlight the particular aspect of the possibility of withdrawing consent, if provided: in this case, the tissue samples that contain genetic data should be identified and destroyed.[19] Finally, to give rise to the proper level of confidence on these research institutions, it is necessary to ensure that the access management of information systems, and in particular to the data they process, is strictly regulated and possibly restricted to only the persons who come into contact with donors at the time of sample

[15] The expression is taken, with special reference to the techniques of de-identification, by Maliapen (2009), p. 3.

[16] Townend et al. (2009), p. 137: "the new genetic data processing possibilities are in potential conflict with these fundamental rights, because the real value of research and biobanking research using genetic data will be in the ITS relation to the medical and environmental life-story of the data subject".

[17] Zarabzadeh et al. (2009), p. 177, the aspects that should be taken to protect the confidentiality of those who undergo the genetic testing are investigated, spec. p. 179: "ensuring the confidentiality of participant data at all times is an essential aspect of biobank operation".

[18] Rivers of ink have been spilled on this issue, in which the doctrine has never stopped being interested: see, among many, Macilotti (2009); Juso (2004), p. 6; Casini and Sartea (2009), p. 1121; Casonato (2009), p. 1052; Brownsword (2009), p. 83; Viciani (2007), p. 315; Godard et al. (2003), p. S88; Viciani (1996), p. 272.

[19] The effect of withdrawal of consent is the immediate destruction of the sample and the data associated with it or its complete anonymisation, preventing their traceability to the donor, with all the concerns already expressed above. This is also appointed by the Authorisation of the processing of genetic data by the Italian Privacy Authority, February 22, 2007, which, in paragraph 6, states that: "[. . .] In accordance with art. 23 of the Code, the consent shall be valid only if the person is free from any conditioning or coercion and is freely revocable at any time. In the case where a person withdraws consent to the processing of data for research purposes, the biological sample is also destroyed if it has been taken for such purposes, except that, by the beginning or following treatment, the sample can no longer be referred to an identified or identifiable person" (this authorisation has been recently re-extended until 30 June 2011 by the deliberation of Privacy Authority of 23 December 2010). See in general Helgesson and Johnsson (2005), p. 315.

collection. The next step should be so-called "anonymity", crucial to protecting the privacy of the individual who deserves further investigation.[20]

8.4 De-identification and Re-identification

The process of anonymisation consists in the dissociation—in the "scrubbing"—of certain identifying information from the sample tissue in order to ensure its non-identifiability. It shall be implemented by the same research biobanks or by a trusted third party in accordance with governance policies that must be properly addressed and analysed.[21]

We can identify four approaches to the management of the confidentiality of the transferred tissue samples to biobanks[22]:

- *Unidentified or anonymous samples*: the personal information that could determine the identifiability of the subject has not been asked at the time of collection of tissue samples or, where this first happened, they were immediately deleted, and in such cases there is no possibility to disclose confidential information.
- *Unlinked or anonymised samples*: tissue samples have been stored without personal identifiers or individual codes and are presented to researchers completely devoid of facts that could point to the identity of the persons who performed the withdrawal of the sample itself. The biobank or a disinterested third party maintains a database with the information needed to identify the samples.
- *Coded or linked or identifiable or de-identified samples*: this type of sample is unable to disclose any kind of information which can identify individual donors; they are, however, accompanied by a code indicated beforehand by the biobank or by its representative to be made available to outside researchers. The re-combination between the anonymous tissue sample and identification data is therefore possible.
- *Identified samples*: tissue samples that are provided to researchers with the identifying information of donors.

The process of de-identification is certainly the most appropriate measure to ensure the privacy of individuals who participate in research. These procedures, when predisposed at the beginning, allow the remapping of the anonymised data to the identifying information.[23] This point is crucial in this analysis aimed

[20] See Caplan (2006), p. 661.

[21] With regard to the governance of research biobanks, see Häyry et al. (2007) and Kaye and Stranger (2009).

[22] See Zarabzadeh et al. (2009), p. 180. See also Maliapen (2009), p. 3.

[23] Maliapen (2009), p. 2, which splits in two the de-identification techniques: those that allow the re-identification (Patient De-identification System), and those that prevent it a priori (Toolkit based Encryption System).

at devising a possible relationship between biobanks and the EHRs. The so-called "re-identification" can actually re-join the pathology of the individual to his genetic background, thereby allowing that the informational flow coming from the patient returns to him through the medium of his EHR.[24]

The risks of improper management of this process are more than obvious; the benefits, however, are equally evident, and enhance and affirm what we are asserting here.[25]

8.5 Final Remarks: The Mirror of Galadriel

The relationship between EHR and research biobanks is still to be explored and constructed. It may be expected that it will soon become central in biomedical research, since, as repeatedly pointed out, it allows the aggregation of valuable information for the patient, including genetic research carried out on his samples and the diseases that afflict him.

The patient is increasingly the focus of the health system. This can be easily demonstrated analysing the digital platforms designed to manage health information, and can be intuited from the scenarios that have been briefly outlined above. The centrality of the patient's role is not only due to ethical or legal reasons; it must be considered that he actually represents the very source of information and, therefore, he first needs to acquire knowledge of his medical conditions in order to better interact with the services the NHS provides. From this point of view, once again the EHR is the means by which information regarding the patient is brought back under his direct control, thus ensuring the concrete realization of the principle of self-determination.

Another interesting profile is described by the so-called "chains of trust and duty". The EHR systems have the possible risk of so-called de-humanisation of doctor-patient relationship: the digital environment would remove the relationship between these two subjects, feature that has set it apart since the dawn of medical science. Even while committed to the current issue, we need to keep this in mind. The patient comes into contact with a particular professional, perhaps through an EHR system, which is placed behind a number of other stakeholders (e.g. laboratories, clinics, research centres and biobanks) which conduct research on data concerning him. The results are returned to the patient through a chain of parties that he basically does not know, but he trusts them as holding a certain status within this chain.[26]

[24] A further study on the general theme of the re-identification of anonymised data can be read in Cunha de Azevedo et al. (2011), p. 641.

[25] Maliapen (2009), pp. 4–5; Townend et al. (2009), p. 137.

[26] For further information see Green (2009), part 8.

The more meaningful aspect of the relationship between EHRs and biobanks is linked to the ability to predict what the interaction between these two new tools could provide. As never before, this combination of a specific disease and the genetic makeup of the patient allow us to put in place protocols and innovative diagnostic tests. We are often, and rightly, debating the ethical and moral principles that must inform the collection of human tissues, and on the legal regimes that must govern it. There is not enough attention placed on the impact of the possibility of predicting the future in more objective terms, even if only with respect to our health, and how this will affect the individual, and more generally society itself.

The ancients, in reference to the ability to predict the future, spoke of "divination". With any ritual or technique where this was carried out, the answer obtained was never directly or easily intelligible, and it often hid less desired scenarios. In J.R.R. Tolkien's masterpiece, *The Lord of the Rings*, there is a very evocative literary image: Galadriel, Lady of Lórien, meets the hobbit Frodo, the ring bearer, in a stage in the journey of the "Fellowship of the Ring". The elf calls him to look inside the "Mirror of Galadriel", a magic mirror that lets one see into the future. However, before granting such a possibility, she warns the hobbit with the following cryptic words: "Many things I can command the Mirror to reveal, [. . .] and to some I can show what they desire to see. But the Mirror will also show things unbidden, and those are often stranger and more profitable than things which we wish to behold. What you will see, if you leave the Mirror free to work, I cannot tell. For it shows things that were, and things that are, things that yet may be. But which it is that he sees, even the wisest cannot always tell. Do you wish to look?" Do we really wish to look inside the Mirror of Galadriel?

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Chapter 9
Informed Consent and Research Biobanks: A Challenge in Three Dimensions

Matteo Macilotti

Abstract The debate about the requirements of informed consent in research biobanks has been heated in the last few years. This debate originates from the peculiarity that characterises the condition of tissue stored in a biobank. Unlike in the traditional research setting, tissue stored in a biobank is not only collected for a specific research project but for an undetermined future research projects as well. Therefore, it appears difficult to inform the person (from whom tissue is obtained) about all possible research projects in which tissue could be used. Against this backdrop, the ethical and legal scholarship has started to explore if "less informed" consent models could be considered legally and ethically acceptable in the research biobank context. Many models have been proposed. The range varies from fully informed consent to blanket-consent models, passing through partially restricted consent, and the so-called broad-consent models. In these models, it is not only the "level" of information that changes, but also the aims of the informational process. In the model of "fully informed consent", the core of the informational process is represented by the specific research project, while in the "broad-consent model", the information provided aims to illustrate the features of the "governance" of the biobank where tissue is stored. Therefore, from consent on the specific research project, we are moving towards consent on a model of governance.

To determine whether this switch can be legally acceptable, it is crucial to analyse the peculiar interests (legally recognised) at stake, in order to identify if a "broader" consent is also adequate to protect the rights of the person involved. In this contribution, I argue that tissue can be viewed via three different dimensions. Firstly, tissue represents a material *res* that "occupies a space" and has its own consistency. From this point of view, the main issue is to determine if this *res* can be owned, who assumes its ownership, and more broadly who maintains its control. Second, human tissue can be seen as a source of data, and in particular of genetic data. In this case, the crucial issue is to establish the rights of a person on the data

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obtained from tissue. It is likewise necessary to establish if the person has the right to consent for the use of these data in biobanking, if they can limit the access to these data, and if they can withdraw their consent. Eventually, it is also necessary to establish the effects of the withdrawal of such consent on the data and tissue. Third, human tissue derives from the human body. The distinction between these three dimensions (that we will call "material", "informational" and "relational") is only theoretical, given that in nature these three dimensions of human tissue are inextricably linked to one another and the bundles of rights originated from them overlap. Therefore, to understand the rights of the human subjects, it is not sufficient to study the characteristics of these three dimensions but it is also necessary to analyse how these dimensions are related to each other.

9.1 Introduction

The debate about the requirements of informed consent in research biobanks has been heated in the last few years. This debate originates from the peculiarity that characterises the condition of tissue stored in a biobank. Unlike in the traditional research setting, tissue stored in a biobank is not only collected for a specific research project but for an undetermined future research projects as well.[1] Therefore, it appears difficult to inform the person (from whom tissue is obtained) about all possible research projects in which tissue could be used.

Against this backdrop, the ethical and legal scholarship has started to explore if "less informed" consent models could be considered legally and ethically acceptable in the research biobank context. Many models have been proposed. The range varies from fully informed consent to blanket-consent models, passing through partially restricted consent, and the so-called broad-consent models.[2]

In these models, it is not only the "level" of information that changes but also the aims of the informational process. In the model of "fully informed consent", the core of the informational process is represented by the specific research project, while in the "broad-consent model", the information provided aims to illustrate the features of the "governance" of the biobank where tissue is stored. Therefore, from consent on the specific research project, we are moving towards consent on a model of governance.

To determine whether this switch can be legally acceptable, it is crucial to analyse the peculiar interests (legally recognised) at stake, in order to identify if a "broader" consent is also adequate to protect the rights of the person involved.

To understand the interests (and the rights) of the human subject involved, the unavoidable starting point is the study of the relevant characteristics of human tissue detached from the body and the relationship between tissue and person. As we will

[1] See, Caulfield et al. (2003), p. 2; Cambon-Thomsen (2004); Kegley (2004); Elger and Caplan (2006).

[2] The list is not exhaustive, and in some cases, the same model is differently named.

appreciate in the following pages, tissue can be viewed via three different dimensions. Firstly, tissue represents a material *res* that "occupies a space" and has its own consistency. From this point of view, the main issue is to determine if this *res* can be owned, who assumes its ownership, and more broadly, who maintains its control.

Secondly, human tissue can be seen as a source of data, and in particular, of genetic data. In this case, the crucial issue is to establish the rights of a person on the data obtained from tissue. It is likewise necessary to establish if the person has the right to consent for the use of these data in biobanking, if they can limit the access to these data, and if they can withdraw their consent. Eventually, it is also necessary to establish the effects of the withdrawal of such consent on the data and tissue. Thirdly, human tissue derives from the human body. This fact is not neutral and it confers to the tissue a particular value. This value is not easy to define because, as we will appreciate, it depends, in great measure, on cultural beliefs.

The distinction between these three dimensions (that we will call "material", "informational" and "relational") is only theoretical, given that in nature, these three dimensions of human tissue are inextricably linked to one another and the bundles of rights originated from them overlap. Therefore, to understand the rights of the human subjects, it is not sufficient to study the characteristics of these three dimensions, but it is also necessary to analyse how these dimensions are related to each other.

Against this backdrop, this contribution will be devoted to the analysis of these three different dimensions of human tissue in order to understand the rights of the research participants in relation to each of these dimensions. In the first part, we will analyse the effect of consent on the material dimension, in the second part, the effect of informed consent on the informational dimension, while in the last part, we will deal with the issue of the relational dimension.

9.2 The "Material" Dimension

From the material point of view, human tissue detached from the body could be seen as *res*, an aggregate of molecules, which upon detachment from the human body becomes an autonomous "material entity".

Therefore, the first issue is to determine, from a legal point of view, what happens to this "res" at the moment of detachment from the body. In particular, it is necessary to verify (a) if samples could represent an object capable of being owned, (b) who can assume ownership of these samples, (c) if the individual from whom the material is taken is a recognised owner, and (d) what is the legal effect of consent.

The possible answers to these questions are complex. Firstly, because different legal systems offer different responses; secondly, because the legal concept of

"property" is more ambiguous than it seems[3]; and thirdly, because the allocation of property rights represents a policy choice.

The difficulty to give even a general answer to these questions is unavoidable even if we try to understand the role of informed consent. In fact, if tissue can be considered as an "object" capable of being owned, then informed consent could be seen as an instrument for the disposal of these property interests (provided that the person is recognised as the owner of the tissue after its detachment).

A logical starting point is to establish first if, after detachment, human tissue can be considered as an object capable of being owned. While an in-depth discussion of the concept of property is beyond the scope of this contribution, it is nonetheless important to define, very briefly, the concept of "property" to answer this question. As already pointed out, the concept of property is highly controversial and it would be impossible to provide a definition that holds true in all legal systems. Taking into account these limits, and seeking to establish a broad overview, we can focus our attention to two different classical reconstructions of the concept of "property". The first one, popular in the common law system, considers "property" as a "bundle of rights"[4] in which there are varying rights and responsibilities depending on the type of property (in the sense of object of property) in question. In other words, property consists of a package of legally recognised rights held by one person in relationship to others with respect to some things.[5] Distinct from the concept of property is the

[3] See, Cribbet (1986). Cribbet contends that the question "What is property?" is unanswerable. The problem arises because the legal meaning of "property" is quite different from the common meaning of the term. The ordinary person defines property as *things*, while the attorney views property as *rights*.

[4] The first proposal was put forward by Sidgwick (1891), p. 70. For the Author, the three components of ownership were, the right of exclusive use, the right to destroy, and the right to alienate. Today, Sidgwick's analysis is rarely referred to. The most influential analysis is instead Tony Honore's list of eleven types of legal relations that he considers to be the major components of full liberal types of ownership (Honoré 1961): (a) the right to possess; (b) the right to use; (c) the right to manage; (d) the right to income; (e) the right to capital; (f) the right to security; (g) the incident of transmissibility; (h) the incident of absence of term; (i) the duty to prevent harm; (j) liability to execution; and (k) residuary character. Several scholars have proposed modifications of Honore's analysis. Lawrence Becker extended the Honoré list with thirteen, instead of 11, components (Becker 1980, p. 187). In particular, he added the right to consume or destroy the object in question, the right to modify it, the right (power) to alienate it through donation, exchange or abandonment. One problem with this approach is that it may pose difficulties in determining which bundles constitute ownership. Most cases of property rights in modern society do not include all types of relations. Honoré's approach to this problem was to apply Wittgenstein's notion of "family likeness". Honoré affirms that "The listed incidents (the 11 components), though they may be together sufficient, are not individually a necessary condition for the person of inherence to be designated the owner of a particular thing". For an evaluation of the consequence of these theories on property over human tissue, see Bjorkman and Hansson (2006), p. 209.

[5] In this theory, there is the replacement of the concept of the "subjective right" with the concept of "juridical relationship". See Waldron (1985), p. 314. The author provides this easy example to explain this concept "Why has private property been thought indefinable? Consider the relation between a person (call her Susan) and an object—say, a motor car—generally taken to be her private property. The layman thinks of this as a two-place relation of ownership between a person

term "ownership".[6] Although "property" and "ownership" are often used interchangeably, the latter is commonly defined as the right to full enjoyment of something to the possible exclusion of all. However, in a real sense, such "full enjoyment" is impossible to reach because it is likely to be restricted by all sorts of rules. Therefore, we can define the concept of ownership as "the 'best' possible entitlement (bundle of rights) under the circumstances, relative to the nature of the something in question and the entitlements of other".[7] Accordingly, a relationship can be considered as "ownership" not only with the presence of the "full bundle of rights" but even when this bundle is limited; it depends on the *res* and the circumstances that we are taking into account.

This concept is clearly explained by Honoré in his classic essay on "Ownership",[8] in which he identified eleven standard incidents of ownership, but he stressed that not all of them had to be present in ownership since their presence depends on the nature of the thing and the context. If this is true, as remarked by the Court of Appeals in the important case of *Yearworth,*[9] "a decision whether something is capable of being owned cannot be reached in a vacuum, it must be reached in context", i.e. by taking into consideration the specific nature of the thing. Therefore, the issue at stake is to understand the nature of human tissue detached from the body.

There has been a distinct reluctance on the part of the "common law" courts to address the issue of tissue's susceptibility to ownership, and we have few cases that can help us. One of the first cases is the judgement of the Australian High Court in *Doodeward v. Spence,*[10] in which the body of a stillborn two-headed baby was preserved in spirit by the doctor who attended its mother. Upon the doctor's death, it was sold and later came into the possession of another person (C), who exhibited it for profit to the curios. A police officer then seized the body so it can be buried. C's action for detinue succeeded. Chief Judge Griffith said: "[W]hen a person has by the lawful exercise of work or skill so dealt with a human body or part of a human body in his lawful possession that it has acquired some attributes differentiating it from a mere corpse awaiting burial, he acquires a right to retain possession of it …". According to the Australian court, body parts per se are not capable of being owned unless there has been some activity that differentiates them from a mere corpse.

Following the *discrimen* drawn in *Doodeward*, the English courts have established the principle that there can be no ownership of a human corpse. In the

and a thing: Susan owns that Porsche. However, the lawyer tells us that legal relations cannot exist between people and Porsches, because Porsches cannot have rights or duties or be bound by or recognise rules. The legal relation involved must be a relation between persons—between Susan and her neighbours, say, or Susan and the police, or Susan and everyone else".

[6] For the historical reconstruction of the term "ownership", see Smith (1976), p. 214.

[7] See Hoppe (2009), p. 48.

[8] See above n. 9.

[9] *Jonathan Yearworth and others v. North Bristol NHS Trust* [2009] EWCA Civ 37. See Quigley (2009).

[10] *Doodeward v. Spence,* High Court of Australia, (1908) 6 CLR 406.

case of *Dobson v. North Tyneside Health Authority,*[11] the Court of Appeals held that the fixing of tissue (in this case, the brain) in paraffin had not been on a par with preserving it for future use as a commercial exhibit (like in *Doodeward*); and as a consequence it could not be considered as an object of "property".

The same principle was confirmed in *R. v. Kelly.*[12] Nevertheless, relevant to our issue, it should be noted that the court speculated in this case that—despite 150 years of common law confirming that neither a corpse, nor parts of a corpse, can, in themselves, be capable of being property—things may eventually change. Lord Justice Rose remarked that, "[T]he common law does not stand still. It may be that if, on some future occasion, the question arises, the courts will hold that human body parts are capable of being property (for the purposes of section 4), even without the acquisition of different attributes, if they have a use or significance beyond their mere existence. This may be so if, for example, they are intended for use in an organ transplant operation, for the extraction of DNA or, for that matter, as an exhibit in a trial. It is to be noted that in Dobson's case, there was no legal or other requirement for the brain, which was then the subject of litigation, to be preserved."

As already stressed, the development of technology has conferred upon tissue a value that cannot be underestimated. If in the past mere body parts could not acquire some value without the acquisition of different attributes, today, in the biotechnology era, tissue has value *per se*, and "use or significance beyond [its] mere existence". This aspect can change, quite fundamentally, the nature of tissue. Property interests related to tissue can therefore be considered as a basis for a "revirement".[13]

A first shift in the traditional non-property rule towards a possible *revirement* is forwarded in the *Yearworth* case, although it would be incorrect to derive from this case a general rule declaring that tissue is now became capable of being owned. The case concerned Mr. Yearworth and five other claimants, all of whom had been diagnosed with cancer and had undergone chemotherapy treatment at Bristol

[11] *Dobson v. North Tyneside Health Authority and Another,* [1997] 1 WLR 596. In carrying out a post mortem examination on a woman who had died of a brain tumour, a pathologist removed her brain and fixed it in paraffin pending possible further examination, which in fact was never conducted. The brain was delivered to D2's hospital for storage. The rest of the woman's body was buried. Two years later, the next of kin sought to examine the brain to secure evidence in support of their action in negligence case against D1. The brain could not be found so they sued D2 for having destroyed or mislaid it. Their appeal against the dismissal of their action against D2 was likewise dismissed.

[12] *R. v. Kelly and Lindsay* [1999] Q.B. 621.

[13] See, Goold (2005), p. 3. The Author has conducted a detailed analysis about the possibility of applying the category of "property rights" to human tissue. The Author concludes that, "there are rather fewer practical legal problems with using property law to regulate human tissue than has perhaps been generally considered. The analysis of the concept of property has demonstrated that human tissue is aptly suited to having property status, and that the various property rights, such as rights to use, to possess, to manage and to the income can almost all be applied to tissue without legal absurdity".

Southmead Hospital. Since the hospital had a fertility unit licensed under the Human Fertilisation and Embryology Act of 1990, the men were offered an option to have samples of their semen frozen and stored for use at a later date due to the potential damaging effect of the chemotherapy on their fertility. Acting on the advice received, the six men produced samples for storage. Each of the claimants consented to the storage of their semen for ten years, the maximum allowable time under the 1990 Act. The storage system at the hospital failed, and as a result, the men's semen thawed and the sperm contained therein was irreversibly damaged. In the judgment of the English Court of Appeals, Lord Judge affirmed that, "the sperm was the property of the men for the purposes of their claims in tort and, as amended, in bailment and that they are in law capable of recovering damages for psychiatric injury and/or mental distress in bailment".

Unlike the English courts, the American courts have not rejected the idea that tissue is a *res* capable of being owned. In the famous case of *Moore,*[14] for instance, the California Supreme Court rejected the claimant's allegation that, according to common law, he remained the owner of his body parts following removal and contended that the statute had so eroded a person's right to resist disposal of excised body parts and other material if he did not remain their owner. Therefore, the court did not exclude that human tissue could be capable of being owned, but it contended that the "bundle of rights" retained by a person after detachment had eroded, such that a person cannot be considered to be the owner.

More recently, in the *Catalona* case,[15] the United States Court of Appeals for the Eighth Circuit was called to decide upon whether research institutions, in receipt of human biological materials donated voluntarily for research, have an ownership interest or if the donors themselves could direct or authorise the transfer of such materials to a third party. The Court agreed with the lower Trial Court,[16] and endorsed the assertion that the patients "donated their biological materials to Washington University (the research institution) as inter vivos gifts" and that "Washington University owns the biological samples", and after the contribution, the patients did not establish an ownership interest. However, the logical premise (not clearly expressed by the Appeals Court) is that the patients *were* the owners of the tissue and tissue can be owned.[17]

The second reconstruction of the concept of property, more common in the civil law tradition, does not consider property as a "bundle of different rights", but a single right that can assume different intensity depending on the context in which it is applied. In this definition, the "bundle of uses" is not specified, nor did it describe what constitutes the "right of property", which remains undefined. Traditionally,

[14] *Moore v. Regents of the University of California,* 793 P.2d 479 (Cal. 1990).

[15] *Washington University v. William J. Catalona*, U.S. Court of Appeals, 8th Circuit: 490 F 3d 667.

[16] *Washington University v. William J. Catalona*, M.D., United States District Court Eastern District of Missouri Eastern Division, No. 4:03CV1065, E. Dist. Mo. 14 April 2006.

[17] For an analysis of the meaning of the "genetic gift" and the possible inconsistencies between this concept and current regulatory views on property in the UK see, Kanellopoulou (2009), p. 36.

the three fundamental characteristics of property are, "fullness", autonomy and exclusivity. The reference to "autonomy" indicates that property, unlike the *jus in re aliena*, does not depend on others' rights that have a bigger extent, while the term "fullness" implies that property is the widest right on a *res* that one legal order can recognise. It does not mean that these rights have no limits, but within the limits imposed by the legal order, the owner is free to exercise his power. It is worth noting that, to preserve "autonomy", it is important that the owner knows *ex ante* what he can or cannot do with the object of property. As we will appreciate in the following pages, this point represents one of the main problems in applying the concept of property on the protection of human tissue because in some circumstances, the owner's advance knowledge of these limits cannot be assured. The third characteristic is the "exclusivity" that represents the power of the owner to exclude others (*jus excludendi alios*) without the need to justify his actions. It is clear that this characteristic must be read in connection with "autonomy".

Historically, the vast majority of legal scholars in Italy have never seriously questioned whether tissue could be seen as a *res*, and therefore potentially subject to property. The main questions in Italy concern the means of acquiring property rights over samples and who can be considered the owner of tissue upon detachment from the body. These questions are crucial in understanding the meaning of informed consent because only when a patient is the owner he could consent and cause the transfer of the ownership of tissue. If this were not the case, consent would not have any effect on any property allocation.

These issues are particularly complex and, given the lack of normative parameters that can provide an express answer, we must base our analysis on general theories of acquisition of property rights. Even with these in mind, it is not possible to give an unequivocal answer, considering the differences that exist between legal systems and their approach to the acquisition of property. Nevertheless, it seems worthwhile to refer, briefly, to theories elaborated in the Italian doctrine about property and human tissue, in search of a possible legal basis for ownership.

In the Italian context, we can identify four main theories. Firstly, the so-called "separation" theory.[18] According to this theory, detachment transforms biological material into a thing potentially subject to property rights, and, secondly, detachment creates property rights in the separated biological material.[19] According to this interpretation, at the moment when tissue is removed from the donor, the individual from whom the material is taken is still considered to be the immediate owner. If we support this theory, the informed consent of the individual could

[18] This theory is widespread not only in the Italian legal system but also in other systems, both in common law and civil law traditions. See, Whitty (2005), p. 199. The author suggests that the detachment of biological materials is a sufficient act to create property rights.

In the common law context see also: Hammond (2002), p. 113; Dworkin and Kennedy (1993), p. 311; Dickens (1977), p. 183.

[19] See, Hardcastle (2007), p. 146.

produce some effects on the allocation of property rights over tissue, which then raises the issue of determining the nature of these effects.

Another recurrent doctrine is the hypothesis of "occupation", according to which tissue removed from the human body would, once separated, be comparable to the legal concept of *res nullius*, or goods that are the property of no one. According to this theory, it is presumed that tissue is abandoned at the time of its removal with the consequence that whoever possesses it becomes their owner. In this case, unlike the "separation" theory, other subjects (e.g. the surgeon, the hospital, the biobank, etc.) could be considered the owner, and, as a consequence, the individual is not able to transfer property rights over tissue through the expression of their informed consent.

A third, less significant, hypothesis identifies a parallel between the rights associated with removed tissue, and rights pertaining to ideas. According to one legislative interpretation, in the same way that an individual is the owner of their own ideas, they would also be considered the owner of their own biological tissues (Article 2576 Italian civil code). Even if this thesis presents some problems of coherence—comparing tissue (tangible things) with ideas (intangible concepts)—individuals could, after detachment, become owners of tissue, and consent could be an eligible instrument to the transfer of property.

There are also those who consider removed tissue as "natural fruits" or "fruits" that are produced directly from the owner's body, albeit with the help of someone else, e.g. a surgeon.[20] According to this legal position, excised tissue is still the property of the patient, even if removed by a surgeon. In this case, as well as in the "ideas" and "separation" theories, consent can be considered as an instrument to manage property rights.

If we support the idea that upon detachment tissue becomes "res nullius", then informed consent has no effect over the allocation of property rights. If, however, we accept the theories that consider individuals as owners of their tissue after its detachment, the remaining logical step is to analyse the possible effects of informed consent on proprietary rights in tissue. In particular, it is necessary to establish if, through the consent-giving process, the patient transfers to a third entity (i.e. biobank, hospital, and research institute) the ownership of human tissue or only a "limited" bundle of rights (for example, if the third entity becomes merely a "custodian" of the tissue).

For the aims of this contribution, it is worth noting that, as regards the material dimension, it is not crucial for the person to know all the specific research projects where tissue will be used, but the specific effects that derive from their consent. In particular, for them, it is important to know whether the biobank becomes the owner of tissue (in the case in which we support the idea that tissue can be object of property rights) or if the biobank is only a custodian of tissue. The broad-consent model can be considered sufficient, if it is able to address to these issues.

[20] Criscuoli (1985), p. 271.

9.3 The Informational Dimension

The material perspective is only one of the dimensions that characterise human tissue. Thanks to the development of genetic research and technologies, human tissue is today mainly considered as a valuable source of medical and genetic data, contributing to the progress of medical science. These data contain useful information about patients, relating to their health, biological identities, and their individual predisposition to specific diseases. From simple aggregates of molecules, tissues are nowadays considered as valued sources of data.[21]

In their "informational dimension", human samples show different features to their "material dimension". Human tissue and human bodies share the same information even after the tissue is separated from the body, if we consider that tissue contains the genome of the body it was removed from. Therefore, from an informational point of view, the detachment of human tissue from the human body does not imply the complete separation of the samples from the body of origin. One particular assertion relating to the material dimension that "once X is separated from A, a physical object is created that is no longer *an* intrinsic aspect of A", can no longer be assumed to be valid. This is because X, even after the separation, is still an intrinsic aspect of A from the informational point of view.[22] This feature has important legal consequences. If, from the material perspective, tissue represents a "res" completely distinct from the body, then adopting the informational perspective must lead us to

[21] As the recent Myriad case showed (United District Court for the Southern District of New York, *Association for Molecular Pathology, et al. v. United States Patent and Trademark Office*, 09 Civ. 4515, 29 March 2010), the distinction has become relevant even in the case of patentability of DNA. Judge Sweet upheld the idea that DNA has a dual nature: it has a chemical form, but its value lies primarily in the information which it encodes. The Judge held that, as the value of the DNA was primarily informational, and as the information was the same in isolated and natural form, then the substance in question did not have markedly different characteristics and as a result was not patentable. See Hawkins (2010), p. 457.

[22] From a descriptive point of view, the double relationship between individuals and their tissues and between individuals and the information related to the samples shares the same scheme. They follow the legal scheme known in the European Continental legal tradition as "subjective rights" (*droits subjectifs*; *subjektives Rechten*), a scheme that implies a subject of right and an object of right and both describe a relation of "belonging" (the term "belonging" is proposed here to describe a relationship that includes all possible relationships between a person and their samples. In the Italian literature, the word used to define this relationship is "appartenenza"). However, there is a multitude of different levels of "belonging", which could be represented as a planetary nebula (see Zatti 2007, p. 3). The legal concept of property, as derived in all continental legal systems from the Roman tradition, would be on the edge of this nebula: in the typical property relationship, it is implied and presupposed that owner and owned object are separate entities. One finds the highest level of "belonging" when the idea of separateness is absent, and the owner and the owned object are indistinguishable. This is also the case of "personality rights", which are not distinguishable from the individual who holds the rights. In this view, the protection of personal identity, for instance—a typical personality right—is not a right that can be evaluated without considering the person to whom dignity refers. The two elements are inextricably linked to one another.

conclude that, even after the detachment from the body, tissue remains linked with the person.

This characteristic complicates the description of the relationship between the person and their personal data through the conceptual apparatus of "property rights". Indeed, conceptually, the owner and the owned object would be "the same", which represents a clear logical conflict.[23] In fact, it is worth emphasising that the debate about whether personal data can be considered as "property" is more complex than it might appear and, once again, is deeply influenced by different legal concepts of "property".

In continental legal systems,[24] rights over personal data (as defined in the next pages) are taken into consideration through the distinct conceptual category of so-called "personality rights".[25] Unlike property rights, personality rights are inextricably linked to the person; they are inalienable, not descendible, and not limited in time. It is thereby possible to allow their use by others, but it is not possible to assign them permanently to others. Rights over personal data are included in this category because personal data are conceived as "objects" capable of depicting some aspect of one's personality.[26] In a sense, they represent to the outside world some aspects of "what we are". If personal data represent an expression of our personality, then it would seem reasonable, abstractly, to affirm that to dispose of these data represents an expression of "self-determination". Therefore, while from the material perspective such a disposal represents a determination of the destiny of a thing external to the person, from the informational perspective it can be considered as self-determination, given that, even after detachment, one's tissue can still provide some information about the person.[27]

[23] For a deeper understanding of the cultural and philosophical premises of the relationship between subject and object, see Radin (2003), p. 194; Id (1987), p. 1849.

[24] The category of personality rights (*Persönlichkeitsrechte*) appeared in the German legal tradition thanks to Karl Gareis, Otto Friedrich von Gierke, and Joseph Kohler who first elaborated the theory of personality.

[25] This legal concept is shaped by the traditional idea of property, which implies an owner of rights who is an entity clearly separate from the object of the rights that the latter owns. See, Coing et al. (1959).

[26] Even though common law systems do not recognise "personality rights", despite their widespread recognition in civil law systems, the relationship between the person and his/her personal information is generally not considered a property relationship in common law systems. In English law, the question as to whether personal information is capable of a proprietary characterisation is not settled and English Courts seem to reject the idea that the relationship between the person and his personal information could be classified as property. The reason is clearly explained by Paul Stanley who notes that "English law does not impose duties upon people with respect to confidential information because it recognises some particular relationship between claimant and the information (a right *in rem*) which requires protection against strangers. Rather it imposes duties between individuals (rights *in personam*) whose consequence is to protect information". See Stanley (2008), p. 149.

[27] Clearly, this reasoning represents a general approach. Concretely, to establish in which manner personal data are capable of describing something about us, it is necessary to analyse the quality of the data case by case.

The important point is to assess what rights a person can claim over personal data deriving from tissue, and whether the right of self-determination exercised through the control of one's personal data is legally recognised. Addressing these aspects is inevitable while seeking to establish the effects of consent in the informational dimension.

In scholarly literature, the relationship between the person and their personal data is normally inscribed under the umbrella of the "right to privacy". Legally, the term "privacy" is very controversial, both because it "means so many different things to so many different people that it has lost any precise legal connotation that it might once have had",[28] and because it assumes peculiar meanings in different legal orders.[29] In the North American legal tradition, home of the modern origin of privacy,[30] privacy is used today in numerous different contexts, from confidentiality of personal information to reproductive autonomy.[31] This wide-ranging scope of applications has led some to call it a "chameleon-like word".[32] An important distinction must be drawn between data protection and privacy: data protection represents only one "planet" in the privacy "galaxy". To avoid misunderstanding, I shall avoid using the word 'privacy' and instead focus attention on "the right to protection of personal data", given that personal data represents the object of the informational dimension of tissue.

At the European level, the right to protection of personal data now represents a fundamental right and is recognised by Article 8 of the Charter of Fundamental Rights of the European Union.[33]

This right seems to have two distinct features. The first one can be identified in the first paragraph of Article 8, which establishes that, "everyone has the right to the

[28] McCarthy (2005), § 5.59. See also, Solove (2006), p. 477. In this essay the author contends that "[P]rivacy problems are frequently misconstrued or inconsistently recognized in the law" and "[T]he concept of 'privacy' is far too vague to guide adjudication and lawmaking". For this reason, he proposes an interesting framework for how the legal system can come to a better understanding of privacy, through a taxonomy that focuses on the different activities that impinge upon privacy.

[29] See Whitman (2004), p. 1160. The Author asserts that "At its conceptual core, the American right to privacy still takes much the form that it took in the eighteenth century: It is the right to freedom from intrusions by the state, especially in one's own home". In Europe, the core of privacy protection is the dignity of the person.

[30] See Warren and Brandeis (1980), p. 193.

[31] See Solove (2002), p. 1087. In this essay, Solove argues that privacy is too complicated a concept to be boiled down to a single essence. Privacy can be best understood as a "family resemblance"-based concept. Solove takes this concept from the philosopher Ludwig Wittgenstein, who affirms that certain things may not share one common characteristic, but they are nevertheless related to one another in different ways. Wittgenstein compared this to members of a family who generally share some traits with each other (eye colour, height, facial structure, hair colour, etc.) although they may not have one common trait. See Wittgenstein (1958), § 65.

[32] See BeVier (1988), p. 455.

[33] By virtue of article 6 of the "Lisbon Treaty", the "Charter of Fundamental Rights of the European Union" has the same legal value as the Treaties. It is important to highlight that the Charter has limited effect in Poland and the UK by virtue of the "Protocol on the application of the Charter of Fundamental Rights of the European Union to Poland and to the United Kingdom".

protection of personal data concerning him or her". This cryptic statement implies the creation of a duty upon data controllers to only process personal data lawfully and also to protect the data adequately against external intrusion. This duty represents the "passive side" of the protection of personal data and is shaped by the classic concept of privacy as a right to freedom from intrusion from others in one's "private life". In the case of human samples, this rule imposes a duty on those who retain samples and data deriving from samples to adopt adequate security measures to prevent the unlawful use of personal data and samples, the latter being considered as "physical vessels" in which data are stored.

With regard to informed consent, this first feature of the right to protection of personal data implies that a person must be informed of who is the data controller (i.e. the biobank); what technical measures and other warranties have been implemented by the biobank to ensure confidentiality; what policies exist for anonymisation and data circulation; and who else will access the data. As a result of this information, the patient can decide if they want to take the risk and provide their consent for the use of tissue and related data. What is worth noting is that, based on this perspective of data protection, it is not necessary for the patient to know what type of research tissue and data are used. Indeed, the fact that tissue and related data are used in breast cancer research or colon research does not change the risk of intrusion and of unlawful use of data.

Data protection is not only concerned with ensuring protection against such intrusions. There is a second feature of the right to the protection of personal data that permits a person to play an "active" role.[34] In part, this second feature is expressed in the second paragraph of Article 8 of the Charter, which establishes that "such data must be processed (. . .) on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified". This norm introduces the possibility for the person to give his/her consent for access to their data, or to have data rectified. Therefore, the right of protection of personal data does not only consist in the edification of a "defensive wall" to prevent unlawful uses of personal data but it also includes a right to actively control the flow of these data. The rationale for this characteristic is found in the reasoning set out above about the relationship between a person and their personal data, where we outlined that to dispose of these data is an expression of "self-determination".

This particular characteristic of data protection is most developed in the European continental legal tradition. Its clearest expression can be found in the

[34] See Art. 29 Data Protection Working Party 2011. The Working Party contends that "the notion of consent is traditionally linked with the idea that the data subject should be in control of the use that is being made of his data. From a fundamental rights perspective, control exercised through consent is an important concept. At the same time, and from the same perspective, an individual's decision to accept a data processing operation should be subject to rigorous requirements, particularly taking into account that in doing so, an individual may be waiving a fundamental right".

so-called right of "informational self-determination", first coined by the German Federal Constitutional Court.[35] It represents a right to decide what shall be disclosed about individuals, and to control one's "external image", through control of personal information. The logical corollary of this right is a series of specific rights relating to personal data, such as the right to express consent, the right to access data, and, last but not least, the right to withdraw consent.

This second feature of the right of protection of personal data is strongly recognised in the special category of "genetic data", defined in the UNESCO *International Declaration on Human Genetic Data* as "[i]nformation about heritable characteristics of individuals obtained by analysis of nucleic acids or by other scientific analysis".[36] Many countries have established a specific regulation for this type of data following the idea that it is peculiar compared to the other health data,[37] given their high "sensitivity". It is beyond the scope of this contribution to analyse the specific rules adopted in each country, nevertheless it seems important to comment briefly on the principle proclaimed in the UNESCO Declaration that has had the biggest impact on national legislation. The Declaration affirms at Article 6 that "clear, balanced, adequate and appropriate information shall be provided to the person whose prior, free, informed and express consent is sought", and that this information should specify "the purpose for which human genetic data and human proteomic data are being derived from biological samples, and are used and stored". Article 8 further recognises that "[W]hen human genetic data, human proteomic data or biological samples are collected for medical and scientific research purposes, consent may be withdrawn by the person concerned unless such data are irretrievably unlinked to an identifiable person" and "[I]f not irretrievably unlinked, the data and biological samples should be dealt with in accordance with

[35] The term "informational self-determination" was first used by the German Federal Court Constitution in the Judgment/ BVerfGE 65, 1, at para. 154 of 15 December 1983. The Court stated that under Articles 1 and 2 of the Grundgesetz, an individual has "the authority to decide for himself, on the basis of the idea of self-determination, when and within what limits facts about his personal life shall be disclosed." See, Kommers (1997), p. 324. See also, the Spanish Constitutional Court Judgments/SSTC 290/2000 and 292/2000, of 30 November 2000. In particular, the Spanish Constitutional Court Judgment 292/2000 recognised for the first time the right to the protection of personal data as an autonomous right. See also the Italian Code for Person Data Protection (Legislative Decree 196/2003). See also Art. 29 Data Protection Working Party 2011, which affirms that "Consent is related to the idea of informational self determination. The autonomy of the person is both a pre-condition and a consequence of consent: it gives the data subject influence over the processing of data".

[36] Art. 4 of the Declaration declares that human genetic data have a special status because (i) they can be predictive of genetic predispositions concerning individuals; (ii) they may have a significant impact on the family, including offspring, extending over generations, and in some instances on the whole group to which the person concerned belongs; (iii) they may contain information the significance of which is not necessarily known at the time of the collection of the biological samples; and (iv) they may have cultural significance for persons or groups.

[37] There is a strong debate about the nature of genetic data and whether they can be considered "exceptional" compared to other types of health data. For an introduction to this debate see: Rothstein (2005), p. 27; Green (2003), p. 138; Poste (1999), p. 25; Murray (1997), p. 60.

the wishes of the person. If the person's wishes cannot be determined or are not feasible or are unsafe, the data and biological samples should either be irretrievably unlinked or destroyed."

In the context of our analysis, these rights imply that it should be possible for a person to control personal data derived from their tissue, and to change their mind about such uses. However, given that tissue "contains" these data, this right implies control over the tissue too. Therefore, this second aspect of the right of the protection of personal data invests in the person a continuing power of control over the tissue, even after the transfer of the tissue to a biobank.

Therefore, unlike the first dimension of the right to the protection of personal data, in this second dimension, the level and the quality of information become relevant, because the person can maintain control over data and can assume decisions only if they have the possibility to know constantly where their tissue and data are exploited.

In light of this analysis, the debate about the acceptability of the "broad-consent model" could acquire significance.

To better understand this point, it is necessary to take a step back. If the right of "informational self-determination" is a consequence of the fact that personal data are conceived as "objects" capable of depicting some aspect of our personality, it becomes relevant: (a) to define in what sense data derived from tissue are able to depict our image; and (b) if different research conducted on data derived from tissue stored in a biobank will have different effects on our external image.

With regard to the first question, the answer is not easily achievable. We could argue that currently relatively few types of personal information can be obtained from tissue and used to determine our external image. However, the amount of information that we can obtain from the analysis of tissue increases by the day with the development of technology. Therefore, given that biobanks store tissue for a long period, it is not possible to provide a reliable answer.

Assuming that it is possible to obtain data capable of depicting our external image from tissue, the second question is whether the different types of research can have a different influence on our external imagine. This question is crucial because only if the answer is positive in respect of the "right of informational self-determination" will it be necessary to obtain consent for every type of research. If there is not this link between self-determination and different types of research, a simple general consent "to make research (any research) with tissue and related data" will be sufficient.

There is no doubt that different types of research investigation can reveal different types of information about participants. Therefore, the type of research could have a real influence over the portrayal of the "external image" of a person. For instance, if we use a sample of blood for conducting research about breast cancer, we could obtain different information compared with the research made on the same sample about obesity.

Nevertheless, any such information could influence the external image of the person only hypothetically. Indeed, the second feature of the right to the protection of personal data has to be connected with the first feature, which obliges the data

controller to implement all measures necessary for assuring confidentiality. Consequently, if different research can, hypothetically, reveal different types of information that could affect the "external image" of the person then, even if this information were not identifiable when used, any impact on the "external image" would arise only when there had been a breach of duty by the data controller, or when technical limits prevented assurances about confidentiality.

Therefore, from the informational point of view, for the person involved it is important to know how the governance of a biobank is configured, which measures are adopted to protect their confidentiality, how it is possible to withdraw the consent (etc.).

9.4 The "Human" Perspective and the Role of Consent

In addition to the two perspectives just analysed—material and informational—it is necessary to consider another level when assessing the "personal relationship" between human tissue and the human body. This perspective (we could name it "human") has a completely different nature from the other two considered above and it has its origin in the derivation of human tissue from the person.[38]

This perspective originates from the idea that the derivation of human tissue from the person cannot be neutral. Human tissue can be considered as a particular *res* compared to the other chattels, a characteristic which depends not only on the fact that tissue is a source of personal and genetic data but also on the fact that it is ontologically peculiar due to its derivation from the human body. This "ontological" peculiarity can be based either on religious belief or on an "anthropological" vision, which gives particular significance to the tissue of body parts. In some cultures, for instance, the body and its parts are considered sacred. In other cultures, even after detachment, body parts are considered to have the same "value" as the value that the body has, as a whole.

While the material and the informational perspectives are "intrinsic" features of human tissue, the existence of this last perspective depends on the individual's "ideas" about the relationship between the human body and tissue detached from the body, and it is therefore conditioned by their beliefs.

Similarly to the informational dimension, the "human" perspective persists after tissue is detached from the body, and, unlike the informational dimension, it remains even after anonymisation of that tissue. The anonymisation does not change the origin of tissue. Even if anonymised, tissue maintains its "human" origin.[39]

[38] See Laurie (2002), p. 302. Previous scholars alluded to that nature when maintaining that "the moral significance of body parts remains even when they are separated from their original source".

[39] See, Kirchhoffer and Dierickx (2011), p. 5. The Authors underline that "even if the samples are anonymised, human dignity is still implicated".

This perspective is ambiguous and its impact on the policies adopted by the legislators is not easy to evaluate. Legislators could adopt two possible strategies in dealing with this perspective, (a) they could not take this perspective into account at all, and (b) they could recognise the existence of this perspective by giving the individual the ability to decide which value to assign to their tissue. In the latter case, the legislator does not establish what is morally wrong in relation to particular uses of human tissue but it merely safeguards the person's ability to express their choice as regards such uses.

The main instrument for the implementation of this strategy can be informed consent. Through consent, an individual can choose if a specific use of their tissue is compatible with their beliefs. It is clear that to exercise this right either a person has a chance to give specific consent to every research project or an ethical committee evaluates the research projects instead of the person. In this second option, it is necessary to inform the patient about the parameters used by the ethical committee in this evaluation.

9.5 Conclusion

In the biobanking context, the formulation of informed consent and its consequent effects depends on the interests that we intend to promote. In this article, we have seen that human tissue could be considered through three different perspectives, and from every perspective, different types of legal interests originate.

From the material point of view, the level of information is almost irrelevant. It is important for the "donor" to know if his tissue is used in research context, but it is less important for him to know the specific research project wherein his tissue will be used. Differently, from the informational point of view, it is important for the persons involved to know how the governance of a biobank is configured, what measures are adopted to protect their confidentiality, and how it is possible to withdraw their consent. The biobank has to provide all the necessary information in order to allow the persons involved to decide if they want to assume the risk derived from the use of their personal information.

From the controversial "human perspective", a punctual information about the specific research project where tissues are used could be relevant. Nevertheless, in this case, an ethical committee could act as filter by evaluating when it is necessary to contact the person to obtain a new consent.

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Part II
Intellectual Property and Biobanks

Chapter 10
The Challenges of Achieving Open Source Sharing of Biobank Data

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Abstract Several recent biomedical research initiatives have sought to make their data freely accessible to others to stimulate innovation. Many of these initiatives have adopted the "open source" model that has achieved prominence in the computing industry. With respect to genomics research, open access models of data release have become common and most large funding bodies now require researchers to deposit their data in centralized repositories. In particular, biobanks, which are organised collections of biological samples and corresponding data, benefit from the implementation of open source principles. Several obstacles loom, however, as barriers to widespread implementation of open source principles in the field of biomedical research. These include the reluctance among researchers to share their data; the challenge of crafting appropriate publication and intellectual property policies; the difficulties in affording informed consent, privacy, and confidentiality to research participants when data is shared so widely; controversy surrounding the issues of commercialization and benefit-sharing; and the complexity of establishing a suitable infrastructure. This article examines each of these and considers an alternative approach, "fair access" biobanks.

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10.1 Introduction

Several recent biomedical research initiatives have sought to make their data freely accessible to others to stimulate innovation.[1] Many of these initiatives have adopted the "open source" model[2] that has achieved prominence in the computing industry.[3] When used in the software context, the term "open source" refers to a software development project for which the computer source code[4] is made publicly available for licensees to use, modify, and redistribute, provided that these licensees make their enhancements available to others on the same terms, an approach known as "copyleft".[5] When applied to data acquired through biomedical research, the term "open source biotechnology", or, alternatively, "open science", means that data from the project is released rapidly into the public domain, subject to certain conditions, including a requirement that data users will not exercise their intellectual property rights in a way that would preclude other users' access to the basic data.[6] This article will use the term "open source", a short form of "open source biotechnology", to refer to this approach to data access. Sharing of biotechnological

[1] See International Consortium Announces the 1000 Genomes Project, http://www.1000genomes.org/docs/1000Genomes-NewsRelease.pdf (22 January 2008) ("As with other major human genome reference projects, data from the 1000 Genomes Project will be made swiftly available to the worldwide scientific community through freely accessible public databases"); The International HapMap Consortium (2003) (setting forth the data access policy for the International HapMap Project and describing it as one committed to "rapid and complete data release, and to ensuring that project data remain freely available in the public domain, at no cost to users").

[2] Among the life sciences initiatives that have consciously adopted one or more open source principles are Science Commons, see About Science Commons, http://sciencecommons.org/about/ (last visited March 16, 2010); the International HapMap Project, see generally Gitter (2007), p. 1475; the Biobricks Foundation, see Endy (2005), p. 449; the Tropical Diseases Initiative (TDI), see Maurer et al. (2004), p. 183, http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0010056; and the Biological Innovation for Open Society (BIOS), see Dennis (2004), p. 494.

[3] See Lerner and Tirole (2005), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=620904 (describing computer software as "the most prominent example of open source production").

[4] Source code is a computer program in its original form, written and readable by human beings. Hope (2004), available at http://opensource.mit.edu/papers/hope.pdf. Because computers can execute only instructions coded as a series of binary numbers (ones and zeroes), source code must be "translated by means of another program into binary form, known as machine or object code". *Ibidem.*

[5] See Hope (2004), *supra* note 4, p. 68 (explaining the copyleft licensing scheme developed in the software community and describing it as "an ingenious twist on the conventional copyright licence"); see also Lerner and Tirole (2005), *supra* note 3, p. 2 ("In an open-source project, ... a body of original material is made publicly available for others to use, under certain conditions. In many cases, anyone who makes use of the material must agree to make all enhancements to the original material available under these same conditions").

[6] See Feldman and Nelson (2008), http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1127571 (May 2008) (using the terms "Open Source Biotechnology" and "Open Science" interchangeably to describe projects for which "participants agree to either grant licenses or enforce their rights in a way that maintains the availability of the inventions and improvements in the future"); see also Gitter (2007), *supra* note 2, pp. 1482–1485 (describing the former International HapMap Project data access policy, which was modeled upon an open source software licensing approach and aimed to ensure that basic data remained widely accessible).

data is particularly important in light of the fact that many results of biotechnological research, such as isolated human DNA sequences, cannot be "invented around", meaning, there is no true substitute for them.

The US government encourages an open source approach to biotechnology, particularly for large-scale, publicly-funded genomic projects such as the International HapMap Project and the 1000 Genomes Project. Inspired by the Bermuda Statement[7] and the Fort Lauderdale Agreement,[8] governmental funding bodies now require researchers to deposit their genomic data in centralised, openly accessible repositories.[9] Moreover, the NIH Data Sharing Policy requires that all projects receiving at least $500,000 in federal funding to share data in a de-identified format.[10] At the same time, however, the US government sends a contradictory message, encouraging researchers to seek intellectual property protection and transfer their research to the private sector.[11] Moreover, US governmental support of open source biotechnology operates mainly in the domain of "big science", which involves government science agencies collecting or funding the collection of data and samples, which is then organised into databases that are made publicly available to the worldwide scientific community.[12] Examples are large, publicly-funded genomic databases such as the International HapMap Project and the Human Genome Project. By contrast, researchers involved in "small science", meaning, research "performed by individual investigators or small and autonomous research groups operating outside large, organised research programs, often with non-federal sources of funding", are not

[7] The Bermuda Statement is an international agreement favoring release into the public domain of genetic databases achieved through public funding. See Human Genome Project, US Department of Energy Office of Science, Summary of Principles Agreed at the First International Strategy Meeting on Human Genome Sequencing, http://www.ornl.gov/sci/techresources/Human_Genome/research/bermuda.shtml#1 (February 25–28, 1996).

[8] The Fort Lauderdale Agreement emphatically reaffirmed the Bermuda Statement. See National Human Genome Research Institute, National Institutes of Health, Reaffirmation and Extension of NHGRI Rapid Data Release Policies: Large-scale Sequencing and Other Community Resource Projects, http://www.genome.gov/10506537 (February 2003).

[9] See, e.g., National Institutes of Health, Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-wide Association Studies (GWAS), http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html (January 25, 2008) ("All investigators who receive NIH support to conduct genome-wide analysis of genetic variation in a study population are expected to submit to the NIH GWAS data repository descriptive information about their studies for inclusion in an open access portion of the NIH GWAS data repository") (hereinafter NIH GWAS Data Sharing Policy). In the UK as well, the Wellcome Trust requires researchers "that it funds to maximise the availability of research data with as few restrictions as possible". Wellcome Trust, Policy on Data Management and Sharing, http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTX035043.htm (January 2007).

[10] National Institutes of Health, Final NIH Statement on Sharing Research Data, NOT-OD-03-032, http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html (February 26, 2003).

[11] See Rai (1999), p. 95 (describing how Congressional enactment of the Bayh-Dole Act in 1980 stimulated the commercialisation of academic research).

[12] Reichman and Uhlir (2003), p. 322.

as influenced by the norms of open access and sharing and instead rely on informal exchanges of data and samples.[13]

This article focuses on the application of open source principles to biobanks, which are organised collections of biological samples and corresponding data,[14] often created for the use of investigators who are not affiliated with the biobank.[15] Biobanks are critical in both large and small science, ranging in size from large-scale national repositories to small collections of samples in academic or hospital settings.[16] Pharmaceutical and commercial biotech companies create biobanks as well, often for the purpose of conducting research for the future development of diagnostic and therapeutic products.[17] Aside from their size, biobanks vary in many ways, such as the extent to which they include samples from family members or from unrelated individuals, the degree to which the samples are linked to a particular person (either identified, identifiable, anonymised or anonymous), and the type of information attached to the sample, such as personal or medical information. In addition to the information attached to the sample, the biobank may include data about the population groups being studied, such as frequencies of genetic markers in that population.[18]

This article examines several challenges to widespread application of open source principles to biobanks. These include the reluctance among researchers to share their data; the challenge of crafting appropriate publication and intellectual property policies; the difficulties in affording informed consent, privacy, and confidentiality to research participants when data is shared so widely; controversy surrounding the issues of commercialisation and benefit-sharing; and the complexity of establishing a suitable infrastructure. The article also considers an alternative to the open source approach toward biobanks, the "fair access" model.

10.2 The Challenge of Fostering a Culture of Data-Sharing Among Researchers

It is challenging to foster a culture of data sharing among researchers, who quite rationally seek to protect their data. In pursuing career advancement, scientists are understandably reluctant to grant data users access to research results achieved after

[13] *Ibid*., pp. 322–323.

[14] Cambon-Thomsen (2004), p. 866.

[15] Boggio (2008), p. 231.

[16] Cambon-Thomsen et al. (2007), p. 373. Among the best known national repositories, also known as population biobanks, are the Estonian Genome Project; the Icelandic Health Sector Database; the International HapMap Project; the UK Biobank; and several US biobanks, such as the Framingham Heart Study and the Marshfield Clinic's Personalized Medicine Research Project. See Elger and Caplan (2006), p. 661.

[17] See Bregman-Eschet (2006), p. 17; Elger and Caplan (2006), *supra* note 16, p. 661 (stating that three-fourths of US clinical trials by pharmaceutical companies include a provision for storing human tissue for future use).

[18] Cambon-Thomsen et al. (2003), p. 629.

devoting years of hard work to "planning a project, securing funding and ethics approval, recruiting the participants, collecting the data and materials, performing analyses, managing the collection and infrastructure, controlling technical quality, and generally nourishing the project through waves of funding and maturation".[19] In addition, data producers fear being "scooped" by data users[20] who may mine data and discover relationships in it that the producer did not discern.[21] Moreover, researchers do not wish to compromise their ability to win future research grants, which depend to a large extent upon findings from their datasets.[22] In addition, researchers bear some responsibility toward the post-docs and junior investigators in their labs, who rely upon these data for their careers.[23] These issues are particularly salient for small science researchers, who are working independently rather than as part of government-sponsored projects.

However, data sharing also offers exciting possibilities, such as opportunities for cross-checking of one's data and fruitful collaborations.[24] As noted by one expert, "[t]here is simply too much for one group to do", and data sharing "[s]preads the analytical burden" and helps researchers to achieve results they would not attain on their own.[25] This is one of the recognised advantages of open source technology development, as noted by the open source aphorism "Given enough eyes, all bugs are shallow".[26] Of particular benefit in the biotechnology context, collaboration among different sorts of researchers, such as geneticists, statisticians, bioinformaticians, and epidemiologists, also achieves results superior to any one of those groups working alone.

Technology offers the potential to foster data-sharing by helping data producers to obtain attribution for their work. Professor Boyle has offered the example of a music

[19] Lowrance (2006), available at http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_grants/documents/web_document/wtx030842.pdf.

[20] The terms "data producers" and "data users" are not mutually exclusive, since scientists may in some situations be data producers, yet be data users in others.

[21] See Nelson (2009), p. 163. Indeed, one expert has noted that certain researchers may in fact fear exposing their data to review in case it is found to be wanting in some way. Nature Opinion Forum: Prepublication Data Sharing: The Toronto Statement, http://network.nature.com/groups/naturenewsandopinion/forum/topics/5433 (Ewan Birney, Senior Scientist at the European Molecular Biology Laboratory working at the European Bioinformatics Institute) (September 11, 2009). However, he noted that in reality researchers typically contact a colleague personally to clarify their questions, as opposed to publicly challenging the work. *Ibidem.*

[22] See Singleton (2007), http://www.genome.gov/Multimedia/OD/GWAS_Boston_07/11-Singleton_Professional.ppt#4 (June 22, 2007) (hereinafter Singleton).

[23] See Singleton (2007), *supra* note 22.

[24] *Ibidem.* It should be noted that while open source sharing of data is possible, open source sharing of actual tissue samples is not, because of the limited amount of tissue that can be collected and stored. Data producers must husband this resource carefully to ensure optimal allocation. See Boggio (2008), *supra* note 15, p. 231.

[25] Singleton (2007), *supra* note 22.

[26] Raymond (2002), http://www.catb.org/~esr/writings/cathedral-bazaar/cathedral-bazaar/ar01s04.html.

site associated with Creative Commons,[27] known as ccMixter.[28] This site allows users to download music from the site and remix the samples into new tracks, while simultaneously maintaining a record of the credits due to each musician.[29] A comparable system would permit attribution to the appropriate data producer while also allowing universities and funding agencies to track the number of uses, and therefore the value, of a researcher's data.[30] This would address researchers' desire for attribution, and assist them in demonstrating their productivity to potential funding agencies.

Professor Cambon-Thomsen has advocated a similar system to measure the usefulness of a biobank as a whole. She has proposed the establishment of a biobank impact factor (BIF), similar to a citation impact factor, to "quantify the use of a biobank, measure the impact of the research resulting from its use, and recognize those who established and maintained a valid resource".[31]

Certain biotechnology resources further require that data users must share their findings with the biobank, thereby reflecting the traditional view that scientific research ought to be shared among researchers and avoiding inefficient duplication of research efforts.[32] For example, UK Biobank,[33] while not an open source project, in that it does require and review applications for data access before allowing academic institutions, nonprofits, and commercial companies nonexclusive data access,[34] has implemented a grant-back policy. All data users are "required to put results from all analyses made on participants' data and samples, and any relevant supporting information, in the UK Biobank database so that they are subsequently available to all researchers with appropriate scientific and ethics approval" and must ultimately place all research findings using its data into the public domain, after a limited period of exclusivity.[35]

A similar grant-back strategy proved to be a source of value and competitive advantage for one private biotechnology company in the mid 1990s, before the public sector Human Genome Project made DNA sequence data publicly available. The firm required licensees of its genomic data, if they successfully used the database to discover

[27] Creative Commons is a nonprofit corporation that aims to facilitate content-sharing in accordance with the law of copyright. Creative Commons, About, http://creativecommons.org/about/ (last visited March 18, 2010).

[28] See Nelson (2009), *supra* note 21, p. 163 (citing Professor James Boyle of Duke Law School).

[29] See ccMixter, About, http://ccmixter.org/about (last visited March 18, 2010).

[30] See Nelson (2009), *supra* note 21, p. 163.

[31] Cambon-Thomsen (2003), p. 26.

[32] Boggio (2008), *supra* note 15, p. 234.

[33] UK Biobank, a research initiative funded by both private and public sources, aims to collect tissue samples and personal data from at least 500,000 individuals in the UK and use this data for research into the prevention, diagnosis and treatment of human disease. UK Biobank, UK Biobank—What Is It?, http://www.ukbiobank.ac.uk/about/what.php (last visited April 11, 2010).

[34] UK Biobank (2007), Ethics and Governance Framework 12–13, http://www.ukbiobank.ac.uk/docs/EGFlatestJan20082.pdf (October 2007).

[35] UK Biobank (2007), Ethics and Governance Framework 12–13, http://www.ukbiobank.ac.uk/docs/EGFlatestJan20082.pdf (October 2007).

and characterise a full-length gene, to grant back nonexclusive freedom to use that gene to all other customers using that database.[36]

The most significant disadvantage of such a grant-back requirement is that some researchers interested in exploiting their findings for commercial purposes undoubtedly will decline to participate when confronted with such a policy.[37] In addition, it is quite difficult to police such a grant-back arrangement for a truly open source biobank. The ability to control access to some degree so as to deny access to violators is essential for effective enforcement of such a policy.[38] Finally, there is a significant possibility that transferring raw data back to the biobank would increase the likelihood of including data with material errors; material that would be difficult to organise and use at a later time; and data that would not prove useful at all.[39] In order to address researchers' concerns about sharing data with their potential competitors, some experts have proposed that researchers should only have to share their aggregate data with biobanks, and that perhaps the data producers could delay sharing their data so they could analyse and publish it first.[40]

Typically, grant-back arrangements work best for data that is sufficiently upstream, such as genetic sequences databases. Indeed, because human DNA sequence data cannot be invented around, downstream users of such data are often motivated to place upstream data in the public domain so as to thwart patenting that would impede the development of downstream products.[41]

10.3 Crafting Appropriate Intellectual Property and Publication Policies

In light of researchers' desires to protect the data they have gathered and advance their own careers, efforts to create a culture of data-sharing are inextricably linked to the question of the optimal intellectual property and publication policies to support data-sharing efforts. Supporters of open source biotechnology generally

[36] See Gitter (2007), *supra* note 2, pp. 1493–1494 (describing the grantback requirement imposed by Incyte Genomics, Inc.).

[37] See Boggio (2008), *supra* note 15, p. 235.

[38] Cf. Gitter (2007), *supra* note 2, pp. 1489–1490 (explaining the obstacles to achieving the open source model with respect to the International HapMap Project without an adequate enforcement mechanism).

[39] See Boggio (2008), *supra* note 15, p. 235.

[40] *Ibidem*.

[41] See Gitter (2007), *supra* note 2, pp. 1478 and 1508–1509 (citing the example of the SNP Consortium, a group of pharmaceutical firms and a nonprofit organisation that collaborated at great financial expense to place genomic data in the public domain so as to preempt the patenting of such information that could be used to develop patentable pharmaceutical products). See also Hope (2008) (noting that, "there is a strong motivation for commercial players to support open source development of any technology upstream of their own place in the relevant value chain").

believe that advances in public health result from making scientific data highly accessible to as many researchers as possible, while simultaneously encouraging scientists to pursue practical applications of the research that lead to patentable products. In the last three decades, it has been more difficult to achieve these goals, as the increasing commercialisation of academic research has undermined the traditional Mertonian notion of collaborative science.[42] For example, researchers in the genomics field in particular have tended to patent their findings, whereas other biobank users, such as epidemiologists, typically do not pursue patent protection.[43]

In order to resolve issues relating to intellectual property and commercialisation, proponents of open source biotechnology advocate an approach that balances the conflicting needs for open access, on the one hand, and patent protection, on the other, by encouraging patenting of technology that leads to downstream products such as diagnostics and therapeutics, while discouraging the patenting of basic upstream data. For example, with regard to intellectual property claims achieved through the use of dbGAP, the NIH's database of information genome-wide association studies (GWAS),[44] the NIH encourages patenting of technology that gives rise to products such as diagnostics and therapeutics, while discouraging the use of patents to prevent the use of or block access to any genotype–phenotype data developed with NIH support.[45] Specifically, the NIH has expressed its "hope" that, "genotype–phenotype associations identified through NIH-supported and NIH-maintained GWAS datasets and their obvious implications will remain available to all investigators, unencumbered by intellectual property claims".[46] Achieving open access to data nonetheless proves difficult to achieve under the NIH policy, which is vague and difficult to enforce, and applies only to entities seeking public funding for research, which are typically academic and other not-for-profit research institutions.[47]

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[42] See Rai (1999), *supra* note 11, pp. 95–96 (describing how the enactment of the Bayh-Dole Act in 1980 stimulated the commercialisation of academic research).

[43] Post (2007), http://www.genome.gov/Multimedia/OD/GWAS_Boston_07/02-Post_Challenges.ppt#1 (June 22, 2007).

[44] Press Release, http://www.nlm.nih.gov/news/press_releases/dbgap_launchPR06.html (December 12, 2006). GWA studies "explore the association between specific genes (genotype information) and observable traits, such as blood pressure and weight, or the presence or absence of a disease or condition (phenotype information)", thereby facilitating the development of new diagnostic methods and treatments. *Ibidem*.

[45] NIH GWAS Data Sharing Policy, *supra* note 9.

[46] *Ibidem*. *See* also The GAIN Collaborative Research Group (2007) (describing the NIH's GAIN project, a GWAS, as promoting data access "by rapidly placing data in the public domain and by encouraging the initial genotype–phenotype associations identified through GAIN to remain unencumbered by intellectual property claims" in order to maximise the benefit provided by these "community resources").

[47] *See* Nelson (2009), *supra* note 21, pp. 161–162 (explaining that, in response to an NIH mandate regarding data sharing, researchers chose to delay compliance so as to see whether and how the NIH would enforce its mandate).

As for the world of small science, those individual investigators or small and autonomous research groups operating outside large, organised research programs, often with non-federal sources of funding, are not as influenced by the norms of open access and sharing and instead rely on informal exchanges of data and samples.[48] Paradoxically, however, Reichman and Uhlir have noted that this lack of an officially sanctioned open access regime might in fact make independent researchers more dependent upon cooperative relationships with other scientists in order to expand their data supplies and coordinate others' data with their own. Thus, small science would benefit from collaborative data sharing, if data producers could be persuaded to endure short-term losses occasioned by the disclosure of their data in order to achieve long-term gains from cooperation.[49]

One way of fostering earlier, prepublication data release is to permit investigators who contribute data to a biobank to enjoy some period of exclusivity during which they will have the sole right to publish analyses of the data.[50] The NIH and the UK Medical Research Council (MRC), a government-funded research agency akin to the NIH,[51] have both adopted this approach. The NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies declares that investigators who contribute data to a NIH GWAS data repository will retain the exclusive right to publish analyses of the dataset for a maximum of twelve months following its release via the NIH GWAS data repository. During this period of exclusivity, the NIH grants data access through data access committees to other investigators, who may analyse the data, but not submit for publication their analyses or conclusions, until the expiration of the exclusivity period. The NIH also expects all investigators who access GWAS datasets to acknowledge in all publications the data producers who conducted the original study, along with the funding organization that supported the work and the NIH GWAS data repository.[52] Similarly, the UK Medical Research Council provides for a period of interim exclusivity for data producers.[53] The MRC data-sharing policy provides that, "[a] limited, defined period of exclusive use of data for primary research is reasonable . . ."[54] The UK Biobank follow suit,

[48] Reichman and Uhlir (2003), *supra* note 12, pp. 322–323.

[49] *Ibid*., p. 346.

[50] Attendees at the 2009 Toronto International Data Release Workshop, which gathered data producers and users in the field of genomics to develop best practices for prepublication data sharing, recognized that data producers might "request a protected time period to allow them to be the first to publish the data set" and declared that the period of exclusivity "should be limited to global analyses of the data and ideally expire within one year". *Prepublication Data Sharing*, 461 *Nature* 168, 170 (2009).

[51] Medical Research Council, About Us, http://www.mrc.ac.uk/About/Structure/index.htm (last visited March 19, 2010).

[52] NIH GWAS Data Sharing Policy, *supra* note 9.

[53] Lowrance (2006), *supra* note 19, p. 36.

[54] Medical Research Council, Medical Research Council Policy on Data Sharing and Preservation Policy, http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Datasharinginitiative/Policy/index.htm#P16_1349 (last visited March 20, 2010).

asking researchers to recruit 500,000 participants and collect their data and samples, in return for which the researchers will gain exclusive access for a period of time or for research into certain specialty areas.[55] In general, the purpose of the period of exclusivity is to provide the data producer sufficient time to produce, organise, document, verify, and analyse the data in preparation for publication in a scientific journal. After publication, the data is made available more broadly, either via a publicly available database or via an application system.[56]

With respect to publication, scientific journals also foster data sharing. Newer journals, such as the open access *Public Library of Science* journals, have made publication contingent on making the data "freely available without restriction, provided that appropriate attribution is given and that suitable mechanisms exist for sharing the data used in a manuscript".[57] *Nature* journals require authors to "make materials, data and associated protocols promptly available to readers without preconditions".[58]

Notwithstanding the rigorous data-sharing policies of some highly respected scientific journals, many others have no written policy on the availability of either bioresources or primary data.[59] Moreover, some journals have taken the position that their power to compel data sharing is quite limited. For example, in March 2009 an editorial in the journal *Epidemiology* called only for a "small step" towards openness, inviting, but explicitly not requiring, "authors to share their data and computer code when the burden is minimal.[60] While acknowledging that data sharing is inevitable, Dr. Miguel Hernán, an epidemiologist at Harvard University and a co-author of the editorial, warned that mandating a sharing requirement for authors "'would be suicidal'" and would drive authors to submit their papers elsewhere, especially in light of concerns regarding patient confidentiality.[61]

10.4 Protecting Research Participants' Rights of Informed Consent, Privacy and Confidentiality

Even if researchers are able to overcome their reluctance to share data with one another, open access models of data release are nonetheless difficult to achieve in light of researchers' legal and ethical obligations toward their research subjects.

[55] See Lowrance (2006), *supra* note 19, p. 36.

[56] See Reichman and Uhlir (2003), *supra* note 12, p. 355. The NIH provides a freely accessible GWAS database, where the UK Biobank permits access via an application system. See *supra* note 34 and accompanying text.

[57] PLoS One, PLoS One Editorial and Publishing Policies, http://www.plosone.org/static/policies.action#sharing (last visited March 20, 2010).

[58] Nature.com, Authors & Referees @npg, http://www.nature.com/authors/editorial_policies/availability.html (last visited March 20, 2010).

[59] Schofield et al. (2009), p. 171.

[60] Hernán and Wilcox (2009), p. 168.

[61] Nelson (2009), *supra* note 21, p. 163.

In particular, research participants are entitled to informed consent, privacy, and confidentiality with respect to the samples and data that they provide. Principles of informed consent enshrined in international accords, as well as national statutes and declarations of non-governmental bodies, dictate that research participants have a right to consent to the use of their tissue and must be informed of the potential for harm, including discrimination by employers or insurers, resulting from the release of their confidential information.[62] In the United States, informed consent is required if personally identifiable information is connected to the tissue sample.[63]

Translating informed consent into practice is particularly challenging in the case of open science biobanks, since these resources tend to be large-scale, involve long-term use of samples or data, and give rise to numerous exchanges among researchers of samples and data.[64] However, adherence to informed consent principles is imperative in that it not only fulfills an ethical obligation to protect research subjects, but also fosters scientific progress by developing an environment of trust that encourages individual research subjects to participate in scientific research.[65] As scholars have noted, research participants may decline to participate in scientific research if they are unable to control the precise use to be made of their tissue.[66]

New informed consent rubrics have therefore arisen to help attain appropriate informed consent for open science databases. Traditionally, as noted by Professor Cambon-Thomsen, informed consent has been "strictly defined as specific consent given for well-defined uses; the donor is given transparent information, the possibility of dialogue with a professional, and time to think about the implications before a decision is taken".[67] She notes that alternative forms of consent that have arisen include "enlarged consent, consent with several options for research use,

[62] See, e.g., 2 Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10, pp. 181–182 (US Gov't Printing Office, 1946–1949) (The Nuremberg Code is an international agreement that prohibits countries from conducting experimental medical treatments on patients without their express informed consent.); World Medical Association (1997), p. 925 (The Declaration of Helsinki is a "statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data"); The Nat'l Comm'n for the Protection of Human Subjects of Biomedical & Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm (April 18, 1979) (The Belmont Report is a set of national recommendations in the US regarding research on human subjects); 45 C.F.R. part 46 (2007) (The Common Rule) (The Common Rule is a US federal policy protecting human subjects of federally-funded research, but in practice has been adopted by many other institutions for their non-federally funded research).

[63] Swede et al. (2007), p. 145 (citations omitted).

[64] See Cambon-Thomsen (2004), *supra* note 14, p. 869.

[65] See Burger (2009), p. 56.

[66] *Ibid*., pp. 69–74 (citing numerous examples of research participants who expressed preferences as to the specific research uses to be made of their tissue samples).

[67] See Cambon-Thomsen (2004), *supra* note 14, p. 869 (citations omitted).

presumed consent and blanket consent",[68] although she opines that, "these last two can hardly be considered consent at all".[69]

Notwithstanding these varying consent options, the informed consent process is limited in its ability to address all privacy and confidentiality concerns of research participants, as Professor Cambon-Thomsen notes. For example, even if research participants are offered the option to withdraw their consent and direct the destruction of their tissue samples, the destruction of samples and data is sometimes not feasible in cases where they have changed hands many times, especially where the coding or encryption system is highly complex. What is more, if the data are needed for follow-up, and the original sample will be used as a control, research participants must be made to understand that although no new results will be generated and the remaining sample will be destroyed, this does not guarantee the destruction of the existing data. While some ethics committees would grant the research participant the right to demand destruction of all of the data, most scientists would argue that once scientific data has been produced with the consent of a person, that person should not have the right to ask for the destruction of the data, but rather only its anonymisation.[70]

Even where researchers do strive to recontact individual research participants regarding future uses of their tissue samples and data, it will not be possible to identify and locate research participants[71] or the participants may simply decline to respond to repeated requests for new consent.[72] Indeed, there is a danger that the participants will develop "consent fatigue" or simply prefer from the outset not to receive extensive information on the use of their tissue samples and data.[73]

Another challenge to achieving informed consent for biobank projects implementing open science data access policies is that fact that group consent has become an important feature of the process, particularly for population-based genetic studies involving large-scale biobanking. In light of controversy surrounding the Human Genome Project's effect upon historically disadvantaged groups, researchers now encourage collective debate before a project begins and individual consents are secured. Indeed, some bioethics committees now recommend such debate. Organising these debates is a complex affair that can even affect the research protocol by incorporating the views of the individuals or groups consulted.[74]

In addition to the challenge of attaining informed consent for research participants who contribute to open access biobanks, there is also the difficulty of ensuring the privacy of those research participants and the confidentiality of their data. In particular, protections must be established in order to prevent discrimination against the

[68] Blanket consent suggests that there are no restrictions placed on the scope and duration of the consent, and "can never be fully informed". Lunshof et al. (2008), p. 408 (citation omitted).

[69] Cambon-Thomsen (2004), *supra* note 14, p. 869.

[70] *Ibidem*.

[71] See Lunshof et al. (2008), *supra* note 68, p. 408.

[72] See Elger and Caplan (2006), *supra* note 16, p. 662.

[73] See Cambon-Thomsen (2004), *supra* note 14, p. 869 (citation omitted).

[74] *Ibidem*.

research participants and to make certain that their medical and personal information is not disclosed to third parties, such as their family or community members, employers, or insurance companies.[75]

Paradoxically, the imperatives of informed consent and the protection of privacy and confidentiality conflict directly with one another. While privacy and confidentiality are best preserved through anonymised data, meaning data for which the link between the sample and data has been irreversibly severed from the identity of the individual research participant,[76] maintenance of the link between the research participant and his or her sample or data is essential in order to permit the research participant to control the use of that sample.[77]

An example of the risks to patient privacy and confidentiality arising from samples and data that retain their link with an individual research participant arose in the case of the implementation of the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS),[78] which took effect on 25 January 2008.[79] One of the major goals of this data sharing policy is to facilitate broad access to data through the creation of a centralized data repository.[80] Pursuant to the policy, all investigators who were funded by the NIH to conduct analyses of genetic variation were expected to submit descriptive information about their studies to an open access portion of the NIH GWAS data repository.[81] Such information included the research protocol, questionnaires, study manuals, variables measured, and other supporting documentation.[82] Also available on the open access portion of the repository were summary-level information and aggregate genotype data, including "allele frequencies by case–control status, association tests odds ratios, and p values for each SNP in the scan".[83] In addition, the NIH encouraged researchers to submit to the repository personal information such as individual-level genotypic and phenotypic data; exposure to drugs and environmental factors; and pedigree data, including information about familial relationships, along with analyses of such data.[84] This more personal data was made available to researchers and

[75] *Ibid*., p. 871.

[76] *Ibid*., p. 869.

[77] *Ibid*., p. 871.

[78] See *supra* note 44 for a definition of a GWAS.

[79] Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS), 72 Fed. Reg. p. 49, 294 (August 28, 2007).

[80] *Ibid*., p. 291.

[81] *Ibid*., p. 295.

[82] *Ibidem*.

[83] National Institutes of Health, Modifications to Genome-Wide Association Studies (GWAS) Data Access 1, available at http://grants.nih.gov/grants/gwas/data_sharing_policy_modifications_20080828.pdf (August 28, 2008).

[84] Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS), 72 Fed. Reg. p. 49, 295. One reason for posting the genotype–phenotype association measures, aside from allowing cross-checking of the data, was "to discourage premature patent claims by placing the phenotype and genotype data and first-line analysis in the public domain". The GAIN Collaborative Research Group (2007), *supra* note 46, p. 1049.

investigators at both domestic and foreign academic and commercial institutions, pending approval by an NIH Data Access Committee (DAC). Such committees were composed of federal staff possessing expertise in the relevant disciplines and were empowered to consult outside experts as necessary.[85]

In order to minimise risks to the privacy and confidentiality rights of research participants, the NIH required that data submitted to the NIH GWAS data repository would be "de-identified and coded".[86] Pursuant to this policy, the institution submitting the data would remove the names and other identifying information from the data, replacing it with a random, unique code that was to be held by the submitting institution.[87]

However, notwithstanding the de-identification procedure, it is not possible to completely de-identify genetic data. The danger is greater when the data is made publicly available.[88] As the NIH, itself, acknowledged during the public comment period for its Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies:

> [T]echnologies available within the public domain today, and technological advances expected over the next few years, make the identification of specific individuals from raw genotype–phenotype data feasible and increasingly straightforward. For example, someone might be able

[85] Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS), 72 Fed. Reg. at 49, 296; Nat'l Insts. of Health, NIH Points to Consider for IRBs and Institutions in Their Review of Data Submission Plans for Institutional Certifications Under NIH's Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) 7, available at http://grants.nih.gov/grants/gwas/gwas_ptc.pdf (2007).

[86] Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS), 72 Fed. Reg. at 49, 295.

[87] *Ibidem*. De-identification "means that the identities of data subjects cannot be readily ascertained or otherwise associated with the data by the repository staff or secondary data users []; the 18 identifiers enumerated [in the HIPAA Privacy Rule] are removed; and the submitting institution has no actual knowledge that the remaining information could be used alone or in combination with other information to identify the subject of the data". *Ibidem*. The 18 identifiers that must be removed pursuant to HIPAA include names; addresses; dates relating to the individual (such as birth date and date of admission to the hospital), except for the year; telephone and fax numbers; email addresses; social security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; URLs; Internet Protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images and any comparable images; and any other unique identifying number, characteristic, or code. 45 C.F.R. para 164.514(b)(2)(i) (2007).

[88] See Lin et al. (2004), p. 183 ("If someone has access to individual genetic data and performs matches to public SNP data, a small set of SNPs could lead to successful matching and identification of the individual"). See also Lowrance and Collins (2007), p. 602 (stating, with respect to protecting information privacy for genomic research subjects that, "[o]nly rarely will a completely open access model be defensible when sufficient amounts of genomic data are present to be unique to the individual").

> to compare information in the GWAS database with genotype or phenotype information obtained from other, unrelated activities and be able to classify the individual who is the source of the data (or a blood relative of that individual). If the data come from a discrete population (e.g., one small community), it could be more straightforward to cross classify individuals on several variables and make inferences about the source of a given sample.
> In addition, discussions are occurring in the scientific community and among privacy experts about the uniqueness of individual genome-wide data and the possibility that in the future such data may by itself become identifiable.[89]

Ultimately, eight months after the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) took effect in January 2008, the NIH removed from its publicly available GWAS database aggregate genotype data for GWAS studies, instead making this data available only through the controlled Data Access Committee process.[90] This policy change resulted from research published in August 2008 demonstrating that new DNA analysis methods render it possible to determine whether an individual's genetic sample was present in a sample that might contain DNA from as many as one thousand people. This is achieved by comparing the publicly available data with genomic data for that specific individual derived from another source.[91] However, by the time the NIH removed the aggregate GWAS data from its publicly available database, the data had been downloaded at least 140 times, and there was no way to retrieve or prevent the circulation of the information already released.[92]

Experts have offered several technical and policy approaches to preserve patient privacy. They recommend, inter alia, the establishment of policies to assess credentials of data users; the execution of clear contracts with data users that define the appropriate use of data; formalisation of liability rules for misuse of data; and the use of a technical data management approach that increases the number of research participants whose data will be aggregated where the data is considered more sensitive.[93] Such policies are quite compatible with a restricted access biobanks, as discussed in paragraph 7 *infra*.

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[89] National Institutes of Health, NIH Points to Consider for IRBs and Institutions in Their Review of Data Submission Plans for Institutional Certifications Under NIH's Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) 4, http://grants.nih.gov/grants/gwas/gwas_ptc.pdf (November 12, 2007) (citation omitted).

[90] See National Institutes of Health, Modifications to Genome-Wide Association Studies (GWAS) Data Access 1, http://grants.nih.gov/grants/gwas/data_sharing_policy_modifications_20080828.pdf (August 28, 2008).

[91] See Homer et al. (2008), http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000167.

[92] See Felch (2008), p. 31.

[93] Malin et al. (2010), p. 15.

10.5 Resolving Issues Involving Commercialisation and Benefit-Sharing

Closely tied to the requirement of informed consent are difficult questions surrounding the degree of commercialisation of innovations derived from biobanked tissue and data, as well as the development of benefit-sharing policies. These issues are particularly salient in light of the growing commercialisation of academic research.[94] In particular, open science must resolve questions regarding the involvement of private companies in commercialisation, the ownership of the genetic material and data, and the appropriate level of financial gain for participants, if any.

The private sector has become deeply involved in the collection and analysis of medical and genetic information, both independently and through partnerships with government or research institutions that share information with the private sector, as evidenced by the Icelandic model.[95] In Iceland, the private US firm Decode Genetics was granted an exclusive license to the Icelandic Health Sector Database, a national medical records database for genetic research.[96] This approach turned out to be quite controversial, and the public remained unconvinced that the promise of free drugs and diagnostics during the patent period to participants, along with the creation of jobs in Iceland, was sufficient recompense in exchange for access to the country's medical records. What is more, the DeCode Genetics project raised numerous concerns regarding the validity of informed consent, privacy, and lack of community involvement.[97] For these reasons, among others, DeCode Genetics filed for bankruptcy in November 2009.[98]

In contrast, no single company has exclusive access to the UK Biobank. Instead, samples and data are held in "custodianship" or "stewardship" by the research governance bodies.[99] Nonetheless, UK Biobank certainly envisages that data will be available to commercial companies, which might secure intellectual property rights.[100]

With respect to benefit-sharing, under US law, courts have denied research participants any property right in bodily tissue and genetic information.[101] In declining

[94] See *supra* notes 42–43 and accompanying text.

[95] See Bregman-Eschet (2006), *supra* note 17, p. 11.

[96] See Haddow et al. (2007), p. 274.

[97] See Simon (2009), http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1413951.

[98] Wade (2009), para B2. For further discussion of some of the reasons for DeCode's failure, see Tomasson (2009), p. 247.

[99] See UK Biobank, Ethics and Governance Framework 3, http://www.ukbiobank.ac.uk/docs/EGFlatestJan20082.pdf (October 2007).

[100] See UK Biobank, Ethics and Governance Framework 18, http://www.ukbiobank.ac.uk/docs/EGFlatestJan20082.pdf (October 2007).

[101] See Moore v. Regents of the Univ. of Cal., 51 Cal. 3d 120, 134–47 (Cal. 1990), cert. denied, 499 U.S. 936 (1991); Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1074–76 (S.D. Fla. 2003); Washington Univ. v. Catalona, 490 F.3d 667, 675 (8th Cir. 2007), cert. denied, 552 U.S. 1166 (2008). Indeed, courts have denied a property right even in the absence of proper informed consent to the research subject. See Moore, 51 Ca. 3d at 131–33.

to recognise such rights, courts have cited inefficiencies and transaction costs associated with recognising an individual's property rights in his or her biological contributions.[102] Judicial denial of claims by research participants of property rights in their tissue and corresponding data, may, however, decrease public trust in biomedical research and discourage individuals from participating in such projects.[103] Thus, open access might be considered a boon in terms of encouraging public participation in biomedical research. If we posit that one reason that research participants contribute to biobanks is in order to promote public health, then one significant motivation to participate may be the fact that the database permits open access.[104]

More recently, however, patient groups such as PXE International have established tissue and data banks and negotiated directly with researchers binding agreements that entitle them to manage intellectual property rights arising from the research results, so as to ensure the availability of diagnostics and therapeutics at reasonable prices.[105] Patient groups also seek to coordinate collaboration among researchers and to minimise concerns about the potential negative impact of collaboration upon funding and publications.[106] This patient group-as-advocate model is harder to implement in an open access context, since the ability of a patient group to negotiate directly with the investigators on behalf of its members is necessarily diminished, especially where the research participant data is de-identified in order to preserve privacy and confidentiality.

In terms of benefit-sharing with research participants, one approach that avoids the unseemly appearance of commodifying human tissue samples is the provision of free genetic analyses and information about relevant discoveries to those participants. For example, the nonprofit Coriell Personalized Medicine Collaborative, which deposits the personal health data it collects in a national database maintained by the NIH,[107] offers research participants personalised information about their risk of being affected by certain genetic conditions.[108] Commercial biobanks can also offer research participants their commitment to license drugs and diagnostics discovered using donated samples non-exclusively, thereby promoting affordability of such medical

[102] See Moore, 51 Cal. 3d at 143–47.

[103] See Gitter (2004), p. 298.

[104] Cf. *ibid.*, p. 260 (noting that the plaintiff parents in Greenberg v. Miami Children's Hosp. Research Inst., Inc. has premised their research participation on the belief that their contributions would promote widely affordable and accessible carrier and prenatal testing for Canavan disease).

[105] See *ibid.*, pp. 262–263 and 320; *see also* Terry et al. (2007), p. 157.

[106] *Ibid.*, p. 162.

[107] See Coriell Personalized Medicine Collaborative, Technical Paper, http://cpmc.coriell.org/Docs/PDF/cpmc_technical_paper.pdf (April 22, 2009).

[108] See Coriell Personalized Medicine Collaborative, Consent to Participate in a Research Study 7, http://cpmc.coriell.org/Docs/PDF/Informed_Consent.pdf (last visited March 21, 2010).

advances,[109] or offer to donate a percentage of the proceeds from patentable products to the health care infrastructure within the community.[110]

10.6 The Challenge of Establishing a Suitable Infrastructure and Defraying the Costs of Access

Even if data producers and research subjects embrace open science biobanking, another impediment to data-sharing is the lack of infrastructure to house the data, creating what one expert has termed "a chicken and egg problem".[111] Among the costs associated with creating a suitable infrastructure to house and maintain the data and any associated physical specimens are the maintenance of physical premises; the development of appropriate information technology; the preparation of data for storage or archiving, such as anonymising the data and documenting the variables; salaries for administrators, managers, and staff; and the creation and maintenance of an accessible database. These costs are all ongoing ones.

The infrastructure challenge is also complicated by the fact that biobank projects typically span long periods of time. Data gathered early in a project may become indecipherable over time by the latest version of database software. Thus, archives must often choose between eliminating old data or, alternatively, paying to preserve the outdated software required to read that data.[112] Moreover, pre-existing projects are frequently particularly unprepared to meet new, mandatory open data access requirements, which are often imposed without any concomitant funding or support.[113]

Granting agencies understandably focus primarily on research, and therefore frequently fail to invest in the infrastructural support necessary to support their archiving requirements, in a sort of "tragedy of the commons". According to Professor Boyle, "Infrastructure is the thing that we always fail to fund because it's kind of everybody's problem, and therefore it's nobody's problem."[114] The internationally collaborative nature of biomedical research exacerbates this problem by allowing

[109] One commercial genetics company, Navigenics, has declared that it will make patented discoveries available on a "non-exclusive, non-discriminatory basis" and "[s]ubject to commercially reasonable financial and other terms" as an inducement to research participants to contribute to its work. Navigenics, Our Policy Regarding Gene Patents, http://74.125.93.132/search?q=cache:LaOd73ZxxGYJ:www.navigenics.com/visitor/what_we_offer/our_policies/gene_patents/+navigenics+universal+royalty&cd=1&hl=en&ct=clnk&gl=us (last visited March 21, 2010).

[110] See Simon (2009), *supra* note 97, p. 78.

[111] Nelson (2009), *supra* note 21, p. 162.

[112] *Ibidem.*

[113] See Gibbons (2009), p. 313.

[114] Nelson (2009), *supra* note 21, p. 162 (quoting Professor Boyle of Duke University School of Law).

each funding agency to leave the problem to another agency. Yet overcoming the infrastructure issue is crucial in order to optimise the benefits of technological progress in the life sciences. Taking human genome sequencing as one example, one source estimates that the cost of storing all known DNA sequence information in openly accessible databases costs less than one percent of the sum necessary to generate such sequence data.[115] In order to defray the operational and associated administrative costs, many biobanks currently charge modest access fees.[116]

The national governments in Europe and the United States have been investing public funds to address the need for infrastructure to support open access data-sharing for big science projects. In Europe, an important project underway is the European Life Science Infrastructure for Biological Information (ELIXIR), a program of the European Bioinformatics Institute, which is part of the European Molecular Biology Laboratory (EMBL-EBI).[117] The mission of ELIXIR is "to construct and operate a sustainable infrastructure for biological information in Europe to support life science research and its translation to medicine and the environment, the bio-industries and society".[118] Another important European initiative is the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), which seeks to coordinate major existing European biobanks and establish clear rules of access to foster exchange of biological materials and data among them.[119] In the US, the National Center for Biotechnology Information, part of the NIH, has been charged with creating and maintaining biomedical databases.[120] These resources, which often collaborate with one another, provide a place to archive, retrieve, search, and manipulate the data they house. However, as noted by one expert, there are challenging questions of scale for such ventures as biomedical data becomes a public good and is therefore expected to be available for use to researchers worldwide to advance the goal of public health.[121]

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[115] European Life Science Infrastructure for Biological Information, ELIXIR: Data for Life, http://www.elixir-europe.org/bcms/elixir/Documents/Elixir_brochure.pdf (last visited March 22, 2010).

[116] See Lowrance (2006), *supra* note 19, p. 35.

[117] EMBL-EBI is a European nonprofit bioinformatics research centre which aims to "provide freely available data and bioinformatics services to all facets of the scientific community in ways that promote scientific progress". EMBL-EBI, Welcome to the EBI, http://www.ebi.ac.uk/Information/ (last visited March 23, 2010).

[118] ELIXIR, Project Information, http://www.elixir-europe.org/page.php?page=information (last visited March 23, 2010).

[119] Biobanking and Biomolecular Resources Research Infrastructure, Background, http://bbmri.eu/index.php/about-bbmri/background (last visited March 23, 2010).

[120] National Center for Biotechnology Information, NCBI at a Glance, http://www.ncbi.nlm.nih.gov/About/glance/ourmission.html (revised 21 May 2004).

[121] Nature Opinion Forum: Prepublication Data Sharing: The Toronto Statement, http://network.nature.com/groups/naturenewsandopinion/forum/topics/5433 (Ewan Birney, Senior Scientist at the European Molecular Biology Laboratory working at the European Bioinformatics Institute) (September 11, 2009).

10.7 A Consideration of Restricted Access Biobanks

Commentators have observed that promulgation of open access to biobanks "may not result in greater and more rapid scientific benefits", but instead "result in duplication of effort, cause problems in the peer review system and create incentives for generating more publicly inaccessible databases, while reducing the number of biotechnology spinoffs from funded studies that require rapid data sharing".[122] These commentators note that such unintended negative effects are to be expected, particularly in the short term, since researchers have established over the years numerous formal and informal practices with respect to data sharing, including co-authorship credit and limits on further use of the data.[123]

Other scholars have therefore urged consideration of "fair access" or restricted access models, which build upon the collaborations already established by scientific researchers.[124] One such biobank is the UK DNA Banking Network (UDBN), which is a secondary biobank, meaning, it aggregates and manages tissue samples and associated data gathered by clinicians who gather the samples in the course of studying particular diseases.[125]

In order to establish UDBN, the UK Medical Research Council[126] offered grants to centers that housed DNA collections. These awards required the collections to be maintained as "shared national resources", and "made available to collaborators". In addition, awardees were "required to transfer a portion of each sample" to the network and "to add any genotype data they obtain to the common database".[127]

In granting access to its collections, the UDBN explicitly rejected the unrestricted "open access" model, instead developing a "fair access" regime, which derives inspiration from the 2003 United Nations Educational Scientific and Cultural Organization (UNESCO) International Declaration on Human Genetic Data.[128] The UDBN distributes data via the project website to third party researchers, who apply online for registration. After verifying the researcher's credentials, UDBN grants access to a restricted area of the website. The third party researchers can then communicate online with the data collectors in order

[122] Foster and Sharp (2007), p. 635.

[123] *Ibid*., pp. 635–636.

[124] See Yuille et al. (2009), http://www.springerlink.com/content/l1082h68g0645517/fulltext.pdf; see also Reichman and Uhlir (2003), *supra* note 12, p. 433 (stating their view that, "the possibilities for maximizing access to scientific data for the public nonprofit research will not be fully realized in a highly protectionist legal and economic environment unless the scientific community agrees to experiment with suitably regulated conditional deposits") (citation omitted).

[125] See Yuille et al. (2009), *supra* note 124, p. 2.

[126] See *supra* note 51 and accompanying text.

[127] Yuille et al. (2009), *supra* note 124, p. 3.

[128] *Ibidem*. According to this Declaration, "States should regulate the cross-border flow of data and samples so as to foster international . . . cooperation and ensure fair access". Workshop on Ethics and Governance in Biobanking 16, available at http://www.oncoreuk.org/downloads/CCB%20Ethics%20Governance%20Workshop%20monograph.pdf (January 2009).

to negotiate collaboration. If a collaborative relationship is successfully negotiated, UDBN permits the data collector to grant the third party access to fuller data.[129]

The fair access model builds upon researchers' willingness to share data with collaborators, and concomitantly denies access to non-collaborators.[130] This approach also accepts a collector's right to "exclusive access to his/her collection for the purposes of the investigational goals stated in the initial collection proposal", recognising that granting a "first mover" advantage is likely to motivate scientific discovery.[131] This model also acknowledges that tensions frequently arise when a potential collaborator requests data access from a data producer.

Secondary biobanks such as UDBN also offer the potential to provide other services to assist with scientific exchange. For example, they can help in negotiating and drafting contractual templates and also mediate between the parties to the agreement.[132]

Moreover, a group of highly esteemed academics has noted that what they term "restricted access databases", meaning databases that require authentication so that only bona fide researchers can obtain access, may be better suited to preserve privacy and confidentiality with respect to genomic databases, if the level of restriction and degree of oversight are sufficient. These scholars observe that a restricted access system permits the database to provide some phenotypic information linked to the genotypic data, thereby enhancing the scientific value of the data.[133]

In the field of epidemiology as well, scholars suggest that it would be beneficial to distinguish the roles of primary investigators, meaning those who gather data and may analyse it, and secondary investigators, who only analyse it, in light of the current research climate. As noted by Professor Samet of the Johns Hopkins Bloomberg School of Public Health, the NIH is increasingly restricting funding for new population studies. Thus, sharing of data from large, publicly-funded studies is essential, and requires careful balancing of the needs of primary and second investigators.[134]

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[129] See Yuille et al. (2009), *supra* note 124, p. 6.

[130] *Ibid.*, p. 4.

[131] *Ibidem.*

[132] *Ibidem.* See also Reichman and Uhlir (2003), *supra* note 12, p. 438 (noting that an external entity operating under the guidance of the affected funding agencies and academic institutions can help with negotiation, mediation, and even dispute resolution with respect to data sharing).

[133] Caulfield et al. (2008), http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.0060073. See also *supra* note 93 and accompanying text (describing one expert's suggestions to preserve research participant privacy via the establishment of policies to assess credentials of data users; the execution of clear contracts with data users that define the appropriate use of data; and formalisation of liability rules for misuse of data, all of which are particularly compatible with a restricted access approach).

[134] Samet (2009), p. 174.

10.8 Conclusion

Sharing of biotechnological data is particularly important in light of the fact that many results of biotechnological research, such as an isolated human DNA sequences, cannot be "invented around", meaning, there is no true substitute for them. Notwithstanding the focus of "big science" on open source biotechnology, there are several challenges to widespread application of open source principles to biobanks. These include the reluctance among researchers to share their data, the challenge of crafting appropriate publication and intellectual property policies, the difficulties in affording informed consent, privacy, and confidentiality to research participants when data is shared so widely, controversy surrounding the issues of commercialisation and benefit-sharing; and the complexity of establishing a suitable infrastructure.

For "small science" projects in particular, restricted access projects appear promising. This is especially true for secondary biobanks, which aggregate and manage tissue samples and associated data gathered by clinicians who gather the samples in the course of studying particular diseases. Restricted access biobanks build upon the informal collaborations established by such researchers, and, as the networks widen, pave the way for wider sharing in the future.

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Chapter 11
Beyond Open Source: Patents, Biobanks and Sharing

E. Richard Gold and Dianne Nicol

Abstract With the increasing importance of collaborative structures to overcome decreasing productivity in pharmaceutical innovation, biobanks have taken on greater importance. This chapter examines the specific ways in which the appropriate use of patents and other intellectual property within biobanks can facilitate these collaborations. As biobanks involve both data and physical materials over which not only intellectual property rights—chiefly, copyrights and patents—but also privacy rights exist, they provide a challenge to governance. This chapter examines two mechanisms that aim at the broadest dissemination and use of biobanks: open source and open access. While open source governance offers significant openness, it presents difficulties in adopting to change over its life. Open access is more flexible but requires significant norm development within the scientific community.

11.1 Introduction

As the costs of drug discovery grow exponentially, innovation has at best remained stable[1] or, at worst, is in decline.[2] Over the last decade, estimates of the costs of bringing a single drug to market have increased by an order of magnitude, from several hundred million dollars to several billion.[3] Meanwhile, a study found that the rate of introduction of new drug molecules has not changed over the past 60

[1] Munos (2009), p. 959.

[2] Gagnon (2009).

[3] Munos (2009), *supra*, note 1.

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years.[4] If one takes into account the decreasing quality of the innovation represented by new molecules, one comes to the sobering realisation that real innovation levels are in decline.[5] If these trends continue, we can expect not only fewer new drug innovations, but also the prospect of paying much more for the few breakthrough medicines that are actually introduced. This has industry and policy-makers concerned.[6]

The reasons for the increasing inefficiency in drug discovery are complex but include, among other factors, declining productivity from the traditional screening methods that led to the pharmaceutical boom in the 1960s[7] and rising regulatory standards. Increasing reliance on fundamental biology and a rise in the types and numbers of actors involved in innovation also contribute to lower productivity.[8] A change in the way that researchers and firms go about drug discovery is inevitable. In particular, there is a growing recognition that greater reliance on research collaborations and data sharing are necessary to increase productivity.[9] Collaborations bring together individuals and institutions possessing different skills and knowledge sets, opening up opportunities for creative approaches to drug discovery.[10] Data sharing allows for the more efficient deployment of resources by avoiding duplication of research and the use of standard software tools. Together, collaborations and data sharing offer important tools to rationalise the cost in time and money of drug discovery.

11.2 Biobanks as Collaborative Research Mechanism

Biobanks represent one mechanism that joins collaboration with data sharing. Biobanks combine collections of human tissue linked with genetic information and other health information.[11] A 2003 law reform report in Australia provides a useful indication of the wide variety of potential research uses of biobank resources (or human genetic research databases, the term used in the report), including the following: "[L]inkage studies to identify the gene sequences associated with inherited diseases; association studies to find correlations between a disease and a genetic change where there is no obvious pattern of inheritance; genetic epidemiology studies of the interaction between genes and environment; and

[4] *Ibidem*.

[5] Gagnon (2009), *supra*, note 2.

[6] International Expert Group on Biotechnology, Innovation and Intellectual Property (2008).

[7] Temin (1979), p. 429.

[8] International Expert Group, *supra* note 6.

[9] Munos and Chin (2009) and OECD (2010).

[10] See, for example, the SAGE Commons at http://sagebase.org/commons/background.php (accessed 6 December 2010).

[11] OECD (2006), p. 35.

pharmacogenetic studies to determine if there is a genetic basis for certain adverse reactions to drugs".[12]

Various types of biobanks are already in existence and more are being established around the world. Some are targeted to particular disease groups, whereas others are intended to be more representative of whole populations.[13] Significant funds are being invested in large-scale population biobanks in a number of jurisdictions, examples of which include the UK Biobank,[14] and CARTaGENE[15] in Quebec, Canada. One key feature of all biobanks is that they are intended to be used as tools for future research.[16] While some of the smaller collections are only likely to be used by the individual research teams that created them, in general, biobanks are intended to be used for a wide variety of research projects by multiple research teams, some of whom may not even be in the same physical jurisdiction as the biobank. It is also almost inevitable that commercial partners will become involved at some stage to facilitate the translation of research into clinical practice and the development of new drugs and therapies. This will be especially true as research focuses on linkages between particular diseases, health and genetic information. In addition, some biobanks themselves have been established by commercial operators.[17]

Despite their utility and efficiency, the construction of biobanks raises a number of difficult ethical, legal and practical issues. These include, according to Kaye, "consent, especially for secondary research purposes; feedback to participants; benefit sharing the public interest; participation in decision making; protecting privacy; access; ownership; and intellectual property rights".[18] While Kaye notes that not all of these issues relate to all biobanks, some combination of them does. Resolving these issues—the subject of other chapters in this book—is critical to enable biobanks to meet the goal of accelerating drug development.

The narrow contribution of this chapter is to examine the specific ways in which the appropriate use of patents and other intellectual property within biobanks can facilitate collaborations aimed at developing new medical treatments. Recognising the variety of possible biobanks, both in terms of content and use, this chapter will compare two mechanisms that have been discussed through which to govern intellectual property. The goal of this comparison is to illustrate how intellectual property and institutional structure combine to address (or deepen) ethical, commercial and societal concerns. The first mechanism is an open source model based on the use of property and intellectual property rights licensed in such a manner as to ensure that

[12] Australian Law Reform Commission and Australian Health Ethics Committee (2003), p. 472.
[13] Kaiser (2002), p. 1158.
[14] http://www.ukbiobank.ac.uk/ (accessed 1 December 2010).
[15] http://www.cartagene.qc.ca/ (accessed 1 December 2010).
[16] NHMRC (2010), p. 7.
[17] Anderlik (2003), p. 203.
[18] Kaye (2005), p. 246.

everyone can use materials and knowledge subject to only minimal restrictions.[19] The second mechanism is an open access/free revealing model in which patent rights are, for the most part, eschewed in favour of governance structures and normative ordering between those who generate and use knowledge.[20] However, before examining these models, we review in more detail the historical and ethical contexts within which they need to be placed.

11.3 Historical Tensions Between Data Sharing and Intellectual Property

Since the start of the Human Genome Project (HGP) more than 20 years ago, there has been an exponential increase in the quantity of raw biomedical data available for research purposes. In isolation, each individual data set generated by a single research team in its own laboratory may be of limited value. When amalgamated, the data being generated can be used both to answer some of the most fundamental questions in modern-day science and as research tools in the development of new diagnostics, drugs and therapies aimed at alleviating human suffering caused by disease. It is little wonder that there is a groundswell of support for banking and sharing of biomedical data within the research and policy communities, not just between laboratories in the same location but in a way that transcends national boundaries. In the international policy arena, for example, UNESCO's *Universal Declaration on the Human Genome and Human Rights* provides: "States should make every effort, with due and appropriate regard for the principles set out in this Declaration, to continue fostering the international dissemination of scientific knowledge concerning the human genome, human diversity and genetic research and, in that regard, to foster scientific and cultural co-operation, particularly between industrialized and developing countries".[21]

This statement is endorsed in other international policy documents directed specifically towards publicly funded research. For example, the stated aims of the OECD *Principles and Guidelines for Access to Research Data from Public Funding* are to promote a culture of openness and sharing of research data, to stimulate the exchange of good practices in data access and sharing and to raise awareness about costs and benefits of restrictions and limitations on access to and sharing of research data from public funding.[22]

The research community itself has embarked on an active program of data sharing, particularly for large-scale datasets of aggregated, anonymised genetic data. The classic example of this data sharing paradigm is the "Bermuda Rules" for access

[19] Hope (2008).

[20] Edwards (2008), p. 731; Weigelt (2009), p. 941.

[21] UNESCO, Universal Declaration on the Human Genome and Human Rights, 29th Sess, 29 C/Res 16 (1997), Article 18.

[22] OECD (2007).

to HGP sequencing information, agreed to by all parties involved in the international public sequencing effort in 1996. Specifically, it was agreed *inter alia* that all human genomic sequence information generated by centres funded for large-scale human sequencing should be freely available and in the public domain in order to encourage research and development and to maximise its benefit to society.[23] Subsequently, the same commitment to data sharing has been made for other large-scale data generating projects, including the HapMap Project[24] and the 1000 Genomes Project.[25] In addition to the scientific benefits likely to arise out of rapid release of information, it also has the potential to provide broader public benefit by facilitating the development of new drugs, diagnostics and therapies.[26]

Broad sharing of large reference databanks across the fields of biology and medicine was endorsed at a workshop in Toronto in 2009.[27] Funding agencies also support data sharing. For example, the 2008 US NIH *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies* (GWAS) requires that datasets remain available to all investigators, unencumbered by intellectual property claims.[28] This last statement hints at one of the major concerns for researchers and policy makers involved in large-scale biomedical data generation: that intellectual property rights could encumber the global research endeavour by deterring or preventing sharing of data.

The early stages of the sequencing effort associated with the HGP coincided with increased availability of patents in the biomedical sciences and a surge in applications for gene-related patents.[29] At that time, the US National Institutes of Health (NIH), one of the lead organisations in the HGP, was itself actively engaged in a program of mass filing of gene sequence patent applications.[30] In a significant policy shift, many of these applications were subsequently withdrawn[31] and the NIH became one of the most active proponents of open access, as ultimately endorsed by the public sequencing consortium as a whole with the Bermuda Rules. Even more recently, the United States Department of Justice, which sets the ground rules for US agencies including the NIH, has taken the position that genomic human DNA sequences are not patentable under US patent law.[32]

In contrast to the rapid release of sequence information by the public sequencing consortium, private sequencing efforts that were being conducted in parallel were

[23] HUGO (1996).

[24] International HapMap Consortium (2004).

[25] http://www.1000genomes.org/ (accessed 1 December 2010).

[26] See, for example, International HapMap Consortium, *supra* note 24, p. 473.

[27] Toronto International Data Release Workshop Authors (2009).

[28] NIH, 2008b. See also Gitter (2010), p. 14.

[29] Barton (1999), p. 3; Eisenberg (2002), p. 1381.

[30] Eisenberg (1992), p. 903.

[31] See Hope (2008), *supra* note 19 at 38. See also Simon (2009), p. 67.

[32] Department of Justice, amicus brief filed in Association of Molecular Pathology v. United States Patent and Trademark office and Myriad Genetics Inc.

characterised by the protection of sequence information through intellectual property rights in the form of patents, confidentiality and copyright, and in reliance on specific data protection legislation in some jurisdictions as well as contractual restrictions. Companies, including Celera Genomics, Incyte Genomics and Human Genome Sciences, focused their research efforts on automated sequencing of many thousands of DNA fragments and sought to protect their findings by filing large numbers of patents.[33] These private sequencers predicted that they would make large profits out of licensing their patents and making their databases available to subscribers. It was assumed that their databases would be attractive to researchers because of their added value in the form of annotations to the sequence information.[34]

Ultimately annotated sequence databases turned out to be less attractive to the research market than originally thought, largely because so much sequence information was already freely available.[35] The anticipated market value of patents claiming sequence rights also appears to have steadily decreased over time. Perhaps the most relevant factor in their slow demise is the ongoing uncertainty as to their validity. The issue of whether gene sequences are patentable subject matter at law remains unresolved by the courts and the legislatures in some key jurisdictions.[36] However, the requirement to show that an invention has utility is now more difficult to satisfy for gene-related inventions in the US following clarification of their examination guidelines in 2001,[37] and satisfaction of the novelty, inventive step and other patent requirements is becoming more onerous in many jurisdictions.[38] Added to this, there are particular challenges in policing patent infringement in the research context. The extent to which unauthorised research and diagnostic uses of gene patents are exempt from infringement actions remains uncertain[39] and there may be exposure to negative publicity when patent rights are rigorously enforced, particularly against public sector organisations.[40]

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[33] See Sulston and Ferry (2002).

[34] Sir John Sulston aptly refers to this as the "goldrush mentality". *Ibid*., p. 109.

[35] For a brief account of the circumstances surrounding these events see Hope (2008), *supra* note 20, p. 38.

[36] In the United States, the ongoing litigation over Myriad Genetics, Inc.'s patents over BRCA1 and BRCA2 continue to leave open the question of the patentability of human genetic sequences. See *Association for Molecular Pathology, et al. v. United States Patent and Trademark Office, et al.*, 653 F.3d 1329 (Fed. Cir., 2011). In Australia, litigation relating to the equivalent Australian patents was instituted by Cancer Voices Australia in July 2010. See http://www.cancervoicesaustralia.org.au/news.htm (accessed 1 December 2010). In Europe, this same state of uncertainty does not seem to apply given the contents of *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions* (2008) 213 OJ L 13.

[37] See Nicol (2005), p. 833.

[38] Hopkins et al. (2007), p. 185.

[39] Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) (2010), p. 4, recommending research and diagnostic use exemptions from infringements be introduced into US patent law.

[40] Gold and Carbone (2010).

The proprietary approach to DNA sequencing largely sowed the seeds for the open innovation movement. The NIH open access policy and the Bermuda Rules were reactive responses to concerns within the sequencing community about gene patents. There are obvious advantages to be gained by putting sequence information in the public domain: first, it reinforces the norm of open science; secondly, it devalues competing proprietary sequence databases; and thirdly, it effectively excludes the patenting option until some additional step is taken.

11.4 Tensions Between Data Sharing, Material Transfer and Privacy

The situation becomes more complex for biobanks because they include tangible materials as well as data. It has been common practice in biomedicine to share vectors, reagents and other materials. However, interviews conducted by John Walsh and colleagues in 2004–2005 suggest that biomedical researchers frequently encounter difficulties in accessing such materials, particularly because of the requirement to enter into formal material transfer agreements (MTAs).[41] There is also other evidence of increasing reluctance to share materials.[42]

When human tissue is the material that is being accessed, the complication intensifies. The question of whether donors have property rights in their own tissue remains legally uncertain and ethically contentious.[43] However, this does not mean that tissue donors have no say whatsoever as to whether their tissue can be used for research purposes and who can use them. On a practical level, donors are unlikely to be willing to voluntarily participate in biomedical research unless they receive some assurance that the tissue they donate or make available for research purposes will be used, stored, and disposed of in a way that protects their dignity, privacy and autonomy. That is, material donors are becoming more sophisticated and will simply refuse to allow doctors access to their materials unless those physicians agree to their terms. Unencumbered open access to tissue collections is unlikely to satisfy donors that due respect will be given to these matters.

Aside from the complication of tissue, concerns have also been raised about the privacy implications of broad sharing of data arising from technological advances in bioinformatics. A Fact Sheet distributed by the US NIH in 2008 states that: "bioinformatics techniques have progressed to the point that with enough genomic data on an individual from another source, it is now possible to determine whether that individual participated in a study by analyzing only the pooled summary data".[44] As a result, the GWAS policy of open access was modified. Individual-

[41] Walsh et al. (2005).

[42] Blumenthal et al. (2006).

[43] See, for example, Rao (2007).

[44] NIH (2008a).

level data (including both genotypes and phenotypes) are now subject to a controlled access regime, whereas summary-level information and aggregate genotype data remain openly accessible.[45] While initially drafted in the context of bio-informatics, the same policies would apply to biobanks in general. What this means is that, realistically, it would be almost impossible to follow a truly open philosophy for resources that include personal information and tissue and this needs to be borne in mind in the analysis of open source and open access biobanking that follows.[46]

11.5 Open Source Biobanks

In information technology, open source software licensing relies on property rights attached to copyright in software to impose enforceable conditions that include viral clauses that require the propagation of openness in successive generations. A number of commentators have posited that open source-style licensing could be translated into biotechnology, using a combination of intellectual property rights and standard contracts—usually licences but, in a modulated form, non-assert clauses—to construct a web of researchers connected through legal agreements that require sharing of materials and knowledge stored within the biobank.[47] In its traditional form, a holder of an initial set of seed technologies and/or knowledge first seeks intellectual property protection over those technologies and knowledge. With this protection in hand, the holder provides licences to all takers, the main provision of which is that anybody who takes a licence agrees to license out his or her own improvements and additions to everyone else on the exact same terms. This "viral" licence ensures that each person who makes use of the knowledge or technology keeps all incremental developments available to all subsequent users.

A softer form of open source—technically speaking, it is not open source but a cousin to it—involves the holder of the initial technology agreeing not to assert his or her intellectual property rights against subsequent users.[48] This approach does not legally require subsequent users to contribute back their improvements and additions to others as does traditional open source. Nonetheless, there may be strong norms within the research community that would generally require subsequent contributions to be similarly contributed back through a non-assert clause.

Open source works well when dealing with data or software since the cost of acquiring rights and licensing them is virtually nothing. This is not true when

[45] NIH (2008b). For another approach see: Wolfson et al. (2010).

[46] This issue is canvassed more fully in Nicol and Gold (2012).

[47] See, for example, Hope (2008), *supra* note 19; Feldman (2004); Joly (2010).

[48] See Rai and Boyle (2007).

dealing with patents. As the costs of patenting can quickly become substantial,[49] an open source framework would need to provide a mechanism to fund patent acquisition, a not insignificant problem. Open source biobanking would also need to address the privacy of tissue donors, something that runs counter to the open ethos of open source.

One further factor that differentiates biotechnology open source from its more traditional forms is the mix of intellectual property rights at stake. As Janet Hope, one of the main proponents of open source biotechnology, explains: "The challenge, then, of modeling open source licensing in biotechnology is to create new licenses that can accommodate the complexity and variety of biotechnology transfer agreements, yet remain faithful to the underlying logic of open source".[50] She acknowledges that biotechnology open source presents a problem of heterogeneity of intellectual property that traditional open source does not: "This technological heterogeneity gives rise to heterogeneous patterns of ownership. . .. Each technology is thus covered—often incompletely—by a patchwork of different protections".[51]

The heterogeneity problem applies less to software and databanks than it does to biobanks consisting of materials.[52] Open source databanks do not fundamentally differ from their software cousins: like traditional open source, these databank structures do not impose additional costs of obtaining or licensing intellectual property. Copyright—the dominant form of intellectual property right in this area—is free and the cost of developing a standard form licence relatively low. The Public Population Project in Genomics Observatory (P3G Observatory)[53] and The Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)[54] are examples of such databanks and related information depositories.

The number of biobanks adopting open source drops dramatically once one adds tangible research materials to the mix. Nevertheless, examples do exist. The Science Commons Licensing Project aims to develop a standard open framework for managing transfer of research materials including cell lines, model animals, DNA constructs and screening assays.[55] Similarly, participants in the Biobricks Project at the Massachusetts Institute of Technology have developed a Registry of Standard Biological Parts for use in synthetic biology projects.[56] The purpose of the

[49] Berrier (1995) found that, in 1995 US dollars: "[T]he total cradle-to-grave costs in the seventeen EPO countries is $134, 401, the total cost in Japan is $30, 498 and $22, 522 for a patent with ten claims and two claim respectively. The total cost in the U.S. is $14,370". These figures would be substantially higher today.

[50] Hope (2008), *supra* note 19, pp. 144–145.

[51] *Ibid*., p. 144.

[52] Joly (2009).

[53] http://www.p3gobservatory.org/.

[54] http://www.bbmri.eu/index.php/about-bbmri.

[55] http://sciencecommons.org/licensing/scmta.

[56] http://parts.mit.edu. See also The Bio Fab Group (2006); Rai and Boyle (2007).

Registry is to record and index biological parts that are currently being built and offer synthesis and assembly services to construct new parts, devices, and systems.

Materials are more difficult to fit within an open source paradigm for three principal reasons. First, materials cannot be shared as easily as data: someone must store, reproduce and handle the materials, none of which are trivial tasks. This not only involves a cost but potential liability if the material contains pathogens or are improperly stored or shipped. Second, materials may have been acquired from donors with significant limitations attached (e.g., purpose of research or obligations to share data) that the material holder must pass on to future users. Third, privacy concerns will continue to follow the materials even in the absence of donor-imposed restrictions. Since the research value of a biobank depends on the ability to link different sorts of data and material—samples, genetic information and health information, for example—it will be generally impossible to guarantee anonymity. While none of these reasons makes it impossible to construct an open source material biobank, together they considerably complicate management, increasing costs and negotiation time. What is of more concern, however, for both databanks and biobanks is the long-term viability of access rules to them and interoperability between them.

As to the first point, both types of banks are long-term resources that must respond not only to today's needs and uses but also to future uses. As new uses for old data and materials develop, older forms of licence agreements will increasingly be unsuitable. That is, old licence terms will be found to either overly constrain research or fail to address unanticipated issues of liability or use. Inevitably, there will be pressure to revise licence agreement terms to reflect the new uses. However, this presents a difficulty for the bank as much or most of its data and/or materials will have been licensed under the older contractual terms. Since it is virtually impossible to modify the terms of these older agreements—one would need the consent of every person who ever contributed any data or materials—the bank will face a dilemma: it can either continue with its increasingly inadequate old licence agreements or it can introduce a new licence agreement but only in respect of new data and materials. This makes administration not only difficult but increases the probably that a user will unintentionally violate the terms of a licence, undermining confidence in the bank itself.

Interoperability may present an even larger concern. As researchers hone in on specific subsets of genetic and health information—for example, to study specific disease/genetic combinations—even the existing large-scale biobanks will individually contain an insufficient number of data points. Researchers will need to obtain records from across several different biobanks in order to obtain a sufficiently large sample. However, there are problems in doing so beyond that of identifying the necessary data and ensuring that they measure the same phenomenon in the same manner. First, donor consent for materials or health data may be different, limiting the use of the combined data sets to the lowest common denominator. Second, licence terms may be different, further restricting use. While each individual biobank may have done a good job in drafting its open source licence agreement,

there is little chance that the different biobanks will converge on exactly the same licence. Even small differences between these licences may plague downstream use.

Overall, open source biobanks face serious practical difficulties, especially when materials are involved. Given the lack of flexibility, it may turn out to be easier to simply abandon old biobanks and start afresh then to live with the multitude of restrictions arising from different licensing, privacy and donor restrictions. This would involve a great waste of resources, not to mention the cost of establishing a new biobank.

11.6 Open Access Biobanking

Open access—also called free revealing[57] depending on the context—is similar to open source in philosophy but is very different in mechanism. Like open source, the goal of open access biobanks is to make knowledge and technology easily and freely available. Unlike open source, open access achieves this goal solely through the development and enforcement of norms within the research community rather than through the use of intellectual property rights. Like the softer form of open source, nothing legally guarantees that knowledge and technology users will contribute their improvements and additions back to the community on the same terms. However, by focusing attention on community norms, open access seeks to use informal enforcement such as membership within research consortia, access to philanthropic and government funding, and invitations to conferences and other knowledge-sharing venues to achieve similar goals. By purposely not seeking intellectual property rights, open access biobanks offer significant advantages over open source. In particular, they are much less expensive due to the lack of patent applications and patent maintenance fees and are flexible and easy to adapt as technology and uses change.

The Structural Genomics Consortium ("SGC") is an example of an open access databank. The SGC is a public-private partnership funded by government, foundations and industry that operates in the field of drug discovery. While the SGC was established to identify the three-dimensional structure of proteins—at which it has been very successful judged by the number of structures it has contributed to public databases and by the number and quality of the scientific publications it has generated[58]—the SGC has since moved into the field of epigenetics in which it is identifying and producing probes to be used as research tools. Under the SGC's open access policy, the consortium will not seek, nor permit its affiliated scientists or collaborators (including from industry) to seek patents that would grant exclusive rights over its research outputs. To ensure that users also maintain open access of their research results, the SGC is working with its

[57] Baldwin and von Hippel (2009).

[58] Weigelt (2009).

funders—major foundations and industrial partners—to agree on norms of sharing that they will enforce, through soft means, on users.

Open access aims at addressing two interrelated concerns. The first of these is that intellectual property rights increase costs and lead to inefficiencies: "The fundamental problem is that industry collectively focuses too many resources on proof-of-concept studies for too few targets, and the studies are done in a proprietary way, with little collective learning. Further, because one 'secret' failure in proof of concept is never enough to dissuade others, these studies encumber the limited resources of industry for years, thereby limiting the ability of industry to pursue new and potentially relevant drug targets".[59]

The second is that the costs of obtaining and licensing intellectual property can be so high as to divert resources away from research and toward applying for and managing intellectual property. This concern applies not only to traditional proprietary models of innovation but also to open source. The costs involved include not only the direct costs of patenting, but in maintaining the secrecy of knowledge until a patent is filed (in order to meet patent law requirements), establishing and updating open source licences, and managing knowledge contributed under different open source licences which can quickly result in an intellectual property thicket of its own.

Open access would seem, therefore, a better fit for biobanks than does open source. Because open access solves the problems of licence term revision and of interoperability, open access strategies can evolve with science and technology practices and permit researchers to extract data from more than one biobank without worrying about conflicting terms. Of course, to achieve these advantages, much work will be needed on norm development within the affected communities. Elinor Ostrom has demonstrated that such norms can be effective tools in resource management[60]; however, the key is to have sufficient community agreement and extra-legal enforcement to create the trust that makes those norms effective.[61] Specialised biobanks are more likely to exist in an environment in which the relevant communities can agree upon and enforce these norms. This would most likely occur where the community benefits from homogeneity of interests and uses of the data and technology. The more general or more heterogeneous the interests involved, the more difficult it will be to reach consensus around norms and their enforcement. In such circumstances, open access may not achieve its goal.

As with open source, open access does not explicitly address the issues of privacy or donor restrictions. Given the absence of intellectual property rights, biobanks will not be able to impose terms respecting privacy as part of its licence. Instead, managers will have to resort to legal contracts governing access to the

[59] Edwards et al. (2009).

[60] See, for example, Ostrom's foundational work in Ostrom (1990).

[61] Akcomak and ter Weel (2008).

biobank itself to ensure that donor privacy and other donor requests are respected. Thus, open access does not resolve this problem any more than does open source.

By separating out questions of property from the governance of the biobank, open access strategies provide significant flexibility in biobank management and leave open opportunities for growth and change as new uses for the biobank evolve. Where strong community norms either exist or can be developed—through, for example, consensus building among thought leaders in industry, foundations, universities and government institutions—open access constitutes a viable option for ensuring flexibility and openness over the life of a biobank. Nevertheless, both open source and open access mechanisms will need to develop tools—likely through membership contracts with the biobank itself—to deal with privacy concerns and donor restrictions.

11.7 Governance, Property and Biobanks

All forms of governing knowledge-based resources, including biobanks, fall on a spectrum between free use of knowledge by anyone for any purpose, to exclusive use by one entity for its own use. Bell and Parchomovsky[62] provide a framework—relying on earlier work by Demsetz[63] and Field[64]—through which to evaluate the configuration of property rights and their exercise along this spectrum. In particular, they provide a map of positions ranging between the extremes of no property and individually held property that allow for a more considered and subtle discussion of property configurations available for developing a biobank. Of particular relevance is their conclusion that there are many options available to policy-makers beyond a choice between pure, unadulterated property and completely free access. By acknowledging alternatives, Bell and Parchomovsky facilitate a more nuanced discussion of novel combinations of property and governance structures.

Bell and Parchomovksy describe three dimensions to describe property rights and their uses: "Every property problem spans three distinct dimensions: number of owners, scope of each owner's dominion, and asset design".[65] The number of owners of an asset can vary from one to the entire population, but most often falls somewhere in between these extremes. While a toothbrush is the quintessential example of an object of property with one owner, houses are frequently owned by two, a condominium building by all of the individual condominium owners and a corporation by all of its shareholders. Similarly, community assets, such as water for irrigation, fisheries, grazing lands and aboriginal lands may be owned by a

[62] Bell and Parchomovsky (2009).

[63] Demsetz (1967).

[64] Field (1989).

[65] Bell and Parchomovsky (2008).

Table 11.1 Side by side comparison of Open Source and Open Access

Dimension	Open source	Open access
Asset design	Each item of data and material is subject to individual rights	The entire set of data and materials constitutes one asset
Number of owners	One owner per item	All contributors and users
Dominion	Almost non-existent for contributors as it is virtually impossible to identify the owner(s) of the asset at stake. Users have wide dominion but subject to any restrictions imposed by the owners. Where these contradict one another (e.g., through different licence terms), user dominion can be critically reduced	Extensive: contribution, use, commercial applications, etc.

particular community. The scope of each owner's dominion similarly varies from, on the one hand, the rights to exclude all others from virtually all aspects of the object of property (e.g., use, destruction, consumption, sale, inheritance and so on) to narrowly circumscribed rights, such as the right to access, for a limited period in a limited geographical area for defined purposes, the object of the property right. For many consumer products, such as a toothbrush, the owner is free to make any use of it that he or she desires short of harming another or his or her property. For other products, such as a computer or a ten dollar or euro note, the owner can make fairly broad use of the object but with important limitations: the owner may not be entitled to reproduce it or its components and may not be able to destroy it. Still, for other goods, such as a rental car, one's rights are even more limited to a time, amount of use (mileage) and driver. Asset design also varies along a continuum between conceptualising the object of property as a single asset to conceiving it as a collection of small units. For example, a large tract of land can either be thought of as one large asset or as subdivided into very small units that, collectively, make up the tract of land.

This three-dimensional understanding of property provides a useful way to compare open source with open access governance of biobanks. Table 11.1 provides a side-by-side comparison of how each of open source and open access structures deal with asset definition, ownership and dominion. This comparison highlights several differences between the mechanisms. First, open source and open access structures conceive of the object of property very differently. Open source understands a biobank to be a collection of a very large number of individual assets made up of discrete data points and materials, each subject to its own set of rights. On the other hand, open access mechanisms conceive of the biobank as a single unit, subject to a single set of rights. Second, open source involves a highly heterogeneous—in terms of interest, geography and resources—and distributed set of a large number of owners. On the other hand, open access regimes posit that all biobank contributors and users are joint owners of the biobank. They all have a say (although not necessarily at the same level) in how the biobank is governed through some form of centralised structure (e.g., a board or other

decision-making body). Third, open source provides each individual owner with very little effective control over the assets that he or she does own. This is the case since most owners will find it difficult and costly to identify infringements of their contributions (especially if subsequently modified or improved) and to enforce rights against infringers. This seriously undermines the value of the legal norms as they cannot, in practice, be realistically enforced. However, the owners of the biobank within an open access regime effectively delegate powers to a board or other management structure. These managers exercise plenary authority of the biobank and set the rules of engagement for contributors and users. Those with a larger say in the management of the biobank—usually large-scale contributors, those who finance the biobank and key researchers—exercise broad dominion while most other contributors and users have significantly lesser effective rights. The effectiveness of the decision-making will depend on how well norms are followed which is, in turn, dependent on trust between actors, clarity of the norms and the tools available to enforce non-legal norms.

This juxtaposition of open source and open access biobanks illustrate two of the many ways in which one could structure a biobank. Both share an emphasis on making data and materials widely available—in contrast to proprietary biobanks aimed at providing access to only a limited set of actors—but do so using two very different conceptions of how to structure property rights and governance structures.

11.8 Conclusion

Viewed as a collaborative exercise to shorten the innovation lifecycle, avoid duplicative costs and maintain the strength of regulatory systems, structuring biobanks within an open source or open access framework seems to be promising. However, several issues need to be addressed before either framework will be effective in reaching those goals.

Open source biobanks ensure broad access by relying on standard form, viral licences that require each user to contribute back his or her additions, modifications and improvements to the entire community. While each initial contribution of new data or material to the biobank is voluntary, all subsequent contributions are legally required according to the terms of the licence agreements. The viral nature of open source licensing ensures that the data and materials will not be severely constrained by intellectual property rights. On the other hand, these viral licences will, over time, constrain behaviour and use as they either become out of date or where the user is subject to two or more different licences with respect to two or more sets of data and/or materials. In the long term, an open source biobank will be difficult to manage for the user as subtle differences between licence agreements will be too hard to monitor and implement. When this occurs, the biobank may well need to be abandoned and replaced by a new biobank with new data and materials unconstrained by previous licences.

By relying on community, rather than legal norms, open access biobanks offer significant flexibility through which to manage the evolving contents and uses of biobanks. Since open access does not rely on legal norms, a significant investment is required in non-legal norm development, communication and enforcement. Further, an open access biobank will require the creation of a board or other management structure that will lead the effort to create norms and to guide enforcement of those norms. This contrasts with an open source biobank in which, at least in theory, all contributors have an equal say over the management of biobank. However, the difference is not significant in practice since even an open source biobank will require some management structure to ensure the quality of the biobank contents, take responsibility for the materials within the biobank and satisfy regulatory requirements.

What these two example biobank frameworks illustrates is that, even when aiming at a similar set of goals, dramatically different property and governance structures may achieve the same result. Which structure ultimately best achieves those goals can be empirically measured, at least after a sufficient amount of time has passed. Nevertheless, one does not have the luxury of waiting for these empirical assessments to be conducted as decisions need to be made today on biobank structures. Given this, where there exists a clearly defined community in which norm development and enforcement is possible, open access would seem to be the preferred route. Where this feature is missing—the community may be too large and heterogeneous, there may be resistance to the use of norms and guidelines, or there may be a lack of leadership within the community—open source may be the better option.

Whether the open access or the open source approach ultimately finds favour, the deep philosophy often associated with the concept of openness will need to be balanced against the ethical concerns associated with the use of human tissue and personal information. Rather than complete openness, it will be necessary to construct mechanisms that restrict access in such a way to create enforceable obligations on users of biobank resources to respect donor rights.[66]

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[66] Nicol and Gold (2012).

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Chapter 12
Opening Research Biobanks: An Overview

Roberto Caso and Rossana Ducato

Abstract In biomedical research and translational medicine, the ancient war between the exclusive right (private control over information) and public access to information is struggling on a new battlefield: research biobanks. The latter are becoming increasingly important (one of the ten ideas changing the world, according to Time magazine) because they collect, store and distribute in a secure and professional way a critical mass of human biological samples for research purposes. Tissues and related data are fundamental for the development of biomedical research and the emerging field of translational medicine, because they represent the "raw material" for every kind of biomedical study. For this reason it is crucial to understand the boundaries of IP in this prickly context. After an overview of the complex interactions among the different stakeholders involved in the process of the production of knowledge, in this paper we will thin out some blurring of language concerning concepts often mixed up, such as "open source", "open access", and their precipitates. Then, the aim is to understand if we can use the concepts in the biomedical context, and which are the open models proposed in literature specifically for research biobanks in order to avoid the tragedy of anticommons.

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12.1 Introduction

In the last 30 years, we have witnessed an overgrowth of Intellectual Property Rights (IPRs) almost in every field of our daily life.[1] According to the traditional view, the protection of IP and the control of information are key to the strategy of many companies and both have been justified with well-known economic and utilitarian arguments[2]: patent, copyright, trademark and other forms of exclusive rights offer incentives to undertake risky projects, represent the main source of appropriating returns, can lead to a "more equitable distribution of profits across all stages of R&D"[3] and are the better antidote for corporate secrecy.

At the same time, the public domain has suffered slow but constant erosion. Legislators have supported this trend towards privatisation, progressively attributing to multiple owners a set of rights to exclude others.[4] Governments have been creating this dangerous dominance through some interventions in patent law and copyright law, such as the Bayh-Dole Act,[5] the Digital Millennium Copyright Act,[6] the Sonny Bono Copyright Extension Act[7] in the U.S. or Directives 91/250/EEC,[8] 96/9/EC,[9] 98/44/EC,[10] 2001/29/EC[11] or

[1] According to Robert Merges, IP law is like Shanghai or other megacities of the developing world, where new constructions and buildings proliferate everywhere without taking into account the urban planning of the old city. The author concludes his metaphor asserting that: "It's an exciting time, to be sure; but a confusing time too". Merges (2011).

[2] See also Ladas (1929), Plant (1934a, b), Nordhaus (1969), Mazzoleni and Nelson (1998), Menell (1999), and Landes and Posner (2003).

[3] Heller and Eisenberg (1998), p. 698.

[4] See Heller and Eisenberg (1998), Lessig (2004a, b), and Boyle (2008).

[5] Bayh–Dole Act is a watershed from the past patent regimes. First of all, it introduces the possibility of patenting results of publicly funded research. Secondly, it allows university and public laboratories to sell exclusive licences to private companies or to create partnership with them in order to economically exploit the research results and to translate their basic research into marketable products. See Rai and Eisenberg (2003) and Corian and Weinstein (2011).

[6] Digital Millennium Copyright Act, 17 U.S. Code. This statute has qualified as a criminally relevant behaviour the circumvention of technological protection measures and the distribution of tools to encompass DRM.

[7] Copyright Term Extension Act, 17 U.S. Code, also known as Mickey Mouse Protection Act, extended copyright terms in the U.S.A. as following: duration of copyright protection is raised from 50 to 70 years after the death of the author and it lasts 120 years after creation or 95 years after publication if it is a work of corporate authorship.

[8] Council Directive 91/250/EEC of 14 May 1991 on the legal protection of computer programs, in Official Journal L 122 of 17 May 1991.

[9] Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases, in Official Journal L 077 of 27 March 1996.

[10] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, in Official Journal L 213 of 30 July1998.

[11] Directive 2001/29/EC of the European Parliament and of the Council on the harmonization of certain aspects of copyright and related rights in the information society, in Official Journal L 167 of 22 June 2001. The importance of IP protection is stressed in whereas 4 and 9.

2004/48/EC[12] in the European Union. Such national or regional legislation is reflected in a number of international provisions like the WTO's Agreement on Trade Related Aspects of Intellectual Property Rights (1994) or the World Intellectual Property Organization "Internet" Treaties (WIPO Copyright Treaty and the WIPO Performances and Phonograms Treaty), and it has also been confirmed by relevant judicial decisions.[13] This progressive transformation has been creating the conditions for new institutional complementarities between IPR and finance, opening *de facto* to capital the door of the "workshop" of knowledge.[14]

A set of interventions in the public and private sector has significantly contributed to this "second enclosure movement", shifting the balance of power towards private control and increasing the risk of non-use or under-utilisation of information.[15] In other words, we have such a wide range of Intellectual Property tools that we can no longer manage it.

In this perspective, many authors talk about the tragedy of anticommons. The tragedy of anticommons is a mirror-image of Hardin's tragedy of the commons.[16] According to the American ecologist Hardin, when multiple individuals can use a shared limited resource (in the original example it was an open-access pasture) without the right to exclude others, they tend to act independently and according to their self-interest, exploiting the resource as much as possible. In this way, the

[12] Directive 2004/48/EC of the European Parliament and of the Council on the enforcement of intellectual property rights, in Official Journal L 157 of 30 April 2004. See whereas 10: "The objective of this Directive is to approximate legislative systems so as to ensure a high, equivalent and homogeneous level of protection in the internal market".

[13] Taking as an example the case law of the United States, because its parabola serves to illustrate the evolution of the trend towards enclosure, regarding patents we can mention Diamond v. Chakrabarty, 447 U.S. 303 (1980), affirming that, "anything under the sun made by man is patentable", and introducing the patent protection for micro-organism; State Street Bank and Trust Company v. Signature Financial Group Inc., 149 F. 3d 1368 (1998), establishing the patentability of business methods in the United States; Appeal from the United States District Court for the Southern District of New York in Case No. 09-CV-4515 (Association for Molecular Pathology v. UPO) overruling the revolutionary judgment of the NY District court which had invalidated the Myriad patents on BRCA gene in virtue of the "product of nature" doctrine. The Court of Appeal overruled the decision of the inferior court and confirmed the principle that isolated DNA is a distinct chemical entity with different physical characteristics from natural DNA, so eligible for patent protection under 35 USC §101. Meanwhile, with regard to copyright Eldred v. Ashcroft, 123 S.Ct 769 (2003) is significant, a decision that seems to attribute to Congress the possibility of extending the validity of copyright without apparently any limit (see Samuelson 2003; Lessig 2004a, b; Kranich 2006); more specifically on file sharing, see the famous ruling of A&M Records v. Napster, 239 F.3rd 1004 (9th Cir. 2001); MGM Studios Inc. v. Grokster Ltd, 545 U.S. 913 (2005)

[14] Corian and Weinstein (2011).

[15] Boyle (2003).

[16] Parisi et al. (2005).

common good is prone to be overgrazed[17]; meanwhile, in the tragedy of anticommons, the social dilemma is the opposite: the common resource risks being underused because individuals have a right to exclude others and no owner has effectively a privilege of use.[18]

The danger of the anticommons tragedy is particularly sharpened in the current biomedical research, the development of which depends inextricably on the opportunity to access and use data, materials, expertise and, consequently, on the possibility of cross-checking pre-competitive information and results.

The scenario described so far gives rise to the risk that rigid and centralised control of information based on many and strong IPRs, shaped on market considerations, invades the proper domain of the scientific community (which is, on the contrary, motivated by the logic of flexible and decentralised control, based on customs and informal norms), decreasing the possibility of access to scientific knowledge.

To counteract this risk, part of the scientific community is promoting the logic of "open intellectual property" to scientific knowledge. In fact, the emersion of initiatives based on contracts (licences) such as the Open source movement or Creative Commons reveals different perspectives with regard to the statutory regime of intellectual property. In the last years, the movement of "open intellectual property" is more and more active in the biomedical field.

In biomedical research and translational medicine, the ancient war between the exclusive right (private control over information) and public access to information is struggling on a new battlefield: research biobanks. The latter are becoming increasingly important (one of the ten ideas changing the world, according to *Time* magazine)[19] because they collect, store and distribute in a secure and professional way a critical mass of human biological samples for research purposes. Tissues and related data are fundamental for the development of biomedical research and the emerging field of translational medicine, because they represent the "raw material" for every kind of biomedical study. For this reason, it is crucial to understand the boundaries of IP in this prickly context.

After an overview of the complex interactions among the different stakeholders involved in the process of the production of knowledge, in this paper we will thin out some blurring of language concerning concepts often mixed up, such as "open source", "open access", and their precipitates. Then, the aim is to understand if we can use the concepts in the biomedical context, and which are the open models proposed in literature specifically for research biobanks in order to avoid the tragedy of anticommons.

[17] Hardin (1968).

[18] Michelman (1967) and Heller (1998, 1999).

[19] http://www.time.com/time/specials/packages/completelist/0,29569,1884779,00.html. Accessed 01.02.2012.

12.2 IP Law, Market and University: A Complex Relationship

The dominions of IP had been constantly expanding insomuch as undermining the flexibility of the scientific social norms. This is evident if we consider, for example, the patent race by academic institutions: there is a tension between the patent requirement of novelty and the need for the scientist to publish as soon as possible. Since the publication of the results frustrates the requirement of novelty, the scientists are prohibited from publishing until the patent is granted.[20] In the biomedical field, the formalism of law is looked on because it tends to encompass areas that were previously managed in a free and independent way by the whole scientific community, thus changing informal rules and attitudes. This passage is evident if we compare the famous cases of Henrietta Lacks and John Moore.[21] In the first case, scientists who discovered the "HeLa" cells—an immortal cell line derived from the biological samples of the woman—distributed them to all laboratories around the world. In the 1950s those scientists had understood the value of that discovery for the progress of science and they decided to share their results with other peers and potential competitors.[22] It was a farsighted choice, if we consider that HeLa cells were used in a huge amount of research fields: from polio vaccine to gene mapping; from the development of the first anti-cancer drugs (such as tamoxifen) to space experiments for testing the reactions of the human body to the absence of gravity. In the second case, two physicians at UCLA isolated a cell line from the spleen of John Moore and they did not have any hesitation: they rushed to find a patent application on that invention and the Regents of UCLA were designed as assignees of the patent. They immediately started to negotiate agreements with two big pharmaceutical companies for the commercial exploitation of the "Mo cell". Add to this that everything happened behind John Moore's back.[23]

Is it just a coincidence that within three decades researchers have acted so differently? The answer to this question can be given if we consider the different role that science has taken over the years. Since the beginning of the twentieth century, science has turned to market, replacing its old form based on the principles of universality and author's prestige with a new form of managerial science characterised by teamwork.[24] This change has been speeded up more recently by

[20] Streitz and Bennett (2003), Kinney et al. (2004), and Murray and Stern (2007).

[21] Moore v. Regents of University of California, 51 Cal.3d 120, Supreme Court of California, 9 July 1990.

[22] Landecker (1999), O'Brien (2001), Lucey et al. (2009), Javitt (2010), and Skloot (2010).

[23] The Moore affair gave rise to a long and famous lawsuit: John Moore, after discovering the business built from his cell by Dr. Golde and Dr. Quan, his two physicians at UCLA, tried to sue them for breach of fiduciary duty in the doctor–patient relationship (both had acted without his informed consent), but above all for the recognition of property rights on the patented cell line (he claimed for conversion). About this case, see Annas (1988), Paganelli (1989), Hipkens (1992), Burrow (1997), and Campbell (2006).

[24] Johns (2009).

legislation which has strongly encouraged university and public research centres to patent discoveries and to transfer their technology to the industry, also through the use of exclusive licenses.[25] The initiative was welcomed, and has yielded significant benefits in the short term. Before 1980, fewer than 250 patents per year were issued to US universities. After the Bayh-Dole Act, the number of patents increased greatly and university licensing revenues had grown from $221 million in 1991, to $698 million in 1997.[26] Patents became a source of additional funding and income for universities; at the same time, the network between university and private sector also allowed companies to cut down the costs for research. Just to remain in the area of drug discovery, thanks to the basic research done by universities and the R&D realised by start-ups in order to bring to market academic results, pharmaceutical companies discovered and validated new drug targets in a faster and cheaper way.

This trend toward enclosure, consisting of an elephantiasis in patenting, arises parallel to another front: the access to knowledge commons. The prime example is represented by what happened in the United States after the Second World War. At the beginning, public funds were assigned for the creation of the first databases indexing military information, and then also medical and educational data.[27] Through these funds, it was possible to create new research centres and federal libraries. The wind changed when the Reagan administration decided to outsource governmental publications, and some federal programs related to libraries, to the private sector. Even academic institutions followed this path, outsourcing the publication of their journals to private companies. Moreover, the mergers in the 1970s between publishers created a situation of oligopoly, so almost all of the scientific production was in the hands of a few big international groups; and consequently the price of scientific journals soared. The conditions for triggering a vicious cycle had been created: at the end universities invested twice for the same thing. In the first instance, they had been investing to fund research that would subsequently be given away for free to publishers; and they invested a second time to regain that same publication, buying for their libraries the subscription to the journal at a higher price.[28]

This evolution in the 1980s is crucial because universities and big biotech/pharmaceutical companies started to colonise the area of pre-competitive research and to make access to knowledge more difficult. Such proliferation of IPRs upstream, while it had a positive effect in the short period, has hindered biomedical research in the long run.[29] Covering basic research discoveries, research materials and reagents with proprietary claims means to inhibit the use of those tools that are

[25] Heller and Eisenberg (1998), Mowery (1998), and Granieri (2010).

[26] Nelson (2001). Some authors downsized the importance of Bayh–Dole Act in the university patent process. See, for example, Mowery et al. (2004) and Mowery and Sampat (2005).

[27] Such as for example, Dialog System. See Summit (2002).

[28] Guedon (2004), Suber (2004a, b), Kranich (2006), and Caso (2009).

[29] Rai and Eisenberg (2003).

fundamental not only for downstream research but also for basic research itself.[30] This dangerous stalemate is confirmed by the decrease in the number of new patented drugs notwithstanding the growing public and private investments in drug discovery.[31] At the origin of this phenomenon there are factors such as the insufficient scientific understanding of biological and molecular mechanisms of diseases, the limited availability of data and biological samples, the lack of collaboration between researchers working in academia and industry and, above all, the complex landscape of IPRs.

12.3 Research Biobanks: Exclusive (or Para-Exclusive) Rights in a No-Man's Land

Data sharing and collaborative research have become an imperative in contemporary science, whose development depends inextricably on: the opportunities to access and use data, the possibility of sharing practices between communities, the cross-checking of information and results and, chiefly, interactions with experts in different fields of knowledge. Data sharing allows both to spread the costs of analytical results that researchers cannot achieve working individually and, if properly managed, to avoid the duplication of research. These advantages are crucial: access to a common pool of pre-competitive data and the possibility to endorse follow-on research projects are fundamental for the progress of biomedicine. This is why new institutions such as research biobanks have gained in importance.

Biobanks are powerful tools and organisational structures essential for translational medicine and biomedical research, because they are treasures of a pool of pre-competitive information and materials tempting both public research centres and BigPharma.[32] On the one hand, they are a source of human biological samples stored according to high standards of quality and safety. On the other hand, a biobank is also an informational "mine"; in its databases are classified clinical/diagnostic information, sample-derived genetic data, donor's personal data, and the type of consent given for the research. Such data have a surplus value for translational and biomedical research because they are constantly updated with donor's follow-up data: it is possible to follow the clinical history, the disease progression, the response to different therapies, etc. In some cases, research biobanks have also created additional resources such as archives of graphical elaborations of protein structure (in 2-D or 3-D).

[30] This recent trend towards the appropriation of data is posing serious obstacles to full and open access to data for scientific purposes. ICSU (2004).

[31] Booth and Zemmel (2004), Cuatrecasas (2006), and Weigelt (2009).

[32] Translational medicine is based on pre-clinical bio-molecular analysis of a critical mass of human biological samples in order to obtain results immediately usable in the clinical context. This allows the identification of biomarkers, i.e. those molecules that can predict the risk of cancer, the presence of a neoplasia and the possibility of identifying the most appropriate and effective drug or treatment for a particular patient. See FitzGerald (2005).

Thanks to technological and scientific progress, what until a few decades ago had been considered a worthless hospital waste (a *res derelictae*), nowadays has become an asset in a legal and economic sense. Thereby, the cloud of enclosure is gathering all over these research structures: biological samples are legal assets, subject to the bundle of property rights; genetic sequence derived from the sample could be patented or covered by a trade secret; biobanks' database is under the protection of copyright or EU sui generis right; also some contents of the databases are covered by copyright; the handling of personal data, health records and genetic information must preserve the donor's right to privacy.

Taking into account this panorama, we can distinguish two different levels in the biobank structure, based on the twofold nature of human biological samples. Biobanks, in fact, store a critical mass of tissues (leftover tissues, blood, saliva, urine, etc.) in their bio-repositories; but, however numerous they may be, biological samples are still exhaustible resources. They are scarce and rival assets that need to be efficiently allocated among stakeholders. On the contrary, data are "ubiquitous": they can be replicated *n* times and distributed to *n* researchers at the same time. Therefore, access to biological samples is crucial but access to the information embodied in the material support is even more critical to the improvement of data sharing. Thus, in biobanking activity two tragedies potentially coexist: firstly, the tragedy of commons with regards to human tissues; secondly, the tragedy of anticommons with respect to data and information related to the sample.

Regulatory gaps and the lack of common and shared reference points have been filled by privatisation trends, at the expense of the collective good and, in an increasing number of cases, at the expense also of private companies. In particular, traditional models seem to stifle a lot of potential for the biobank activities. For example, the tools ordinarily used for fruition of data and materials, the Material Transfer Agreement (MTA), are cause of unrest among researchers, because of the cumbersome nature of the mechanism, the length of the procedures and the high transaction costs.[33] Against this impasse some authors are invoking (and business models are moving towards) the "open" philosophy.[34]

12.4 Towards "Open Science": Some Basic Legal Tools

The vision that closed model systems, and patents in particular, encourage an efficient management of research, balancing the return on investments and the benefits for the whole community, has been strongly challenged in recent years.[35]

[33] Streitz and Bennett (2003), Ku (2007), Rodriguez (2008), Lei et al. (2009), and Noonan (2009). Specifically on the problems related to MTA and possible solutions offered by Science Commons, see Margoni (2012).

[34] Hess and Ostrom (2007), Hope (2008), Edwards et al. (2009), Weigelt (2009), Lei et al. (2009), and De Robbio and Corradi (2010).

[35] Kitch (1977) and Gallini and Scotchmer (2002).

This change is evidenced not only by the signal given by some "rebel" researchers (e.g. Ilaria Capua),[36] but even by big pharmaceutical companies (e.g. Novartis and Glaxo-SmithKline).[37] BigScience becomes "open" certainly not because of altruism, but simply because they realised that cooperation is more convenient than competition based on IPRs.

In order to understand how the "openness" is spreading to the realm of biotechnology, we have to contextualise the original concept of "open source" in the world of information technology and software. Afterwards, we will discuss whether such concepts work if applied to scientific research in the "bio-" fields.[38]

12.4.1 Opening Software

Open source is a revolutionary and provocative concept, developed since the early 1970s as part of computer science, and it represents a new way of thinking about computer programming and software in its entirety: from conception to final release and distribution. This movement is composed of two different souls: Free Software and Open Source Software. The first is linked to the name of Richard Stallman[39] and has an ethical aim. According to free software philosophy, proprietary software is a social problem that shakes the values of communality and sharing to its foundations. Software must be freely available and accessible without restraints as a desirable social outcome. On the contrary, Open Source Software is a definition created in 1998 on the occasion of the release of the source code of Netscape's browser by Eric Raymond. According to these alternative currents, open source is a more efficient choice if compared to the traditional closed model.[40] The collaboration of different programmers, who at the same time are users, and the decentralised production monitored by strong normative expectations and social sanctions are a synonym of quality, and they also reduce the time for development and the costs of production. Therefore, open source software shows a broad range of economic advantages.

Unless the starting point is different (the former school has a more philosophical and political approach, whereas the latter has a more utilitarian vision), the

[36] The Italian virologist identified the genetic sequence of the avian flu virus and decided to make it available to the worldwide scientific community by uploading it to GenBank, disregarding the invitation of the WHO to file it in a limited-access database. See Enserink (2006).

[37] Strauss (2010).

[38] The following classifications were also illustrated by Prof. Richard Gold during the seminar "Models for Sharing Data" within the Biobank Lab, held at the University of Trento in May 2010.

[39] In 1983, he announced the GNU project, an operative system compatible with Unix, the proprietary software more widespread in research laboratories in American universities. Stallman's novel idea consisted in the creation of a licence (copyleft, "all rights reversed") giving much more power to the user than to the owner. About the origins of free software, see Stallman (2002).

[40] Raymond (2000).

pragmatic result is the same. In fact, according to both Free Software and Open Source Software, in addition to the object-code (the machine-readable format) the source code is also distributed (the "human language") to the public of user-programmers.[41] In this way, they cannot only use the software, but copy, modify and redistribute it.[42] According to the General Public License manifesto, free software gives users the four "fundamental freedoms": (1) run the program, for any purpose; (2) study how the program works, and change it to make it do what you wish; (3) redistribute copies; (4) distribute copies of your modified versions to others.

Both "open projects" are distinguished by a special legal regime that allows progressive development. The GNU GPL, in fact, is a viral licence because it "infects" all subsequent products containing the original code: the programmer gives up IP exploitation to follow-on users as the latter are not allowed to distribute the modified software with a proprietary licence.

It is hardly necessary to point out that this movement is not the negation of intellectual property, but rather represents a new way of interpreting it. It would be a mistake to think that copyleft means the absence of copyright. Viral licensing is properly designed under copyright law, but it allows users to modularise the availability and distribution of their works, while also posing some limits and obligations.

12.4.2 Opening Biotechnology

In the field of biomedicine, the open source philosophy has been transposed into "open source biotechnology".[43] Of course, such a transplant is not a trivial question because the open source model and open source licensing have been developed around the idea and the structure of copyright. Instead, in what we call open technology, we have to deal with patents.

At first sight, *open source patent* may seem a tautological expression, because the information related to the invention is already publicly accessible and available through the mechanisms of disclosure or deposit.[44] In fact, even though the invention is disclosed, it does not mean that the information and data embodied are non-excludable. Patent itself may inhibit the public use of that invention

[41] A way to overcome this problem is a particular technique called reverse engineering, where the reverser analyses the programs and tries to understand how they work without having the source code. See Lessig (1999) and Nichols and Twidale (2003).

[42] Stallman (2002).

[43] Gitter (2012).

[44] Dasgupta and David (1987).

through exclusive licences. In this context, "open source" refers to an issue of accessibility rather than disclosure.[45]

Taking ideals behind the free software movement, the open source patenting develops "the aspirational goal of biological scientists [to] closely track those of the open source community in desiring to keep information and discoveries communal and accessible".[46] Here, the "viral" licence works in the following terms: the licensees cannot appropriate the fundamental "kernel" of the technology and cannot improve it exclusively for themselves[47]; data and results of research should fall into the public domain, but only under certain conditions, for example, by waiving an "unfair" use of IPRs. The participants in the open source project, therefore, would agree to grant licences or to exercise their rights in order to make inventions and improvements available to the whole community.[48] In this scenario, the patent holder should license the invention with a licence that protects those technical solutions and improvements from possible attempts of appropriation, for example by commercial competitors.

That has already been done by the BIOS's CAMBIA, an Australian nonprofit research institute that has extended this model to the transfer of biological samples.[49] Users of the BIOS "concordance" do not assert IP rights against each other's use of the technology, materials and methods to do research, or to develop products either for profit or for the public good. Consequently, the improvements must be shared according to a BIOS license, while the products and inventions developed from the same technology can be patented. In the latter case, however, the improvements that have been patented must return (grant back clause) to the BIOS and to other licensees on the same terms of the original licence or must be freely cross-licensed.

Another example of this trend is represented by "HapMap Project",[50] an international consortium involving ten research centres located in Japan, the UK, Canada, Nigeria, China and the USA. The scope is to create a map of genetic variations in human beings in order to offer a valid instrument in support of biomedical and clinical research and make this information freely available. According to the Data Release Policies, in fact, all data generated must be released "quickly"[51] in the public domain. The user accepts the terms of this agreement

[45] Boettinger and Burk (2004).

[46] Ibid., p. 225.

[47] See BIOS concordance.

[48] About the adoption of the open source model in the biotech field, Hope (2008).

[49] http://www.bios.net/daisy/bios/home.html. Accessed 01.02.2012.

[50] Internation HapMap Project, http://hapmap.ncbi.nlm.nih.gov/. Accessed 01.02.2012. See also The International HapMap Project (2003).

[51] See http://hapmap.ncbi.nlm.nih.gov/datareleasepolicy.html. It is not well specified how quick the release into the public domain has to be.

through a "click-wrap" licence. In this way, the database is freely accessible to all bona fide researchers and users cannot tie down data and information by filing "patent parasite"[52] application over the resulting discoveries. They are forced to share information among the participants in the HapMap project, so bound by the same contractual provisions. In any case, the possibility of patenting is not excluded a priori: if it is possible to show a specific utility, researchers can apply for a patent "as long as this action does not prevent others from obtaining access to data from the Project",[53] licensing the invention so that the information used is still accessible to other participants.

Some scholars have emphasised the advantages of this approach. In fact, the absence of IP income is counterbalanced by a social recognition for the participants.[54] This can also means economic rewards in terms of future job offers, proposals for collaboration in commercial open source companies and access to venture capital market.[55]

However, the adoption of this system does not dissolve some key issues. First of all, the translation of the open source model outside the field of information technology raises a series of challenges.[56] At first instance, it seems obvious that research equipment and laboratories in the biotechnological field are more advanced and costly rather than the resources necessary in the computer context.[57] Secondly, the timing and development are very different in the two sectors. While in software, you can quickly have a response by the whole community of programmers about the improvements made, in the biomedical field the process from discovery to marketing can take years. In addition, this model seems to ignore the exorbitant costs of drug discovery, clinical trials, intellectual property (e.g. the cost of patent application), and the length of regulatory procedures.[58] The adoption of open source in biotechnology would, therefore, run a high risk of rejection. Open source is a culture of sharing developed in the hacker community with different needs from the biotech world. Pharmaceutical companies want to get patents and license as much as possible, while the researchers want to have credit and reputation

[52] According to Daniel de Beer a "patent parasite" is a patent developed from the original material "to which just a tiny change has been made". De Beer (2005), p. 366.

[53] HapMap Project, Data Release Policies.

[54] von Hippel and von Krogh (2003).

[55] Hope (2008), Chakravarty et al. (2007).

[56] As pointed out by Gold (2010).

[57] Lerner and Tirole (2005).

[58] de Beer (2005).

for their works.[59] Open source, therefore, may not provide the right incentives for effective collaborative research.

12.4.3 Open Access Publishing

Open Access (OA) is the free online access. That means the freedom to access data without most copyright and licensing restrictions.[60] In the OA context two different routes have been distinguished, regularly labeled as gold road and green road. The first one refers to OA journals; the second one to self-archiving previous published works. In any case, they correspond to different phases of the same movement.[61]

The core of open access works as follows: the institution shall pay the cost of publication of its researcher, who retains some rights (authorship, in particular) and surrenders others—throughout licences such as Creative Commons[62]—in order to make the publication freely available.[63] Here, production costs are borne by the authors and institutions, while distribution costs—held down thanks to digitisation—are shared with new intermediaries.

At the end, OA reduces costs, circumvents the limits imposed by increasingly stringent regulations on copyright, licensing agreements and DRM. OA offers also reputational incentives, because it represents a means to disseminate authors' ideas, to disseminate their intellectual production, to promote themselves before other peers; but it is also a tool to get free and quick access to the literature necessary for implementing and deepening their own scientific production. OA is also an opportunity for libraries to mitigate the costs of journals and subscriptions.[64] Also, society and the progress of knowledge, in general, can benefit from such a system because the openness is the primary method for correcting errors and mistakes through the sociological mechanisms of peer review and citation.[65]

However, authors play the key role in building a system based on open access, as the fate (open or closed) of their works is in their hands. It is a cultural problem (in the sense that part of scientific community still ignores what OA is) but is also a challenge to remove the existing disincentives (such as the Ingelfinger rule) and to find those incentives that could propitiate this mentality.[66]

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[59] Gold and Nicol (2012).

[60] Suber (2004a, b).

[61] Guedon (2004).

[62] Creative Commons (CC) is a charitable corporation that promotes the sharing and circulation of knowledge in compliance with copyright law. Although it offers standardised models, its modular licenses (attribution, noncommercial, no derivative works, share alike) and their combinations can provide flexibility in setting the interests of parties. Source: http://creativecommons.org/.

[63] Caso (2009).

[64] De Robbio (2010).

[65] Boyle (1997).

[66] Suber (2004a, b).

12.5 Open Models in the Field of Research Biobanks

Research biobanks have been metaphorically described as a library. This comparison is not so abstract since biobanks have databases and digital archives. They are already digital libraries but, maybe, do not yet know it.

Digital databases of the biobanks may contain a variety of information. First of all, information related to the "owner" of the sample like personal and clinical data, and additional information such as eating, life or relationship habits. Biobanks' databases can also index information derived from the material support, i.e. genetic data or sensitive information that can reveal the health conditions of the patient. In particular, genetic data are a very peculiar category because they concern not only the person they belong to but also his entire biological family. Quite often biobanks proceed to aggregate the data and to make the first analysis. Therefore, the results of these analyses and the generated cohorts are included in digital files and stored in the archive for following research. Moreover, since the main purpose of a biobank is to provide samples and data to researchers, while one of the main bonds of the latter is the reporting of his activities and the grant back of analysis' results, biobanks also collect the research reports and, if available, the publication derived from the study of the biological and informational resources provided.

Within the digital archives of the biobank can therefore be stored copyrighted materials, and simple data. Regarding researchers' reports and publication, the new methods offered by the Open Access in the field of scientific and academic commons (OpenWetWare,[67] PLoS,[68] Open Archive Initiative,[69] etc.) represent a great chance to transform research biobanks into an invaluable resource and an Institution.

Concerning the diffusion of raw data, things may be a little bit different. Science Commons, for example, has been developing a protocol for the circulation of scientific data.[70] Moving from the awareness of the need of data's interoperability, the OA database protocol aims to provide the legal functions necessary to create a legal tool for the legal integration of different databases or data products.[71] The key principles at the base of the initiative are the promotion of legal predictability and certainty, the user-friendly approach and the reduction of transaction costs. The protocol suggests converging on public domain by: waiving statutory or intellectual

[67] http://www.openwetware.org/. Accessed 01.02.2012.

[68] http://www.plos.org/. Accessed 01.02.2012.

[69] http://www.openarchives.org/. Accessed 01.02.2012.

[70] http://sciencecommons.org/projects/publishing/open-access-data-protocol/. Accessed 01.02.2012.

[71] At first, Science Commons encouraged database licensing under the CC licences or the GNU Free Documentation Licence. The initial approach was abandoned for three main reasons (category errors, false expectations, attribution staking) and now the scope is to converge on public domain. http://sciencecommons.org/projects/publishing/open-access-data-protocol/. Accessed 01.02.2012.

property, deleting the contract control, implementing the interoperability with databases and data not available under the Science Commons Open Access Data Protocol through metadata, simplifying the citation requirements.[72]

In any case, these initiatives are lame and are likely to be abandoned if appropriate structures of governance are not established in order to allow their sustainability. It is necessary to involve all stakeholders in the design and management of these innovative projects, facilitating dialogue, participation and transparency.[73]

In response to this gap, new paradigms are emerging for access to pre-competitive information, such as collaborative partnerships. Many new cases of private-public collaboration are demonstrating their value and biobanks may claim their intellectual power on them.

It is the case, for example, of the Structural Genomic Consortium (SGC),[74] Sage Bionetworks,[75] the European Bioinformatics Institute (EBI) Industry Programme,[76] the Predictive Safety Testing Consortium (PSTC),[77] the International Union of Basic and Clinical Pharmacology (IUPHAR).[78] Life Science Grid—Eli Lilly, Pistoia[79] and Innovative Medicines Initiative (IMI).[80]

These new business models are developing in the area of biomedical research the idea of open innovation.[81] That was expressly declared by Weigelt and Edwards when they launched SGC, an innovative project to foster the free circulation of pre-competitive data, based on the osmosis between private and public sector and the adoption of open access structures.[82] According to SGC Data Policies, all products and results (material and expertise) are released into the public domain, but the enforcement of this system is secured by a participatory and transparent governance

[72] Ibidem.

[73] Kranich (2006).

[74] http://www.thesgc.org/. Accessed 01.02.2012. SGC is a non-profit organisation founded in 2004 with the aim of promoting the development of new drugs, investing in basic research and releasing to the public every type of information (from reagents to know-how) The SGC's primary goal is to determine the three-dimensional structure of proteins, in order to understand the molecular mechanisms of their biological function. Then, the data obtained are deposited in the Protein Data Bank (PDB), a freely accessible archive, which since 1971 collects information about 3D structures of large molecules, including proteins and nucleic acids (http://www.pdb.org/pdb/home/home.do).

[75] http://sagebase.org/. Accessed 01.02.2012.

[76] http://www.ebi.ac.uk/. Accessed 01.02.2012.

[77] http://c-path.org/pstc.cfm. Accessed 01.02.2012.

[78] http://www.iuphar.org/. Accessed 01.02.2012.

[79] http://www.pistoiaalliance.org/. Accessed 01.02.2012.

[80] http://www.imi.europa.eu/. Accessed 01.02.2012.

[81] Chesbrough (2003).

[82] Weigelt (2009) and Edwards et al. (2009).

structure, a number of clear operational rules and legal instruments, such as the adoption of CC licenses for the exchange of pre-competitive information.[83]

Sage Bionetworks is another example in this sense. It is a not-for-profit organisation founded in Seattle in 2009 with an ambitious goal: to create a Commons where computational biologists can improve an integrative bionetwork in order to expedite the pathway to knowledge, treatment, and prevention of disease (1st Sage Bionetworks Commons principle). The purpose is to build an innovation space where scientists are not limited to aseptically exchange data, but, as active participants, they are calling to create new tools (models disease) or improve those developed by other colleagues.[84] So through an open IT infrastructure (the Sage Bionetworks Platform), standard tool-sharing mechanisms, secure measures and a cloud computing system, this model aims to become a powerful resource for data sharing and interoperability of different data sets. Thanks to its governance structure,[85] Sage Bionetworks aims to protect the rights of patients in terms of privacy and self-determination expressed in the informed consent, ensuring participation and transparency. Probably this model is the one which better interprets the democratisation of innovation imagined by von Hippel.[86]

The list of examples could go on longer. In brief, what all these projects have in common is the recognition of the need for a community-based approach and for the widest possible access to data. However, they assume that public domain might not be the most efficient response for their purposes. For this reason, such partnerships pay attention also to the subsequent steps of circulation such as the licensing.

12.6 Conclusions: Governing the Components of the Research Biobanks

The English word "biobank" has in itself a theme connected to the world of finance (bank). In Italian, we use the term "bioteca" which clearly has a resonance with the word "biblioteca" (library). It is a terminological choice suggesting a paradigm shift. The enclosure movement is dramatically expanding its borders to crucial sectors of innovation such as the pre-competitive area and is trying to colonise strategic structures like research biobanks. In this sense, the latter, like real banks, risk being transformed into a *caveau*.[87] Scholars have warned against this dangerous drift, underling the institutional and public role of biobanks: the latter is the steward of a critical mass of material and information, fundamental for biomedicine and translation medicine, which have to be used in a far-seeing and efficient way.

[83] Ibidem.

[84] Derry et al. (2011).

[85] http://sagebase.org/downloads/SageBio_Governance.pdf. Accessed 01.02.2012.

[86] von Hippel (2005).

[87] De Robbio (2010).

How to build this knowledge commons of the twenty-first century?

First of all, lawyers and policy makers should consider how the components of IP, technology, social norm and contracts interact in the specific context of research biobanks. As we have already emphasised, the biobank has a dual nature: a material and informational one. Therefore, the exchange of biological materials will be managed through an MTA, while for the data appropriate access policies must be created.[88]

Why should researchers share information with others? Although the benefits of data sharing are universally recognised, the development of this process still faces technical and, above all, cultural problems. Obviously, we must play on reputation and authorship, the unmoved mover of the openness of information. Scientific data sharing must be encouraged by creating appropriate reputational incentives, like a sort of h-index. The more you share with biobanks and the scientific community, the more you are cited and the more are the benefits. A researcher with a higher h-index could have priority access to material resources (biological samples) over other colleagues. Of course, access to immaterial resources of the biobanks should be granted for any research purposes, as broadly as possible, to all bona fide scientists, just after an online registration.

The same "feedback" incentive could be a valid tool also for the biobank itself and can address its funding problems. Anne Cambon-Thomsen has proposed the creation of a BIF (*Biobank Impact Factor*), a sort of citation impact factor for biobanks.[89] The tool should quantify the biobank's use, view the number of access, calculate the range and the impact of the research obtained, giving credit to those who created and maintained a valid resource. A high number of citations means research funds for both the biobank, the laboratory and the research group.

Funding, of course, is another relevant issue for biobanks. How can they finance themselves? Through public funds? Private funds? Access fees? Other data?

For example, O+ehun,[90] the network biobank of the Basque Country (Spain), is growing thanks to public and private funds but also thanks to grant back clauses. In a nutshell, the Basque biobank "obliges" researchers who access its biological resources to submit periodical reports on their results. Here, trust is an important element, because scientists collaborate actively feeling themselves a part of the

[88] The contractual component is the ideal solution in order to settle the parties' interests, but in the biobank context MTA is more the problem than the cure. Collaborative initiatives such as Science Commons have offered contractual models to make the transfer of research materials easier, thanks to a flexible, modular, web-based and user-friendly tool. However, this MTA has the usual disadvantages of standard agreement and its modularity partially alleviates the problem by providing a limited space for autonomy. On the one hand, standardisation helps to reduce transaction costs and to facilitate circulation, but on the other hand, it creates difficulties in the field of open licences. Furthermore, a standard contract is always deficient in participatory aspects, because the contents of the agreement do not result from a negotiation, but it is unilaterally imposed. On the problems related to the standardisation of contracts, see Roppo (1975), Boggiano (1991), and Alpa and Bessone (1997).

[89] Cambon-Thomsen (2003).

[90] http://www.basquebiobank.com/. Accessed 01.02.2012.

same network: they use the samples and data collected by their colleagues and they want to create a common resource in the interest of the local research community. This provision also reflects the principles of altruism and reciprocity, which ideally should underlie scientific research. Furthermore, feeding the findings back reduces the risk of duplication of research. It is crucial to grant back the results of the analysis (other pre-competitive information) to the biobank, and to return not only the complete analysis (in order to permit the scientific review process) but, especially, the "blind alley", that is the negative findings that can orient next developments and efforts.

Someone could argue that a grant back clause could discourage researchers interested in publication from taking part. In order to address this problem, for example, the NIH grants a period of exclusivity for the data producer. In fact, the Policy for Sharing of Data Obtained in NIH Supported or Conducted GWAS Studies declares that investigators who contribute data to a NIH GWAS data repository retain exclusive right to publish analyses of dataset for a maximum of 12 months following its release via the NIH GWAS data repository. During this period of exclusivity, NIH grants data access through Data Access Committees (DAC) to other investigators, who may analyse the data, but are expected not to submit their analyses or conclusions for publication until expiration of the exclusivity period.[91]

These recent trends towards openness show fascinating perspectives but may paradoxically become a closure unless we learn to handle all these new possibilities. Lawyers must return to being the finest interpreters of contract law, in order to modulate a system of incentives that take into account the following steps: defining the organisation (public, private or partnership); establishing the governance structure and transparent data access policies; types of contracts and licences, considering the dual nature of the biobank and consequently the different object (digital information or biological material). The complexity lies in the management of the interface between copyright and patent. It represents the main challenge of this contractual drafting where lawyers still have something to say.

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Chapter 13
The Roles of Material Transfer Agreements in Genetics Databases and Bio-Banks

Thomas Margoni

Abstract In this paper, we will analyse the role (or better the roles) that a specific document, the Material Transfer Agreement (MTA), has accrued in the exchange of bio-materials between research institutions. We will see how fundamental such documents have become in the most recent years, and that an uncontrolled proliferation of them could bring about a highly inefficient market situation. We will further see how standardisation will partially fix the problems connected to the exchange of bio-materials and bio-samples. However, whilst standardisation possesses undeniable advantages, it has to cope with a minimum level of flexibility, otherwise it will not be able to catch the huge varieties of situations involved. We will finally observe, how new digital and web-based collaborative efforts can contribute to achieve such trade-off between standardisation and flexibility.

13.1 Introduction

Biobanks are an emerging, yet fast developing phenomenon in the field of genomic and proteonomic research.[1] As in every field characterised by a rapid growth of (commercial) interests, the legal and contractual aspects are gaining momentum. The exchange of biological and research materials is becoming more and more formalised, and—differently from a few years ago—providing institutions now

[1] A Biobank can be generally defined as a storage facility of biological and genetic material that will be used for study, development of research and experiments. Biobanks are usually maintained by public or private research institutions, such as universities, hospitals, medical or pharmaceutical companies. Biobanks do not conserve exclusively the material but also a great deal of information, such as the clinical information relevant to a specific biological sample. Biobanks are huge databases of samples and information that raise a great deal of legal issues ranging from privacy to intellectual property, and contracts.

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tend to impose the use of specific contract forms that detail the rights and obligations attached to the material. Such contractual agreements are commonly referred to as "Material Transfer Agreements", or MTAs.

In the origins of biobanks and of genetic research more generally, the exchange of bio-material was "free", or at least "informal". Such situation is common to many avant-garde fields during their generative period, which usually unfolds within the boundaries of public or academic research. Historically, academics and public scientists disseminated their research findings and results through free and open channels such as informal sharing, journal publications, or presentations at conferences and seminars. In many instances, those basic discoveries had little direct commercial value and only occasionally were deemed worthy enough to try the patenting option. However, the same discoveries quite often proved highly useful for other researchers to elaborate upon.[2] The disclosure, i.e. making the findings public, was the main rewarding scheme.[3] "The reward structure of academic science reinforced that practice, awarding prestige and tenure on the basis of discoveries published in journals and provided openly to the scientific community".[4]

As said, though, this is history. The evolution of the sector has more recently taken a different path. Reasons are many—mostly market and industry-driven. Nonetheless, the law has also played a role in this shift.[5] New legislation has substantially influenced the funding system of public research centres such as Universities,[6] and courts have judicially sanctioned the patentability of biological products and organisms.[7]

In order to speculate about a possible evolutionary legal scenario in the biotech field, we can try to analogise from another field, which is also based on new

[2] See Hansen et al. (2005), p. 5.

[3] Thus excluding some of the Intellectual Property tools here recalled, such as trade secrets. A trade secret is protected as long as it remains secret, which contrasts with the necessity to publish the results. Patents, when allowed, also are a tool whose real utility needs to be tested in relation to the scientific sector, the funding/employing entity and the business method pursued. Delays in publishing connected to the patent application, and costs, sometimes represent a barrier in a sector where the reward is based on a "publish-or-perish" base.

[4] See Hansen et al. (2005), p. 5.

[5] See Caso (2005).

[6] See for example the Bayh-Dole Act, U.S.C. Title 35, Part 2, Chapter 18, § 200 "It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; [. . .] to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; [. . .] to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area".

[7] The first case affirming patentability in this field is Sidney A. Diamond, Commissioner of Patents and Trademarks, v. Ananda M. Chakrabarty, et al., 447 U.S. 303 100 S. Ct. 2204, 65 L. Ed. 2d 144, 206 U.S.P.Q. 193; subsequently many other cases have build upon this. Affirming patentability of purified substances that are naturally occurring, Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95 (S.D.N.Y. 1911).

technologies, but has already achieved maturity. Let us turn our attention to the origin of the computing industry.

At the beginning, software was just a by-product of what, at that time, was the real core of the computing industry: hardware. Hardware was the added value, and the software was just some additional information that was important, but not essential. It had the same importance as manuals and documentation. At that time (the 1960s and 1970s) one big company, IBM, was dominating this field, and was based mainly on the production of huge computers, square meters in dimension, for the simultaneous processing of many thousands of calculations. It is interesting to note how, during this time, most hardware was not sold, but rented. Software had no autonomous value at all, also because it was strictly hardware-dependant. A given piece of software would have not run on a different computer. Hardware was not standardised and every machine was almost unique, especially at the beginning. However, with the pass of time, hardware got cheaper, electronic engineering and programming were taught at universities, computers got smaller and more standardised. Software became more sophisticated and could be exported to different hardware that is compliant with a specific design.[8]

The idea of Personal Computers (PCs) arose, meaning computers that could be owned by smaller labs or even individuals. IBM did not understand such shift, but Microsoft (yet to be incorporated) did. Microsoft business was, and is, based on "software as a product". What had been the rule thus far, when software was a niche research area of a few visionary researchers, changed drastically. The possibility to exchange lines of software code in source form without having to get the approval of a legal department, or a software licence signed, slowly but inexorably disappeared.

The enforcement of technical and legal protections for software has been strong: binary distribution, trade secret protection, copyright protection, copyright expansion and the related Public Domain erosion, the still contentious patentability, Digital Rights Management (DRM) and Technological Protection Measures (TPM) and so on.[9] As a response, a counter-movement has emerged: Free Libre Open Source Software (FLOSS). Contrasting the technical, legal and contractual "closure" of the mainstream computing industry, FLOSS ethical and business methods are based on access to the source code and the freedoms to run, study, modify and redistribute the software.[10]

In the field of biotechnologies and the exchange of bio-samples and bio-materials is happening something similar to the brief summary of 40 years of history of computer science just told. It is too early to say whether exactly the same evolution will happen, being the biobank market still in its emerging phase. However, it is evident the parallels between the twenty-first century biomolecular researcher that sends a line of cells to his fellow at another institution, to that of the twentieth century computer scientist who sent a line of code to another colleague conducting a

[8] Among the many studies that have analysed this period of technological evolution, of particular interest is Zittrain (2008).

[9] See Perry (2005), Perry (2000), Caso (2004), Rossato (2006) and Perry and Margoni (2010).

[10] See http://en.wikipedia.org/wiki/The_Free_Software_Definition.

complementary experiment. In both cases, at the beginning of the story, when cell lines or code lines were commercial-less cutting-edge experiments, sharing and free exchange were the default. Not just because there was no commercial interest involved, but also because it was the quickest and most efficient way to evolve in such field: collaboration. With the advent of industries and markets strongly based on such innovations, it is natural that companies and incorporations become interested in gaining total control over the future patterns of their own financial investments. Whether it is not under debate that such strategic behaviour is central for companies engaged in a very competitive market such that of new technologies, the same does not necessarily hold true for the technological evolution per se.

In this paper, starting from the reported analogy, we will analyse the role (or better the role*s*) that a specific document, the Material Transfer Agreement (MTA), has accrued in the exchange of bio-materials between research institutions. We will see how fundamental such documents have become in the most recent years, and that an uncontrolled proliferation of them could bring about a highly inefficient market situation. We will further see how standardisation will partially fix the problems connected to the exchange of bio-materials and bio-samples. However, whilst standardisation possesses undeniable advantages, it has to cope with a minimum level of flexibility, otherwise it will not be able to catch the huge varieties of situations involved. We will finally observe, how new digital and web-based collaborative efforts can contribute to achieve such trade-off between standardisation and flexibility.

13.2 Definitions

Material Transfer Agreements (MTAs), are legal agreements governing the transfer of research materials and tools between universities, public and private research centres and the government. The kinds of clauses contained in such MTAs—whether they assign the property of the biological material or only offer a temporary right to use such material, and the connected limitations and conditions—will be analysed further ahead in this paper. At this stage, it suffices to our definition the aforementioned: the MTAs is the document accompanying the bio-material where we can find all the legal provisions that bind our giving or receiving the material, and the use we can do with it.

Regarding the object of such agreement, i.e., what we called so far bio-material or bio-tools, or again research material, it represents a huge and heterogeneous category, comprising cell lines, DNA segments, isolated and purified DNA, bacterial cultures, nucleotides, proteins, plasmids, archeas, antibodies, transgenic organisms, pharmaceuticals, chemicals, know-how, and many other similar products, that are developed by a given research infrastructure. It is worth noting that such a variegate category is composed by elements that may be protected by different legal tools, such as patents, trade-secret or confidential information, copyright, database rights, privacy, a sum of all/some of the above, or none. It is self-evident that given a specific MTA, its validity or enforceability, may be influenced, sometimes strongly, by the fact that the object of the agreement is protected or not by the legal tools above briefly mentioned.

13.3 Why Exchange?

At this point one might question why to exchange those materials. If they are so valuable, as reflected by their growing commercial value, why an entity should be interested in exchanging them, rather than in keeping as its best protected secret?

The reasons are many and vary following the nature of the entity, the nature of the object, and the nature of the market or industry. It is a common sense to affirm that to reinvent what has been already invented is at best a waste of time. More technically, to double the monetary, temporal, and human investment, in order to re-implement what already exists, is a clear system inefficiency. While such situation might be a legitimate consequence of specific business decisions, it is hardly conceivable under a pure scientific standpoint.

A balanced evaluation of such situation strongly depends on the type of business and funding models of the involved players. We have seen that one of the multiple players involved in the exchange of material are public research entities: in such case the protection of the financial investments plays a more modest role. Public research institutions and universities are usually committed to pursue scientific objectives that do not necessarily have to create immediate financial revenues. This is not to affirm that such entities are not compelled by a trade-off between their institutional goal (research) and their economic budget and cash flow. However, the goal of such entities is not to pay a dividend to their shareholders, rather to achieve public policy objectives. The difference in role and in funding is confirmed by the average delay time in providing bio-samples which is significantly lower in cases of public bodies.[11]

Regarding the nature of the object, it is a glaringly different scenario that of a final bio-product from that of a research tool. In the former case, in fact, it would be inconsiderate to share a potentially successful product with direct marketability, with a potential competitor's laboratory. Even accompanied by the most restrictive MTA, such sharing would make little sense for the providing laboratory. In contrast, in the case of the research tool, the situation can be close to the opposite: the research tool main objective is to help and assist in the research phase and this is its market function. The final product is completely irrelevant, the research tools is just that, a tool, an instrument that helps the activity of research. In such case, it would be much more likely that the contacted lab will send the research tool, which will be accompanied by an adequate MTA, establishing what can be done with it and what not, and the conditions.

Finally, also the relevant market or industry may make a difference in the willingness or ease with which a given lab will share its bio-assets. Some markets or industries are extremely competitive and the research that they develop has a

[11] See Campbell et al. (2002), p. 473; Dove (2002), p. 425; Hansen et al. (2005); Baca (2006); Walsh et al. (2007), and *infra* in this article.

direct or almost direct applicability to a given marketable product. Chemicals and pharmaceuticals are examples of such category. On the other side, we may have labs that develop their activities in basic research, where the direct marketability of a product is usually remote. In those cases, though, the fame and quality of a given result are powerful tools to attract funding and prestige to a specific lab. In the latter case, once again, it will be more likely to obtain the required material.

13.4 The Function of MTAs

We have already pointed out the variegate status under which a given bio-sample could be protected. Almost all the legal tools offered by the broad category of Intellectual Property—e.g., patents, copyright, trade-secret, confidentiality, databases—plus some others such as privacy and data protection, are potentially involved.

For any of the aforementioned situations the "default rules" are different, that is to say, what can be done and what cannot be done with a given bio-material will vary significantly whether it is protected by, say, copyright or patents. If we consider that the legal tools are not only the two just mentioned (copyright and patents) but all those identified above, and in many cases the same material has the potentiality to be protected by more than only one legal tool, we see how many combinations we can obtain. Such a situation, that can be iconoclastically seen as a legal minefield, is serious enough as to stifle scientific development, by stopping sharing and collaborations between labs, between private and the public sectors, and finally between scientists in general.

Given the depicted scenario, the utmost importance that a well structured MTA can achieve becomes manifest. In particular MTAs can be said to fulfill the following main tasks:

- To set out the boundaries for how the material is to be used;
- To determine the relationship between the parties involved in the transfer of the material;
- To offer greater levels of certainty that the use of the materials is within the use originally contemplated;
- To contribute avoiding those liabilities arising from misuse of the material;
- To help preserving intellectual property and attribution rights.

Additionally, MTAs are eligible for indicating another set of more "complex" rules, such as the so called *reach-through*, *grant-back*, or *co-authoring* clauses. However, the legal enforceability of the latter set of clauses is particularly debated, depending on the relevant legal system, as they may violate rules on contract formation, consumer-protection, anti-competitive behaviours, and moral rights.

13.5 The Intrinsic Limits of MTAs

The main limit of an MTA is rooted in its very nature, that to be a private ordering tool.[12] In other words, for an MTA to be successfully implemented it is necessary that the two (or more) parties agree on the (sometimes quite complex) content. To say this is to transfer the problem to a different layer, which is functionally superordinate to the conclusion of the MTA: the negotiation. During such phase the parties (or more often their legal departments) exchange offer and acceptance to reach a common agreement on the many different aspects connected with the transfer of the material.

At this stage, we can observe a first major issue with MTAs: what the legal department is pursuing, sometime does not correspond to the needs of the involved researchers. Here, we have the opportunity to observe clearly the dichotomy between the scientific roots and the financial ones of the bio-medical research. On the one side, in fact, the legal department is trying to protect the legal assets of the (public or private) institution, while on the other one, the researchers are trying to achieve new results and solutions. A good communication between the involved researchers and the legal representatives (and a common vocabulary and background to the two) is essential in order to achieve a good document that protects adequately both the assets of the entity and the interest of scientific evolution.

In light of what set out above, it could be inferred that a well written MTA, that represents adequately and clearly both entrepreneurial and scientific interest, is the solution to all, or at least many, of the problems connected with the transfer of bio-materials among labs and research bodies. Unfortunately, things, as usual, are not that straightforward, and as much as any other tool, also contracts, are just a tool, and its ultimate success depends on how it is used and implemented.

The scenario where, upon the necessity of a cell line that is known to be developed by another research lab, it suffices to ask for it, sign the MTA, and to obtain the material without further delay, is too many times unrealistic. Much more common in the real practice are situations where your colleague declares to be happy to send you a reagent fundamental for some experiment you are conducting, however it is not in his power to offer the final authorisation. Nevertheless, you can have your university to sign an MTA, by contacting her legal department. Usually, when the MTA negotiations are finally concluded, the field season is over, your grant has expired turning the experiment, and consequently the reagent you have finally obtained, completely useless, and what is worse, you wasted a lot of time with no results.

In the biological and biomedical fields, as much as, or even more than, in any other field, timely responses to requests are fundamentals. To obtain the material you need, 6 months after your request, usually turns your experiment completely irrelevant, creates a huge waste of time for yourself and your colleagues, and causes discredit to you and your research, since most likely you have not been producing any result during the past semester.

[12] See Elkin-Koren (2005).

Access to research material is also, and many times, mainly, a matter of reducing *transaction costs*. By transaction cost we refer to those non-monetary (but monetarisable) costs related to:

- Time (how long does it take from the request to the eventual reception of the requested);
- Contracts negotiations (personnel, legal representatives, communications from/to legal and scientific departments);
- Rights negotiated (clear understanding of the commercial and business consequences of the transfer or reservation of specific rights);
- Information (how well informed and cross-educated are the subjects involved in the legal negotiations of biological and genetic materials);
- Compatibility (many times the requested/offering lab's material is under some further contractual limitation, originating from precedent negotiations, which turn your request not processable, beyond and regardless of the willingness of the contacted lab).[13]

According to the aforementioned, different studies have been conducted confirming that delays are a major problem in this environment. Almost one out of two researchers has experienced delays when requesting material from another lab.[14] The reported average waiting time was 4 months when the request was directed to Universities or other public research bodies, and of 6 months when directed to the private sector.[15] However, when delays to the reported waiting time occurred, such delays accrued 8.7 months.[16] Impressive is also the rate of unfulfilled requests, that is, 12 % when directed to public institutions, and 33 % when directed to private ones.[17]

The reported situation is variegate, and differently affected by waiting times and delays depending on the specific field, country, market, product, and other specificities. It is, nonetheless, characterised by a common aspect: the extremely high amount of time required to obtain materials necessary for experiments. Delays are related to the increasing complexity of the terms that are negotiated in the MTAs.

A survey conducted by interviewing Canadian private and public research centres that declare to use on a regular bases for their transfers MTAs, shows some of the most common prohibitions and permissions to the research to be conducted with the material, under the form of contractual clauses.[18] Of particular interest is the high variance if we compare the different clauses, which causes a huge heterogeneity among the MTAs used, with the well known compatibility issues (see Fig. 13.1). The same study, also reports extremely high levels of

[13] See Walsh et al. (2007).

[14] Lei et al. (2009).

[15] Id. Walsh reports an average delay of 1–2 months, see Walsh et al. (2007).

[16] See Lei et al. (2009), p. 36.

[17] See Walsh reports an average delay of 1–2 months, see Walsh et al. (2007).

[18] Perry and Krishna (2007).

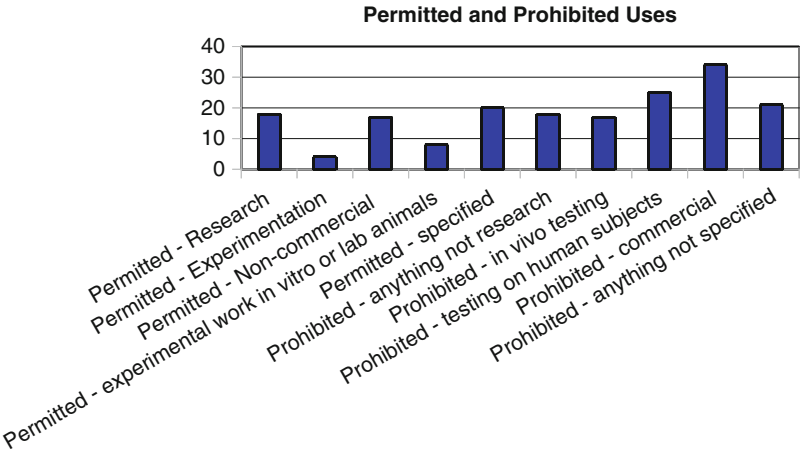

Fig. 13.1 Type of uses contemplated by MTAs (Perry and Krishna 2007)

indetermination regarding the temporal horizon of such agreements, where more than 80 % do not state it, or leave it for future determinations.[19]

An incredibly high variance is observable also if we compare the presence/absence of the most common terms/definition usually found in MTAs. In fact, whether it is commonly present an adequate definition regarding the identity of the parties and the identification of the material object of transaction, all the other definitions are only partially implemented (see Fig. 13.2). The latter category can be further subdivided in two: technical definitions and legal definitions. Technical definitions such as: modifications, progeny, original material, unmodified derivative, commercial purposes, are defined in between the 16 % and 24 % of the cases. Legal definitions such as: agreement, disclosure, effective date, intellectual property, confidential information, invention, do not achieve the 10% of the MTAs where are clearly defined (see Fig. 13.3).

It is apparent how the so far depicted situation is extremely far from the ideal solution where transaction costs are reduced to the minimum, and contractual clauses, relating either to technical or to legal concepts, are clearly defined. In fact, what the data shows, is an extremely poorly harmonised situation, where besides the most basics elements of the agreement (such as the identification of the parties, of the material object of transaction, and of the main usages) all the remaining aspects are only occasionally identified and determined. This is particularly true for legal concepts that in this field are of utmost importance (intellectual property, confidential information, effective date, duration). The most immediate consequence of this environment is an extremely litigious situation, which causes extra (legal) costs and loss of time, in the short period, and a general dis-incentive to enter into agreements in the long period. A lose-lose situation.

[19] Id.

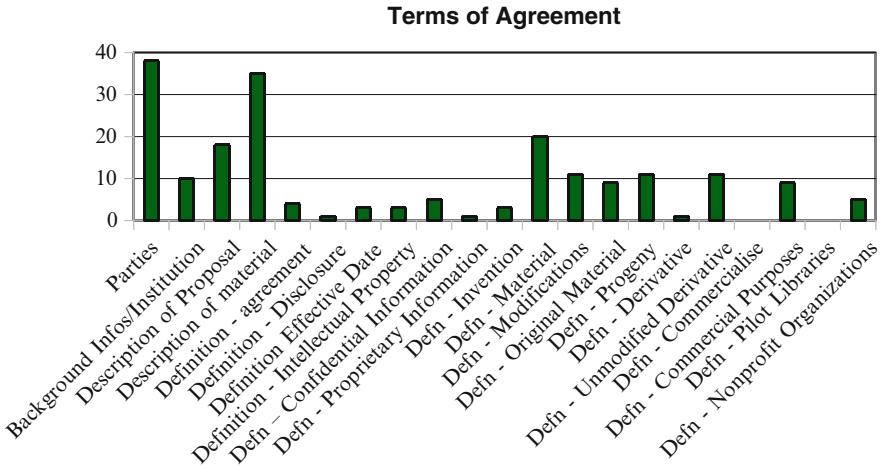

Fig. 13.2 Most common terms in MTAs in Canada (Perry and Krishna 2007)

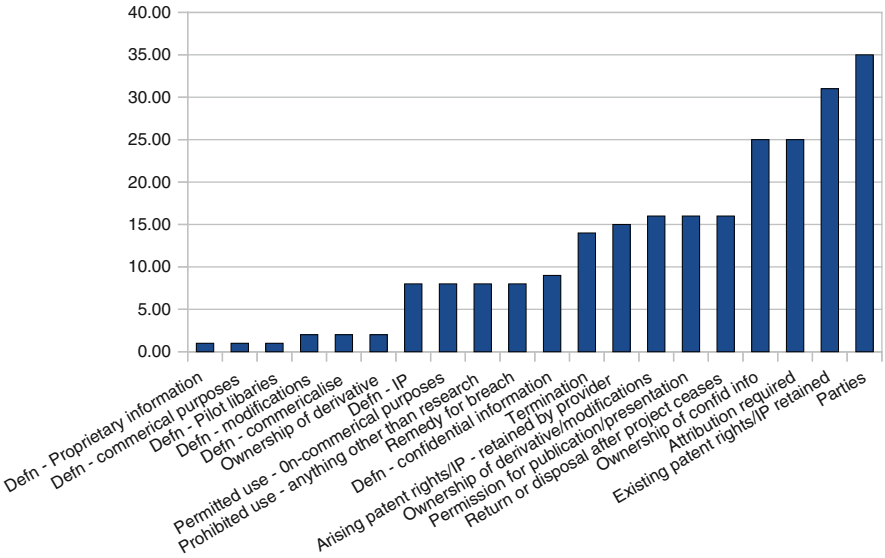

Fig. 13.3 Most common terms in MTAs in Australia (Perry et al. 2006)

13.6 Is Standardisation the Solution?

A partial solution to such scenario has been proposed with some success some time ago. The outlined problems are not entirely specific to the genetic field, and can be observed more generally in every environment where contractual negotiations are coupled with a particularly competitive and aggressive market. Add to this the

absolute novelty of such business sector, and the related lack of commercial customs and standardised clauses, and the picture is complete.

The answer both in the more general contractual field, and in the more specific one here analysed, carries the same label: standardisation. The phenomena of standard form contracts is a well known one to legal theorists and practitioners, and many commentators have written well structured analysis, setting out pros and cons of such phenomenon.[20]

The Uniform Biological Material Transfer Agreement has been drafted and set out 16 years ago, in 1995,[21] by a joint effort of AUTM and National Institute of Health.[22] Such standard contract form template, trimmed around the idiosyncrasies of biological and genetic material transfers, represents still nowadays a very well written piece of document. Such intrinsic quality is reflected in its initial success and diffusion.

As it is possible to read on the *UBMTA Federal Register Materials,* the background reasons that brought to the creation of the UBMTA are related to the importance that the National Institutes of Health (NIH) and the Public Health Service (PHS),[23] recognise the fact that "open access to the results of federally-funded research is a cornerstone of PHS's research policy. In the case of many research projects, this includes not only access to information provided through publications, but also access to biological research materials necessary to replicate or build on the initial results. *Frequently, the exchange of research materials between scientists in separate organizations involves case-by-case negotiation of material transfer agreements* [emphasis added]".[24]

The PHS vision regarding a standard agreement for generalised usage is concerned with addressing the most contentious contractual obligations stated by MTAs and with simplifying the process of sharing biological materials among public and non-profit organisations such as Universities and public research bodies. "The consistent use of the UBMTA by public and non-profit organizations could reduce the administrative burden of sharing materials as investigators come to rely

[20] Among the massive literature on this matter, in English language, see: Prausnitz (1937); David Slawson (1984); Posner (2003) at 116; Katz (1998); Slawson (1971).

[21] The Association of University Technology Managers (AUTM), is an association founded in 1974, and "provides professional development and networking opportunities for technology transfer professionals at all career levels and from established and newly forming organizations worldwide", it is currently composed by more than 350 members such as universities, research institutions, teaching hospitals and government agencies as well as hundreds of companies involved with managing and licensing innovations derived from academic and nonprofit research, see http://www.autm.net.

[22] The National Institute of Health (NIH), is a part of the U.S. Department of Health and Human Services, and is the "nation's medical research agency, making important medical discoveries that improve health and save lives", see http://nih.gov/.

[23] The Public Health Service (U.S.) was created by the Public Health Service Act, 1944 with the mission to "protect, promote, and advance the health and safety of the United States", see http://www.usphs.gov/.

[24] See Uniform Biological Material Transfer Agreement (1995).

on common acceptance of its terms by cooperating organizations". The PHS finally recognises that if used for the majority of transfers, the UBMTA could set standards for materials sharing that would be of long-term benefit to the research enterprise and to the public health.

The practical functioning of the UBMTA also deserves mention. In fact, in order to simplify and reduce even further the cost connected with negotiations between parties, the UBMTA should be approved at the organisational level, and handled in a master agreement or treaty format, so that "individual transfers could be made with reference to the UBMTA, without the need for separate negotiation of an individual document to cover each transfer". As a result, transfers of biological materials would be accomplished by an Implementing Letter containing a description of the material and a statement indicating that "the material was being transferred in accordance with the terms of the UBMTA [. . .] Thus, sharing of materials between organizations, each of which had executed the UBMTA, would be significantly simplified. At the same time, any organization would retain the option to handle specific material with unusual commercial or research value on a customized basis. Thus, the use of the UBMTA would not be mandatory, even for signatory organizations".[25] Currently, 420 research institutions have signed the Master UBMTA Agreement.[26]

The efforts produced toward the creation of a uniform agreement have also contributed to fix some of the issues that at the time of the drafting process, were felt as particularly compelling by the scientific community, industrial players and technological transfer departments. In fact, before the final version, the NIH published a draft prepared by PHS and invited public comments. Thanks to this crowd-sourced public debate, some taxonomic aspects have found a precise definition, in particular:

- Modifications. Such term is common in MTAs however, is usually poorly defined if at all. The UBMTA defines precisely that modifications are developed by the recipients and contain or incorporates the material as given by the provider.
- Profit–non-profit organisations. Another common distinction in many MTAs regards the financial/institutional goal, although, once again, without a widely accepted definition of the concept. The UBMTA implements the definition as codified by the Bayh-Dole Act.[27]
- Substances other than modification, progeny, or unmodified derivatives. The UBMTA clarifies that any other substance created by the recipient through the use of the material, which are not modifications, progeny or unmodified derivatives

[25] Id. at 12771–12772.

[26] See Signatories to the 8 March 1995, Master UBMTA Agreement, of the Association of University Technology Managers (AUTM), available at: http://www.autm.net/AM/Template.cfm?Section=Technology_Transfer_Resources&Template=/CM/ContentDisplay.cfm&ContentID=4636. Accessed 15 January 2011.

[27] 35 U.S.C. 18(201)(i) states: "(i) The term 'nonprofit organization' means universities and other institutions of higher education or an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1986 (26 U.S.C. 501 (c)) and exempt from taxation under section 501(a) of the Internal Revenue Code (26 U.S.C. 501 (a)) or any nonprofit scientific or educational organization qualified under a State nonprofit organization statute".

of material are owned by the recipient, who is free to license them without any interference by the provider of the material.
- Reach-through. These types of clauses are sometimes present in a variety of MTAs, and usually refer to the claim of property rights on the results obtained by the recipient. The UBMTA does not provide for any type of "reach-through" rights for the provider of the Material, i.e., it does not claim any property right in products developed by the recipient through the use of the transferred material.

This brief overview points out some of the positive aspects of the UBMTA. However, throwing and eye on the past 15 years, we can undoubtedly say that its overall usage and application—after its initial success—has been rather limited, and many research universities have drafted their own MTAs.[28] Let us spend a few words on why a good document has proved not as successful as it should have.

The main problem connected to the UBMTA is to be *monolithic*. In fact, as it is usual for standard contract forms, the UBMTA was and still is a "take-it-or-leave-it" tool. It fixes the problem connected with endless negotiations and human and capital resources overhead, by turning the whole regulatory framework of such MTA into an invariant set of clauses. This represents a very effective way to fix one of the main problems we have seen in connection to MTA negotiations. However, the solution is so drastic that sometimes is worse than the problem. So much standardisation created a monolithic body that has lost the ability to adapt and catch all the tiny, but many times significant, differences that the biotechnological environment possesses.

Further, it is also worth noting that the UBMTA has been geared exclusively to a University-to-University relationship, and whether nothing impedes that a commercial or for-profit entity decides to use it, the private sector does not represent its natural playground.

Another type of bias is connected with the legal nature of such tool. Standard form contracts suffer from many other flaws that the legal theory has successively identified and that can be briefly summarised as follows:

- Knowledge of content. Many times the contract is not negotiated by the parties, but one party submit a pre-compiled form to the other who is left with the only choice to adhere to it or not. Precisely for such reason, the latter does not read (carefully enough) all the clauses that is going to accept. Such type of strong standardisation represents an incentive to a "blind" acceptance of the contract that favours future litigations. Another name for standard form contracts is "adhesion contracts".
- Complete disclosure of the terms of the agreement. Such problem might be less relevant in the case of the UBMTA, since even when the recipient of the material only receives the implementing letter—that refers to the Master UBMTA—the signatories institutions have a legal obligation to adhere strictly to the terms of the UBMTA. However, such scheme, where the institutions are signatories of a master document, and scientists only of an implementing letter, can contribute to worsen the awareness of what one of the two parties, usually the recipient, is

[28] See in the same direction, among others, Rai and Eisenberg (2004).

obliged to, or prohibited from, doing. This situation is a clear contribution to unconscious contract non-compliances.

- Since clauses are given for a plurality of situations, especially in cross-jurisdiction bargaining, there are chances that some of the provisions will be deemed unenforceable by the relevant court of justice. Such problem are usually fixed by the insertion of a choice of jurisdiction or/and venue clause, however, once again, this represents a typical situation where the stronger party can impose particularly burdensome obligations to the weaker party.
- Conform behaviour. If a standard form contract is the default in a given environment, it becomes less likely that a party, even when is not completely convinced of the content, will decide not to sign the contract. In a non-legal environment, it might become harder to justify a non-conform contractual orientation. Sometime, in our specific case, the necessity to have the material right away, will contribute to post-pone the worries connected to one or more clauses, which might be of only eventual application ("should you obtain a patent using our material . . ."), but could indeed bring about an undesirable situation (" . . . you are obliged to name us co-authors").
- Finally, the inequality of the power of the parties involved. Usually, in fact, one of the two parties has less contractual power (less money, less human resources, informational deficits, etc.), which adds up to the urgency for such party to obtain the material, creating an undue burden on the already weaker party. While it is true that in the case of the UBMTA such situation is less likely thanks to the inherent balance of the document, this aspect still represents a major legal and doctrinal issue for the category of standard form contracts.

13.7 Can Technology Help Improve Such Situation?

If we agree with Walsh,[29] we acknowledge that one of the major issues connected with the transfer of bio-samples is related to its prompt availability and circulation among labs. We should also remember that delays are caused much more often than expected by transaction costs (time, informational deficits, and human resources) rather than by Intellectual Property rights, which may or may not attach to the object of transactions.

In light of that, the goal of the UBMTA—reduction of transaction costs—could be pursued through a different path, one that offers a certain level of standardisation, without imposing a too strong rigidity. Such solution takes the name of *digital and web-based technologies*.

[29] See Walsh et al. (2007).

13.7.1 Metadata-Driven Approach

The following 932 characters of code can efficiently contribute to fix the problem:

The material is available from under the following offers:

Science Commons MTA.

The offer expires on <span proper/media/ECCB-8A44/Logo_lawtech.jpgty="sc:expires">04/06/10
The transmittal fee is 1
The offer is available to nonProfit institutions
Offer is limited to use with protocol aaa

Such code is a *metadata*, that is, a piece of code that can be appended to the digital representation of the material that a provider or a receiver is interested in either offering or using. The enormous advantage of such implementation is connected with the web-based infrastructure that this scheme enables. A metadata-driven approach is a methodology that can be implemented by many different players and projects in different ways. In this paper we use as a reference example one of this projects, probably the most developed in this area, that is characterised by an open and public work-flow, and by a deep understanding not only of the biological and scientific part of the problem, but also of the legal and technological one. Such project is called Science Commons,[30] and was born as a particular application in the field of science, of its "older brother", the more famous Creative Commons.[31] To recall such connection is fundamental, as the methodological approach (openness, web-based, modularity, and representation in human, legal and machine code of the contractual terms), has been borrowed from the latter. The Science Commons (SC) project also recognises the validity of the UBMTA, and in fact implements a version of it, to which it has added the metadata and the commons-deed forms of representation.[32]

The Science Commons MTA project originates from the necessity of reducing the costs associated with the transfer of material, as they have identified—through their

[30] See http://sciencecommons.org/projects/licensing/.

[31] See http://www.creativecommons.org.

[32] "[This work led us] to not only build our own agreements to address university-industry transfer but to incorporate two key existing university-university agreements—the Uniform Biological Materials Transfer Agreement (UBMTA) and the Simple Letter Agreement (SLA)" at: http://sciencecommons.org/projects/licensing/.

own surveys and data[33]—the same results that we have already seen in this study.[34] A metadata and web-based approach, though, is not only helpful with regard to the understanding of the contractual terms. It possesses also the capability of facilitating the identification and location of the material that a scientist or a lab is seeking, reducing the amount of time (usually weeks or even months) to the time of a web-based inquiry. The metadata-driven approach allows for an easy integration into search engines, as well as into literature databases so that "scientists can 'one-click' in-line as they perform typical research". Such web-based infrastructure further allows for tracking materials propagation and reuse, "creating new data points for the impact of scientific research that are more dimensional than simple citation indexes, tying specific materials to related peer-reviewed articles and data sets,"[35] through the use of the *ccHost* platform.[36]

Another major feature of the Science Commons approach is still connected to the web-based approach that strongly characterises such initiative, but affects more directly the "generative" moment. As we have pointed out above, one of the limitations of the UBMTA is that it is "monolithic", meaning that a one-fits-all contractual agreement should be used for a variety of situations, and we have already seen how far from reality this may be. SC offers such *modularity* through a web-based answer-driven form, whereby it is possible to frame the MTA following the needs of the provider. Of course, we are not in presence of an unlimited set of possibilities, as this would not be feasible and would invalidate the effort of reducing the transaction costs connected with endless negotiations and incompatibility of contractual agreements. By trying to create a balanced trade-off between standardisation and modularity, SC offers to the providers of material a series of options.

By using the relevant web-form,[37] the interested provider is asked to insert information that identifies herself and the material, both by content description and by providing an URL. After the identification of the offering party and the object of transaction, the type of offer can be chosen. It is possible to choose between the UBMTA, the Simple Letter, the SC MTA, and finally a Custom Agreement. The latter requires the insertion of an URL that points to an on-line resource containing the relevant agreement. In such case, SC offers the support of the meta-data and the web-based advantages set out above. In the former two cases—UBMTA and Simple Letter—the provider will be asked to insert the "Termination date" and the "Transmittal fee", the only two options that those MTAs allow.

The depicted scheme expresses all its potentialities when the provider chooses the Science Commons Material Transfer Agreement (SC MTA). In this eventuality the provider can chose:

[33] See http://sciencecommons.org/projects/licensing/empirical-data-about-materials-transfer/.

[34] See Walsh et al. (2007), Lei et al. (2009), Perry and Krishna et al (2006), and Perry and Krishna (2007).

[35] Id.

[36] See http://wiki.creativecommons.org/CcHost.

[37] See http://mta.sciencecommons.org/chooser.

- The recipient class (all types, only non-profit, only for-profit);
- Restrictions connected with the use of the material that may relate to:
  - Field of use (all research, restricted to disease, all uses except disease, or restrict to "protocol" where it is possible to enter the protocol description);
  - Whether scaling up is allowed;
  - Whether retention of material is allowed;
- Additional information regarding the offer:
  - Termination date;
  - Transmittal fee.

Upon insertion of such information, the form will automatically generate the contractual agreement implementing all the information provided, in three different formats:

The Science Commons Material Transfer Agreement (the legal code),[38]
The Meta-data (the machine-readable code),[39]
The Commons deed (the human readable code).[40]

Further, an implementing letter is also provided.[41] Finally, the web-based enhanced scheme for wider circulation of material, takes—currently—advantage of the iBridge Network,[42] in an effort of creating an on-line portal for the providing and obtaining of the biological materials, on the base of the three different languages of expression we have seen above. Basically, a provider of material can "upload" his material on the iBridge website, and by doing that he will be offered with the chance to choose between the MTAs implemented by the Science Commons project, and will receive an MTA (either the UBMTA or the SCMTA) under the form of a legal code (the MTA), a human readable code (the Commons deed) and a machine readable code (the metadata). Further, such information will be indexed on the iBridge site. In this way, a scientist looking for a material will use the iBridge website as a kind of specialised search engine, where to look for a specific material, with the option to refine the query on the base of the legal terms contained on the MTA. In the intentions of the drafters, such scheme, when fully implemented, should prove as efficient as other web-based tools are for books or other physical goods: "We have taken full advantage of Web technology to build a technology infrastructure that can support powerful searching and tracking of available materials. By putting all of these pieces together, we envision our materials transfer system to be one day as efficient as eBay for auctions, or Amazon.com for ordering products, or Google for searching for content".[43]

[38] See http://mta.sciencecommons.org/agreements/sc-ou/2.0/legalcode.

[39] See http://mta.sciencecommons.org/chooser.

[40] See http://mta.sciencecommons.org/agreements/sc-ou/2.0/.

[41] See http://mta.sciencecommons.org/agreements/sc-ns-rd/1.0/letter?source=mta&providerOrg=a&providerAddress1=a&materialDesc=b&legalURL=agreements/sc-ns-rd/1.0/legalcode.

[42] http://www.ibridgenetwork.org/.

[43] See http://sciencecommons.org/projects/licensing/.

13.8 Conclusion

We have observed how in a field where technological innovation develops at an extremely rapid pace, and where advancements in technology allow new discoveries in the biological and genomic sector, science finds itself between openness and closeness. On the one side, there is a basic set of knowledge, especially in the area related to genetics and DNA sequencing, that needs to be free and freely available. On the other side, capitals need to be attracted in order to fund the more expansive projects that might have only a long-term, eventual success. Intellectual Property, especially in this field, is a contentious issue, meaning that depending on the jurisdiction,[44] and in the same jurisdiction, on the courts and on the time,[45] a given set of genetics instructions might be deemed patentable or not. However, we observed how, besides and regardless of IP-based concerns, in the specific field of bio-banks and bio-materials transfers, another "enemy" needs to be fought: transaction costs. We reported various sets of data, which confirm the situation: endless negotiations, informational deficits, time and human capitals, incompatibility between different contractual models, lack of standardisation, excessive rigidity: All these aspects represent another big barrier to scientific collaboration and technological evolution. Efforts to fix the problem are not new, the UBMTA represents a good attempt, and building on it, plus adding digital and web-based advances, currently the Science Commons project seems a very promising model.

However, once again, we cannot confuse the finger with the moon. Contracts are not the goal. Contracts are the tool to achieve a goal that in this case is that of favouring scientific collaboration and technological evolution, by lowering the costs represented by legal barriers (IP) and transaction costs. However, contracts are not the perfect tool, and they suffer from many flaws. We have briefly identified those connected with standard form contracts. More generally, however, we have to recall that access to knowledge and participation to scientific and technological growth are a public policy goal. Hardly, they can be achieved *only* through a private ordering tool.

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[44] See The Trilateral Search Guidebook in Biotechnology (2007).

[45] See Sidney A. Diamond, Commissioner of Patents and Trademarks, v. Ananda M. Chakrabarty, et al., 447 U.S. 303; Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95 (S.D.N.Y. 1911); Commissioner of Patents v. President and Fellows of Harvard College 2002 SCC 76, 219 D.L.R. (4th) 577, 21 C.P.R. (4th) 417, [2004] 235 F.T.R. 214; Association for molecular pathology v. United State Patent and Trademark, 09 Civ. 4515, 2010 (S.D.N.Y.).

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Chapter 14
Quasi-Patents and Semi-Patents in Biobanking

Gideon Parchomovsky and Michael Mattioli

Abstract Until recently, genetic researchers were like early mapmakers charting the world's coastlines with only compasses and notepads. The map of the human genome, like an ancient map of the world, was sketched in crooked and uncertain strokes. In the year 2000, things changed. The completion of the Human Genome Project yielded the first-ever molecular blueprint of the human body. In time, this blueprint may develop into a detailed atlas of preventions, diagnoses, and cures for deadly diseases. The research necessary to reach this goal will rely on biobanks—repositories of biological materials and associated data. Today, wide varieties of such facilities are in operation at universities, hospitals, corporations, and non-profit entities worldwide. Some examples include the United Kingdom Biobank, the Duke Biobank, the University of Pennsylvania Tumor Tissue Bank, the National Gene Vector Biorepository at the Indiana University School of Medicine, the Mayo Clinic Biobank, the da Vinci European Biobank, and Genetic Alliance Biobank. Often suspended in paraffin wax or liquid nitrogen, the tissue samples in biobanks come from a variety of sources: participants in clinical trials, patients who undergo surgery or routine medical tests, recruited donors, and contributions from patients' families. These samples are usually accompanied by useful information, such as a tissue donor's age, sex, race, cancer history, family medical history, allergies, and medications [Heaney C et al. (2009) The perils of taking property too far. http://www.stanford.edu/group/sjlsp/cgi-bin/orange_web/articles/index.php?CatID=1009. Accessed 7 May 2010]. Today, the storage of human tissues and associated data is a sophisticated practice. Even as biobanks grow in size and sophistication, their

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future is uncertain. At most biobanks, critical questions regarding the allocation of property, both real and intangible, remain unanswered. Who should own physical samples and data? Who should have access to samples, data, and research findings, and on what terms? Patents present further quandaries: who should have access to patented inventions stemming from research? Should exceptions be made for the non-commercial use of patented ideas? Should the fruits of biobank research be shared with donors in order to encourage future donations? In this article, we formulate possible answers to these questions.

14.1 Introduction

Until recently, genetic researchers were like early mapmakers charting the world's coastlines with only compasses and notepads. The map of the human genome, like an ancient map of the world, was sketched in crooked and uncertain strokes. However, in the year 2000, things changed. The completion of the Human Genome Project yielded the first-ever molecular blueprint of the human body. In time, this blueprint may develop into a detailed atlas of preventions, diagnoses, and cures for deadly diseases.

The research necessary to reach this goal will rely on biobanks—repositories of biological materials and associated data. Today, wide varieties of such facilities are in operation at universities, hospitals, corporations, and non-profit entities worldwide. Some examples include the United Kingdom Biobank, the Duke Biobank, the University of Pennsylvania Tumor Tissue Bank, the National Gene Vector Biorepository at the Indiana University School of Medicine, the Mayo Clinic Biobank, the da Vinci European Biobank, and Genetic Alliance Biobank.

Often suspended in paraffin wax or liquid nitrogen, the tissue samples in biobanks come from a variety of sources: participants in clinical trials, patients who undergo surgery or routine medical tests, recruited donors, and contributions from patients' families. These samples are usually accompanied by useful information, such as a tissue donor's age, sex, race, cancer history, family medical history, allergies, and medications.[1] Today, the storage of human tissues and associated data is a sophisticated practice.

However, even as biobanks grow in size and sophistication, their future is uncertain. At most biobanks, critical questions regarding the allocation of property, both real and intangible, remain unanswered. Who should own physical samples and data? Who should have access to samples, data, and research findings, and on what terms? Patents present further quandaries: who should have access to patented inventions stemming from research? Should exceptions be made for the non-commercial use of patented ideas? Should the fruits of biobank research be shared with donors in order to encourage future donations?

[1] Heaney et al. (2009).

These are nuanced questions with no simple answers. Designing a biobank's property policies requires delicately balancing incentives and burdens among donors, researchers, and sponsors. If the scales are tilted too far in one direction, the support and participation of key stakeholders could be lost. To make matters more complex, most countries lack comprehensive laws or regulatory regimes governing biobanks. In the US, for example, a patchwork quilt of federal and state laws may apply to the handling of physical samples, intellectual property, and raw data.[2] As biobanks reach across international borders, legal fragmentation and a consequent lack of predictability increase.

Patents present problems, but also opportunities. The majority of patents that stem from biobank research relate to human genes. These may include patents covering specific gene sequences and processes for obtaining them, as well as patents identifying correlations between particular genes and human conditions. While the availability of gene patents may encourage important medical advances, patents relating to human genes have been aggressively wielded by some companies to block non-commercial research. This tension has placed gene patents in the eye of a political and legal tempest for years. Recently, the debate has gained force in the wake of court decisions that have narrowed the scope of research exceptions to patent infringement, and called into question the patentability of human genes.[3]

Today, biobanks can learn from the successes and failures of patent holders that came before. For example, in the mid-1990s, a biotechnology firm called Myriad Genetics successfully identified and patented a gene sequence associated with breast and ovarian cancer. After selling a test to identify these mutations in 1996, Myriad attempted to corner the market by aggressively asserting its patents against researchers, many of whom were not Myriad's business competitors.[4] The University of Pennsylvania Research Laboratory was one of several non-commercial research institutions that received strongly-worded cease-and-desist letters from the company. Before long, Myriad's hawkish stance tarnished the company's reputation and eroded its foothold in the international market for genetic testing. The validity of Myriad's patents was later the subject of a high-profile lawsuit that reached the Supreme Court.[5] Today, experts point to Myriad's experience as a cautionary tale that demonstrates the risks of aggressively asserting gene patents.[6]

Similar insights arose in the early days of the Human Genome Project ("HGP"). In the early 1990s, the National Institutes of Health ("NIH") adopted guidelines that

[2] Statyn (2009).

[3] *See Madey v. Duke*, 307 F.3d 1351 (Fed. Cir. 2002); *Ass'n for Molecular Pathology v. USPTO,* 09 Civ. 4515 (S.D.N.Y., opinion, Mar. 29, 2010).

[4] *See* Heaney et al. (2009), *supra* note 1 at 51–57.

[5] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 132 S. Ct. 1794, 182 L. Ed. 2d 613 (2012) (granting writ of certiorari, vacating judgment of and remanding to the United States Court of Appeals for the Federal Circuit for further consideration).

[6] *See Id.*

harmonised with the 1980 Bayh-Dole Act, allowing federally-funded researchers to obtain patents on discoveries.[7] Before long, though, this patent-friendly attitude changed. The NIH itself filed patent applications on short sequences of genes, sparking what was later described by commentators as "an international firestorm" of public criticism.[8] Since that time, the NIH and many post-HGP biobanking initiatives have generally disfavoured patenting, at best viewing it as a sometimes-necessary evil.[9]

There are also patent success stories to learn from. Stanford University's program for licensing methods of sequencing recombinant DNA has been hailed by one commentator as "one of the most successful university technology licenses" in history, yielding hundreds of millions in patent licensing revenue for Stanford, billions in product sales, and important non-profit research.[10] From the very start, Stanford provided a far broader research exception than the law specifies, by not requiring nonprofit research institutions to pay licensing fees.[11] From commercial partners, Stanford solicited input concerning its patent policies. This open attitude showed that the university placed long-term relationships ahead of quick licensing collections. Moreover, Stanford was creative: rather than charging commercial users a single royalty, it set up a graduated scale of royalties and a menu of IP "products" that could be licensed.[12] Ultimately, Stanford's broad research exemptions, respect for commercial partners, and flexibility represent a benchmark in successful gene patent licensing.

Fostering a spirit of collective endeavor does not end with wise patent policies. Biobanks must also set sound policies for the sharing of scientific data and research findings—practices central to genetic research. In 1992, when the Human Genome Project ("HGP") was still in its early days, the NIH approved a set of guidelines governing the publication of data generated by HGP-funded research. Stating that data sharing is "essential for progress toward the goals of the program", the NIH required rapid and far-reaching dissemination of research data.[13] These early guidelines planted the seeds of what has since become a valuable genetic informational commons.

Commentators cite the UK Biobank and the HapMap Consortium as two recent examples of successful data sharing policies in action. The UK Biobank makes data sharing a requirement for all researchers.[14] As its policies state, "[a]ll research users will be required to put results from all analyses made on participants' data and samples, and any relevant supporting information, in the UK Biobank database so

[7] 35 U.S.C. § 200-212. *See also* Contreras 2010.

[8] *Id* at 24.

[9] *See., e.g., Id.*

[10] Feldman et al. (2007).

[11] *See Id.*

[12] *Id* at 1803. *See also* Heaney et al. (2009), *supra* note 1 at 57–58.

[13] *See* Contreras, *supra* note 6 at 23.

[14] *See* Heaney et al. (2009), *supra* note 1 at 61.

that they are subsequently available to all researchers with appropriate scientific and ethics approval".[15] Balancing researchers' competing need for access to data against their occasional need for limited exclusivity, the UK Biobank allows researchers to keep certain information confidential for a limited period of time "as they prepare papers for publication, file patent applications or otherwise pursue reasonable competitive advantage for their efforts". The International HapMap Consortium, a human genome mapping project, aims at similar goals by way of a click-wrap license that forbids underlying data and research findings from being incorporated into restrictive patents.[16] However, the HapMap Consortium's restrictions on patents are limited, reaching only as far as is needed to ensure access to project data.[17]

Biobank data sharing policies are only as useful as the data they govern. As a result, one of the most pressing concerns of many biobanks today is encouraging tissue sample donations. Under current law, donors do not retain broad property rights in their body parts. In the seminal 1992 case of *Moore v. Regents of California*, the Supreme Court of California ruled that a tissue donor with leukemia did not retain ownership rights in blood cells and other tissues that had been excised from his body and subsequently used by his physician to obtain a patent.[18]

A similar result was reached in the 2003 case of *Greenberg v. Miami Children's Hospital*, where a Florida district court ruled that a doctor's use of donor cells to receive patents did not amount to conversion, because the donors had no property interest in the materials.[19] The Eighth Circuit Court of Appeals issued a consistent ruling in the 2007 case, *Washington University v. Catalona*.[20]

Taken together, *Moore*, *Greenberg*, and *Catalonia* set a precedent that donors in the US do not own the tissues removed from their bodies, and have no claim to possible profits. (On a metaphysical level, this result is akin to Aristotle's famous statement that a finger, once severed from its owner, ceases to be a finger at all.) Fortunately for patients, the law requires that researchers receive informed consent from their subjects before performing any procedures.[21] As a result, researchers and donors can strike biological bargains before tissues are ever removed. Recognising this, some biobanks have tried to balance the scales more evenly by delivering benefits back to donors. For example, the Coriell Personalized Medicine Collaborative and the Personal Genome Project provide free genetic analysis and related information to participants. Commentators have advocated similar types of benefit-

[15] UK Biobank Ethics and Governance Framework, Version 3.0, 13–14 (Oct. 2007).

[16] *See generally* The International HapMap Project 2003.

[17] *Id.*

[18] *Moore v. The Regents of the University of California*, 51 Cal.3d 120 (1990).

[19] *Greenberg v. Miami Children's Hospital*, 264 F.Supp.2d (2003).

[20] *Washington University v. Catalona*, 437 F.Supp.2d 985 (2006).

[21] *See* Heaney et al. (2009), *supra* note 1 58–59.

sharing policies, such as providing donors with access to drugs and diagnostic tests at special rates, or directing funds back into research or healthcare infrastructure.[22]

Some believe that the best way to facilitate such benefit sharing is through a charitable trust model.[23] Under this approach, a biobank acts as a trustee, holding legal title to all tissue samples and associated data. The beneficiary is the general public. Among other advantages, commentators believe that the trust model would place hospitals—the sources of many tissue samples—in the role of stewards, rather than brokers. Moreover, a trust model could allow donor groups to have a greater advisory role in the use of their tissue tissues. On the other hand, pundits note that it may be difficult to incorporate patents into the architecture of a charitable trust at genomic biobanks.[24]

The brief history of biobanking has raised complex problems concerning property rights: patents can both encourage and hinder research; Data sharing may benefit research generally, but not necessarily individual scientists; Tissue samples need responsible stewards. While these may seem like isolated issues, they are in fact different faces of a single multi-dimensional puzzle. And, like the twisting surfaces of a Rubik's Cube, a change made along one axis necessarily impacts the whole. This chapter presents a framework for understanding the biobank property puzzle, and from this framework, introduces two new models for genetic asset management.

14.2 Configuring Property in Three Dimensions

As researchers continue to advance genetic science, lawmakers, courts, and the public are still struggling to define its legal boundaries. In fact, shortly before this chapter was written, the Supreme Court rendered a decision that attracted widespread media attention by appearing to limit the patentability of certain types of gene-related innovations.[25]

Amidst this legal flux, research centres rely on private contracts to govern genetic assets. When drafted with care, such agreements can create a sense of predictability that the law alone still fails to supply, and a degree of cohesion in what remains a fragmented legal domain. But perhaps most importantly, agreements can be fine-tuned to help biobanks maximise their potential. In crafting and enforcing property laws, the government simply does not aim to maximise value in this way. Rather, public orderings of property are geared more toward

[22] *See* Simon (2009), pp 77–78.

[23] *See, e.g.*, Simon (2009), p 77.

[24] *Id.*

[25] Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 S. Ct. 1289, 182 L. Ed. 2d 321 (2012) (holding that patents claiming methods of calibrating drug dosage were invalid as claiming fundamental laws of nature).

establishing order in circumstances where individuals are unable to strike bargains due to high transaction costs.[26] Thus, private contracts are an effective tool for biobank policymakers.

But to achieve their goals, biobank policy makers must grapple with the same questions that vex lawmakers and judges. What is the nature of genetic property? How can patents incentivise, and not frustrate research? To the extent that data sharing among researchers is helpful, to what degree should biobanks mandate it?

New solutions to these puzzling questions emerge when property itself is viewed in a new way. Contrary to conventional thought, real estate, consumer goods, and even patents are not immutable absolutes but are in fact mixtures of three fluid variables: assets, owners, and dominions.[27] These three dimensions define the universe of property just as length, width, and height define the boundaries of the physical world.

A simple example illustrates this concept: consider the management of property rights in a newly-designed residential home. A traditional Blackstonian view of property would assume that the property's potential owner would exclusively draw all benefits the house has to offer. Based on this view, the potential owner would decide whether or not to build the home by weighing the costs of construction against the total utility and enjoyment the building provides. However, this conventional view is probably incomplete: the building will likely outlast the lifetime of the builder, and the enjoyment of the house's appearance will mostly accrue to neighbors and passers-by. Likewise, local ordinances will limit the potential buyer's freedom to build expansions, or operate businesses on the premises. Property, as we naturally tend to think of it, is a conceptual shortcut that does not completely capture our nuanced relationships with the world, the law, or with each other.

Viewing the same home in terms of assets, owners, and dominions (often referred to herein as the "three-dimensional view") reveals compromises that can be made among its potential beneficiaries. The utility of the house reaches beyond mere shelter and extends to intangible assets, such as its appearance. Thus, the ownership of the structure itself could go to the buyer while the "ownership" of the building's exterior appearance (a spill-over benefit) may go to passers-by. Alternatively, the buyer could be denied dominion rights to change the building's appearance, but could maintain full ownership of both the interior and exterior of the building. This second solution is exemplary of the estate system, where real property is not defined in terms of soil or grass, but as abstract estates that define packages of land rights. In yet another alternative, the many beneficiaries of the home might band into a housing cooperative and convey ownership to a corporation. The three-dimensional view reveals how property value and production can be maximised through contractual arrangements.

[26] Bell and Parchomovsky (2008).

[27] *See generally*, *Id.*

Biobanks can draw on this view of property. In particular, the abstract assets that are central to biobanking—patents, raw data, and research findings—are amenable to legal reconfiguration. In part, this is because intangible assets are inexhaustible and non-rivalrous.[28] Unlike roads or parcels of land, one individual's use of these resources does not threaten use by others, and does not deplete from a limited supply. For example, a patent owner can license its rights—thus sharing its dominion—exclusively to a single business partner, or non-exclusively to a large community of collaborators without subdividing, allotting, or apportioning its property as one would need to do with tangible goods. Even the exclusive rights to make, use, or sell patented inventions can be severed and individually licensed through contract alone. The same is true of raw data and findings drawn from research. The following discussion illuminates how reconfiguring intangible genetic assets along property's three dimensions reveals new ways of maximising investment and research at biobanks.

14.3 Design Principles

The primary goal of biobank asset management is to facilitate genetic research. In the past, this goal has been frustrated by two competing and deeply-intertwined forces: the need for data sharing among researchers, and the possibility of commercialisation that fuels costly research. Researchers will not sow unless they stand to reap.

The proposals presented in this chapter seek to balance these two demands. At the outset, it is helpful to first define the nature of the assets to be governed, and the direct stakeholders. The relevant players include academic, commercial, and non-profit research institutions, and individual researchers working on their behalf. The assets held among these participants may include patents, research findings, raw data generated in the course of research, and tissue samples.

The utility of patents is multifarious: written descriptions and figures provide valuable instruction on how to practice an invention, while patent claims define boundaries of exclusion. Additionally, patents may sometimes possess an abstract value, independent of their content, when strategically composed into portfolios.[29] Like patents, raw research data and findings are valuable resources that all researchers can build upon. But research findings have a particular value to the scientists that generate them, as they can serve as the basis of publishable writings. And unlike patents, data and findings typically contain no, or very few, powers of exclusion. (It has been suggested that laws protecting electronic databases in some countries may apply to compilations of genomic data, but this possibility remains largely untested.)[30] Finally, tissues samples—the fount of all genetic knowledge—are exhaustible, rivalrous resources.

[28] Lessig (2001).

[29] Polk Wagner and Parchomovsky (2005).

[30] *See* Heaney et al. (2009), *supra* note 1 at 48.

14.4 Ownership of Samples and Data

Before discussing the ownership of patents, it is useful to discuss the sources of these valuable assets—human tissue samples and associated data. As discussed earlier, the law typically divests patients of possession over donated biological materials, and instead assigns ownership to doctors, researchers, and their institutional affiliates. Against this legal backdrop, biobank policymakers must craft ownership schemes that are likely to encourage optimal levels of research and investment.

We propose a biobank property regime in which tissue samples and associated data are co-owned and managed by a consortium of universities and non-profit institutions. Under this plan, a public trust would be established, in accordance with, the consortium would manage and hold legal title to the samples and data for the benefit of the general public.[31]

This ownership structure could provide significant benefits. Importantly, a consortium of academic and non-profit research centres would not be susceptible to many of the conflicts of interest and shareholder pressures that frequently arise in the corporate domain. As compared to a corporation, these entities would thus have greater flexibility to balance competing goals, and to consider and respond to the many normative policy concerns raised by biobanking. Moreover, universities and non-profits would possess the necessary expertise, experience, and commitment to genetic research to make prudent decisions concerning the management of samples and data.

A charitable trust could also have appeal for donors and researchers. For example, commentators have suggested that donation forms and agreements could grant biobank donors membership on internal boards or election to a board of trustees.[32] Moreover, unlike a private corporation, a trust would not be required to sell off its inventory in the event of a bankruptcy.[33] The promise of meaningful advisory power and long-term security of tissue samples could thus encourage donor participation. Finally, the purpose of a charitable trust—to benefit the public—complements the altruistic goals that define biobanking as not only a scientific endeavor, but a social one.

With respect to funding, universities and non-profit entities would be well-suited to raise funds for basic research from government grants and awards. Commercial applications would be encouraged via footholds for commercials entities, as discussed in the sections that follow.

[31] Winickoff and Winickoff (2003).
[32] *Id.*
[33] *Id.*

14.4.1 Quasi-Patents[34]

Revisiting the analogy of cartography, consider the different ways that maps can facilitate exploration and conquest: they guide travelers across unfamiliar terrain, and they also define territorial boundaries. With lines and legends, colors and codes, property owners use maps to stake their claims.

Genomic maps are similar. The first map of the human genome, completed in the year 2000, guided researchers to make important medical discoveries. Along the way, these same researchers filled in the details of the map, and claimed certain portions of the vast human genome as their own. Like property lines, patents define boundaries of exclusion. And, like property owners, patent holders can generally keep out whomever they wish. For example, under American law, "*whoever* without authority makes, uses, offers to sell, or sells any patented invention, within the United States" is a patent infringer.[35] The policy goal behind this broad right of exclusion lies in the belief that patents can encourage investments in research. The need for such investment is particularly critical to genetic research—a field where valuable discoveries rarely result from cheap "Eureka" moments, and are usually the product of substantial persistence, capital, and combined creative energies.

But could a more tailored property regime strike a better balance between researchers and their benefactors? Put another way, who do gene patent holders need to exclude the most? History suggests that the answer is commercial competitors. The cautionary tale of Myriad Genetics, discussed earlier, is exemplary: after patenting two lines of genes related to cancer testing, Myriad swiftly embarked on an aggressive crusade to enforce its patents. One of the company's first targets was the University of Pennsylvania, which at the time was researching the causes of ovarian and breast cancer. When Myriad's strongly-worded cease-and-desist letter to the university was publicised, a majority of researchers in the field were led to believe that Myriad was blocking basic non-commercial research simply to turn a profit.[36] This view is cited as "one of the most important factors in mobilizing international reaction against Myriad".[37] Stanford University's successful licensing of genetic patents, discussed earlier, points to a consistent conclusion. The university's success stemmed from its decision to allow non-commercial researchers to practice its patents on a royalty-free basis. At the same time, Stanford succeeded in collecting millions in licensing fees from commercial users. These two widely-discussed examples suggest that gene patents are most effectively asserted against commercial, rather than non-commercial users. The logical

[34] Parchomovsky and Mattioli (2011) (presenting the concept and use of quasi-patents in private and public settings).

[35] 35 U.S.C. § 271.

[36] Gold and Carbone (2008).

[37] *Id* at 13, 16 (noting that in reality, Myriad's internal policies on non-commercial research were more liberal than many believed, but the company failed to communicate this fact to the public).

conclusion of this observation is that gene patents afford their owners a broader dominion than is necessary.

Based on these lessons, we propose a biobank property regime in which patent holders may only exclude commercial competitors. In three-dimensional terms, this proposal represents an adjustment of the patent holder's dominion, and a division of ownership rights in the substantive utility of the patent between the patent holder and its non-commercial users. Through quasi-patent rights, a biobank could thus allow non-commercial research to advance unfettered, without discouraging critical investments of time, capital, and expertise.

The concept of quasi-patents is inspired by the concept of quasi-property, which was developed by the Supreme Court in the 1918 decision of *International News Service v. Associated Press*, 48 U.S. 215. That case involved a dispute between two large agencies in the waning days of World War I. The Associated Press ("AP"), a cooperative network of newspapers based in the East, sued the International News Service ("INS") for appropriating the underlying facts of AP news reports and then transferring them by telegraph to its affiliates on the west coast. Writing for the majority, Justice Pitney ruled in favour of AP, despite the fact that the underlying information that the INS had taken was not copyrightable. The Court's ruling was based instead on a concept that it called "quasi-property"—a federal common law right of exclusion to fresh news that may only be exercised against competitors, but not against the general public. By ensuring that competitors could not reap where they had not sown, the Court believed its solution would preserve both the gathering and dissemination of news.

In extending this idea to the realm of patents, policy-makers would be wise to consider Justice Brandeis' dissent in *INS v. AP*. Among other things, Justice Brandeis cautioned that a quasi-property system might prove more difficult to administer in reality than the majority seemed to appreciate. For example, such a system requires lawmakers to define who constitutes a competitor. Yet, this challenge is not insurmountable. In fact, courts make this determination routinely in the areas of antitrust and trademark law, and can employ the doctrines and tests developed in these legal realms to decide the competitors of quasi-patent holders.

A different challenge for our proposal stems from the fact that competition is a dynamic force. Accordingly, competitors can enter and leave markets fluidly: a firm that was not a competitor of a quasi-patent holder in the past may become a direct competitor in the future, and vice-versa. We are fully cognizant of this possibility. We posit, however, that courts will have no problem accounting for such market changes. Courts should enforce quasi-patents only against firms that at the time of the alleged infringement were in competition with the quasi-patent holders. This is a simple and straightforward rule that can be easily administered by courts.

A final challenge raised by quasi-patents is the potential for non-commercial users to patent their own improvements. Such improvement patents could conceivably later be used to exclude original patent holders, undermining the entire quasi-patent model. This challenge may be addressed by requiring all non-commercial users to freely-license any new related patents (e.g., continuations, divisionals, etc.) to all downstream users. Even better, it is possible to require all improvers of

inventions protected by quasi-patents to settle for quasi-patent protection for their improvements.

Despite the aforementioned administrative challenges, we believe that the quasi-patent model strikes a balance that may be helpful to biobanks. By only permitting enforcement against competitors, semi-patents preserve an important incentive without hindering basic research. But, as the next section shows, dividing commercial users from non-commercial users is just one way to reconfigure the pieces of the biobank property puzzle.

14.4.2 Semi-Patents[38]

An alternative to dividing property owners into different groups is to partition assets themselves. Once again, the model of a territorial map is illustrative: assume that a map depicting a large tract of land, Largeacre, has been created by Jane. The map indicates the locations of roads, rivers, and canyons, but it also reveals the position of valuable underground oil deposits. Naturally, Jane does not wish to reveal the location of this buried treasure to others. But, she may wish to share topographical details of the map to help prevent her neighbors and travelers from getting lost in the wilderness. To that end, Jane creates a new map that only shows the surface of Largeacre, thus "splitting" the original asset into two distinct parts: the raw topographical information and the specific *application* of that information as a guide to a valuable resource.

A more nuanced form of asset division appears in the music industry. Recording an album produces more than just music: photographs, album cover artwork, liner notes, and even performance videos are frequently created in the process of preparing a final release. Originally, materials like these were bundled along with vinyl records. But, with the rise of digital distribution over the Internet, most music distributors decided to strip-away these extras, and instead transferred only digital music files to consumers. By splitting or "unbundling" the original asset, distributors achieved a new balance that satisfied the public. However, distributors went one step further by selling music on a per-track basis. No longer were music fans forced to purchase entire albums simply to purchase hit singles they wished to own. Unbundling individual songs meant a significant cost savings for consumers, and interestingly, created a new impetus for recording artists to write and record compelling music. (Gone were the days of "Side-B" filler tracks.) Dividing and repackaging assets is a practice that has defined some of the most important moments in the history of music distribution.

A similar approach can be followed at biobanks. Like the oil prospector's map discussed earlier, the assets managed by biobanks include valuable information

[38] Parchomovsky and Mattioli (2011) (presenting the concept and use of semi-patents in private and public settings).

(e.g., raw research data and findings), and patentable practical applications of the information. Like the "extras" created in the course of recording an album, raw research data and findings are often not the final goal of scientific endeavor, but valuable byproducts. And, just as a map can serve as a navigational tool as well as a guide to valuable natural resources, so too can the information produced by genetic researchers guide the direction of future research while fueling commercially valuable applications.

This model of divided genetic assets, which we refer to as semi-patents, is an alternative solution to the biobank property puzzle. In this regime, researchers would be free to assert their patents against whomever they wish, but their right to exclude would be contingent on cooperation with a mandatory data sharing policy.[39] Failure to cooperate with this data sharing requirement would result in invalidity of a member's patent rights—in effect, making data sharing a new requirement of patent validity. An advantage of this model over quasi-patents is that dividing assets eliminates the challenge of dividing users (i.e., commercial versus noncommercial). Moreover, the universal sharing of raw data and findings mandated under a semi-patent regime could have a more meaningful impact than the limited sharing of patent rights envisioned by quasi-patents. As the director of the NIH and former director of the HGP wrote in a recent Nature article, "free and open access to genome *data* has had a profoundly positive effect on [the] progress" of genetic research.[40]

Semi-patents change the rules of patent acquisition and retention by conditioning ownership on productive behaviour. Similar dependencies already govern both real and intellectual property in other respects. For example, our proposed regime may be analogised to the Rule of Prior Appropriation in water rights, according to which the first owner to use a source of water for *beneficial* purposes is granted rights over other would-be owners. In other words, the grant of the right is dependent of the appropriator's use of the water in a way that is consistent with society's interest. Similarly, the rules forbidding inequitable conduct in the field of patent law provide that a patent cannot be enforced by applicants that make false representations to the PTO. Thus, through the use of private contracts, the semi-patent model achieves results similar to those implemented elsewhere in the law.

Along with its advantages, the semi-patent model presents a challenge: how soon should data be released by researchers after it is generated? In order to patent new ideas or publish journal articles, researchers often require periods of exclusivity over their findings. And yet, delaying the release of new data can delay the march of progress. Policymakers have struggled with this tension since the early days of the Human Genome Project. The HGP's original December 1992 guidelines attempted to strike a fair balance by mandating rapid sharing of data, while also granting a six-month window to allow researchers to prepare papers and patent

[39] For a general discussion of encouraging a patent-friendly environment while limiting restrictions on access to data, see Simon (2009).

[40] Collins (2010).

applications.[41] By 1996 however, a more negative view of patenting had developed. The Bermuda Principles, adopted that year by the NIH, replaced the old six-month window with a requirement of near-immediate data release. At the time, some argued this radical ethic would not significantly advance the HGP's goals, and that it would instead undermine researchers' ability to publish and patent.[42] Nevertheless, the Bermuda Principles were directly adopted by many genomics projects and influenced countless more.[43]

After the human genome was sequenced in 2000, criticism of rapid data policies increased. Several genetic research collectives addressed the problem by making their members promise not to co-opt one another's data for publication. For example, policy guidelines adopted by the NHGRI in 2000 expressly prohibited users from using public data "for the initial publication of the complete genome sequence assembly or other large-scale analyses".[44] It was hoped this "embargo" solution would preserve the quick release of data and facilitate greater publication, but anecdotal reports suggest these policies were frequently ignored.[45]

The semi-patent model attacks this old tension in a new way. By making data sharing a requirement of patent validity, the model places data users and data generators in complementary rather than competing roles. Drawing from the original guidelines that guided in the HGP, the semi-patent model would grant researchers a limited period of exclusivity to prepare publications and patent applications. Although delaying the release of data was not favoured in the past, there is reason to believe it may be effective as biobanking evolves. In a 2003 meeting in Fort Lauderdale, scientists, legal scholars, ethicists, and funding representatives concluded that patents can be critical to hypothesis-driven research, as opposed to research directed toward specific goals, such as the identification of a particular gene.[46] As a result, many at the meeting argued that rapid data-release rules are inappropriate for hypothesis-driven work. This view was echoed in a 2009 meeting of experts in Toronto.[47] Commentators believe these developments signal a new phase of genetic research in which patents will play an important role.[48] Consequently, the limited periods of exclusive use envisioned by the semi-patent model are worthy of consideration. And, unlike data embargoes, semi-patents place the responsibility to release data with those who generate it.

As explained earlier, data sharing under the semi-patent model is primarily encouraged through the punitive measure of rendering offenders' patents invalid.

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[41] *See* Contreras, *supra* note 6.

[42] *Id.*

[43] *Id.*

[44] *Id* (mentioning similar efforts at an International Strategy Meeting in 2000, a GAIN Meeting in 2006, and a NIH GWAS Policy Meeting in 2007).

[45] *Id.*

[46] *Id.* at 39.

[47] *Id.*

[48] *Id.*

Additionally, rewards offered to whistle-blowers could act as secondary incentives to release data, and could offset the potentially high costs of policing the system.

Semi-patents thus preserve many of the advantages of traditional patents as incentives to research while encouraging the spread of data. This balance is achieved first through a division of intellectual assets between those helpful to the community at large (i.e., research data or conclusions) from powers of exclusion valuable only to individuals. A dependent relationship is established between these two assets, such that individuals within a community are rewarded only if they share with the entire community. While this model necessitates compromises such as limited periods of exclusive use, such tradeoffs could be dwarfed by the wealth of data and useful findings a semi-patent regime might generate.

14.4.3 Implementation

The property models presented in this chapter can be readily implemented by biobanks via licensing agreements. Mandatory licenses are already used by existing genetic research projects to govern the conduct of researchers and institutions. There are also several examples of licenses that have been developed to govern property rights outside the realm of biobanks. For example, the Eco-Patent Commons, introduced by the World Business Council for Sustainable Development, requires members to accept certain mandatory ground rules concerning the sharing of patents related to environmentally beneficial technologies. The Open Invention Network, a similar effort in the realm of software led by IBM, Sony, Novell and others, was launched in 2005. Similarly, the General Public License ("GPL")—likely the most widely-used public technology license—was developed by the Free Software Foundation to facilitate the sharing of software copyrights and patents.

Biobanks seeking to implement the proposals presented in this paper could require interested commercial entities to waive their rights to obtain full-fledged patent protection. Instead, commercial participants would be required to opt-in to either a quasi-patent or semi-patent model. If crafted with care and made publicly accessible, such an agreement could encourage cooperation among biobank members, and attract potential future participants. Further, licensors would likely be unsuccessful in unfairly recovering damages for patent infringement after breaching the license: the defense of implied license based on equitable estoppel would likely protect licensees from such predatory practices.

With respect to drafting, biobanks can draw valuable lessons from Stanford University's licensing initiative, discussed earlier. Commentators cite as a major source of Stanford's success the fact that the University frequently and openly consulted with concerned stakeholders. Similar public licensing efforts, such as GreenXchange, are following a similar path by consulting with the public and interested experts. The architects of biobank property regimes would do well to consult with the genetic research community, donors, and the public at large.

14.5 Conclusion

In this contribution, we described two new approaches to managing patents, raw data, and research findings at biobanks. Quasi-patents and semi-patents attempt to resolve a longstanding tension in the field of genetic research: the function of patents as incentives to innovate, and the competing need for researchers to freely build upon one another's work. Although research policymakers have grappled with this problem in a variety of ways, the most common solutions favour data sharing at the cost of patenting.

Quasi-patents and semi-patents attack this old problem in new ways. Quasi-patents, which can only be enforced against one's competitors, are a specially-tailored type of traditional patent that respect the importance of basic research. Semi-patents, which are conditioned on compliance with a data sharing policy, attempt to place patents and data sharing in complementary roles. Both models can be understood as reconfigurations of property's fundamental components: quasi-patents represent a shift of dominion, while semi-patents involve a splitting of the asset combined with new rules of acquisition and retention.

These new privately restyled patent rights can help researchers and scientists continue to chart the unexplored frontiers of human health.

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Chapter 15
Accessing Accessions: Biobanks and Benefit-Sharing

Mark Perry

Abstract The ability to access the materials and data in biobanks is vital to many areas of research. This paper reports a survey of a sample of biobanks worldwide to see the types of information that is provided by their sites as to their mode of operation, in terms of intellectual property policies, cost, material transfer agreements and so forth. The types of material held in a sample of biobanks in different jurisdictions is discussed, along with proposals for further research in the area. Following an introduction to some of the issues facing biobanks and their relationship to accessing various materials, an example of the additional work done by one recently visited biobank site is described. The focus of this research has been on biobanks that have non-human biological resources rather than purely human biobanks.

15.1 Introduction

Biobanks have been defined in many different ways. In the past, it was assumed that biobanks were simply collections of materials maintained by a cryogenic facility or more recently, ". . . collections of samples of human bodily substances. . . that are or can be associated with personal data and information on their donors".[1] However, these are narrow descriptions typically used to describe the subject of a particular study. Herein, biobanks are regarded as including not only the above, but also any collection of biological materials, whether the source be human, plant, or animal, fungi, bacteria, microorganisms or other living families, as well as bioinformatic data on such organic materials. Today, it is artificial to completely disassociate

[1] German National Ethics Council (2004), at 9.

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databases with gene sequences, for example, the gene sequence of a spider mite, from the organic samples of the mites themselves.

Other papers in this collection will be talking about the norms involved, the development of models, and putting forward various structures that people can use in accessing biobanks. This paper will not be looking at these or the dialogues between technologists and lawyers, law and technology as such, technology tools, ethics, regulation or the laws governing biobanks. This paper is an early study on the practices of a variety of biobanks regarding accessibility of materials and data, and the types of materials held in their collections. The description of a recently visited biobank and research centre is given as an example of the work being done in addition to that of the primary purpose, that is, maintaining biological samples and data.

15.2 Biobank Data

Examined herein are some of the practices of biobanks that are currently in operation, with a focus on the types of materials that are available, the availability, the ownership, the cost, and the types of transfer agreements involved. Of the 82 biobanks examined, useful data was gathered from 31. Although this is an initial study on a small scale, it does involve biobanks in a number of different jurisdictions as shown in Table 15.1.[2]

Although some human material biobanks are covered in this preliminary survey, mainly as a contrast, the focus is on plants and animals. This means one of the areas that we do not need to consider is consent forms, although the rights of Indian leopards or spider mites is an interesting legal question—getting samples can be an issue, of course.

The British exhibit at the Shanghai Expo, which looked like a giant dandelion seed head, was constructed to include materials from Kew Gardens with around 60,000 Perspex tubes containing seeds.[3] Kew Gardens is a leader in plant material collection and they aim to have, by the end of the decade, 25 % of the world's crops represented, physically, in their biobanks.[4]

There are different kinds of metrics and categories involved when you are looking at biobanks. For example, the biobank may be screening, testing, or simply banking, or combination of those for each of the samples that are received. The biobank also needs to have the appropriate hardware, whether this be a wet laboratory, test kits, cryogenic fridges to store samples, or computing resources,

[2] The 31 sites with data, plus LaCONES (not included in survey data).

[3] Information on the UK exhibit is at http://www.ukshanghaiexpo.com (accessed 20 January 2011).

[4] As of December 2010, the Royal Botanical Gardens, Kew has banked the seeds of 27,651 species with a total of 1,654,753,608 seeds. This includes a dozen species that are now extinct in the wild. See http://www.kew.org/ (accessed 20 January 2011).

Table 15.1 Name and formal address (where known) of sources

Biobank	Location (postal address, with country)
NordGen Plants	Nordic Genetic Resource Center, P.O. Box 41, SE-23053 Alnarp, Sweden
CGIAR (Consultative Group on International Agriculture Research)	CGIAR Secretariat, The World Bank, MSN G6-601, 1818 H Street NW Washington, DC 20433 USA
The Australian DNA Bank	Australian Plant DNA Bank Ltd., PO Box 157, Lismore, NSW 2480 Australia
Conservation Genome Resource Bank for Korean Wildlife	Seoul National University College of Veterinary Medicine 85-802, San 56-1, Sillim-Dong, Gwanak-Gu, Seoul 151–742, South Korea
Canadian Plant Germplasm System	PGRC seed genebank, is part of the Saskatoon Research Centre
Genethon	Généthon – 1bis, rue de l'Internationale – 91002 Évry Cédex, France
National Laboratory for the Genetics of Israeli Populations	National Laboratory for the Genetics of Israeli Populations, Department of Human Molecular Genetics & Biochemistry Sackler Faculty of Medicine Tel-Aviv University, Tel-Aviv 69978 Israel
EUPRIM-Net	Department Research Coordination – Stabstelle Forschungskoordination German Primate Center – Deutsches Primatenzentrum Kellnerweg 4 D-37077 Gottingen, Germany
National Gene bank	9 EL-Gamaa St, Giza, Cairo – Egypt
National Germplasm Resources	10300 BALTIMORE BLVD. RM. 102, BLDG. 003, BARC-WEST Beltsville, MD 20705 Maryland, United States of America
Telethon network of Bio banks	Italy, consortium of various biobanks mentioned at http://www.biobanknetwork.org/members.php
The Sainsbury Laboratory	The Sainsbury Laboratory, Norwich Research Park, Colney, Norwich NR4 7UH, UK
NIMHANS, Bangalore, India	NIMHANS, Hosur Road, Bangalore, India
New York Brain Bank at Columbia University	NYBB/Taub Institute, Children's Hospital of New York-Presbyterian, Room T-8, 3959 Broadway New York, NY 10032 Telephone: 1-212-305-2299, Fax: 1-212-342-0083, E-mail: nybb@columbia.edu
UK Bio Bank	UK Biobank, Units 1 and 2, Spectrum Way, Adswood, Stockport, Cheshire SK3 0SA
Royal Botanic Gardens Kew DNA Bank	Royal Botanic Gardens, Kew, Richmond, Surrey, TW9 3AB, UK
Missouri Botanical Garden	St. Louis, Missouri, USA
Generation Scotland	Scottish Family Health Study, Department of Medicine and Therapeutics, Level 7, Ninewells Hospital, Dundee DD1 9SY
Asterand	Offices in USA, Europe and Japan
The International Moss Stock Center (IMSC Freiburg)	International Moss Stock Center (IMSC), University of Freiburg, Plant Biotechnology, Schaenzlestrasse 1, 79104 Freiburg, Germany

(continued)

Table 15.1 (continued)

Biobank	Location (postal address, with country)
Telethon Genetic Biobank Network	Telethon Genetic Biobank Network is constituted by all biobanks supported by Telethon
EuroBioBank	No address
National Institute of Agrobiological Sciences (NIAS)	Genebank, National Institute of Agrobiological Sciences, 2-1-2 Kannondai, Tsukuba, Ibaraki 305–8602, Japan
CABRI (Common Access to Biological Resources and Information)	CABRI currently contains the catalogues of BCCM, Brussels, Belgium, CABI Bioscience, Egham, UK; CBS, Utrecht, The Netherlands; CIP, Institute Pasteur, Paris, France; DSMZ, Braunschweig, Germany; ECACC, Salisbury, UK; INRC, Genoa, Italy; NCIMB, Aberdeen, UK
Ambrose Monell Cryo Collection (AMCC)	AMCC, American Museum of Natural History(AMNH), Central Park West at 79th Street, New York, NY 10024-5192
UK DNA Banking Network (UDBN)	UK DNA Banking Network (UDBN), CIGMR, Stopford Building, Oxford Road, Manchester U.K.
Riken Bio Resource Center (Riken BRC)	Riken Bio Resource Center (Riken BRC), 3-1-1 Koyadai, Tsukuba-shi, Ibaraki 305–0074 Japan
Frozen Ark Project	The Frozen Ark Office, School of Biology, University of Nottingham, University Park, Nottingham NG7 2RD, UK
Alpha Cord Umbilical Cod Blood Network	Alpha Cord, USA – Home Office 2200 Century Parkway # 9-Atlanta, Georgia 30345
The Swedish National Biobank Program	Not available on website
National Plant, Fungi and Animal DNA Bank in Poland	National Plant, Fungi and Animal DNA Bank in Poland. Museum of Institute of Zoology Polish Academy of Sciences 00–679, Warsaw Poland
LaCONES[a]	Laboratory for the Conservation of Endangered Species, Attapur, Rajendranagar, Ranga Reddy District, Hyderabad, India

[a]Not included in dataset, but site visited

software and personnel (wetware). The biobank may be looking at humans, animals, or plants, or a combination of these. There are also public, as in publicly funded, as well as private, or a combination of public and private biobanks. Some biobanks are open, whilst others have restricted or closed access.

Table 15.1 shows location of the banks accessed, focusing on North America, Europe, Japan and Korea. There have been surveys and a number of studies on biobanks and methods of collection, typically in relation to the taking of physical human samples, with emphasis on the ethics and consent issues that surround such biobanks' collections. For example, the comprehensive work *Biobanks in Europe: Prospects for Harmonisation and Networking*.[5] This European study is on human

[5] Eleni Zika et al. (2010).

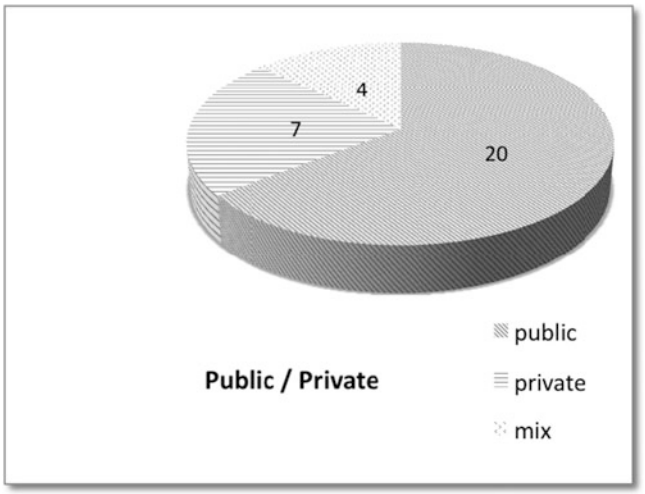

Fig. 15.1 Proportion of Public/Private/Mix $n = 31$

biobanks with a sample of 126. However, the report is mainly focused on consent and other issues of high concern with human materials. It does not deal with non-human material biobanks.[6] In contrast, the work presented here looks at location, ownership, types of accessions, types of agreements, accession policies, intellectual property policies, with a survey of 82 biobanks, of which 31 provided the kind of information that was required.[7] Of the 31 examined, 20 were publicly owned. Some of them had mixed ownership, and only a few were privately owned. As can be seen in Figs. 15.1 and 15.2 the majority of the publicly owned biobanks involved plant and animal samples. Most of the privately owned ones consisted of human samples.

[6] Indeed, most of the resources that catalogue biobanks seems to focus on human biobanks. For example BBMRI, *BBMRI Portal* http://www.bbmriportal.eu/ (accessed 20 January 2011), references 284 biobanks, of which 278 are human only.

[7] Other surveys have typically focused on a particular jurisdiction, in addition to the European survey there was one in the UK and one in the USA. Furthermore, most are for human samples, such as the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI.): "BBMRI is a pan-European and internationally broadly accessible research infrastructure and a network of existing and de novo biobanks and biomolecular resources. The infrastructure will include samples from patients and healthy persons, representing different European populations (with links to epidemiological and health care information), molecular genomic resources and biocomputational tools to optimally exploit this resource for global biomedical research". At *Welcome to the BBMRI Portal* http://www.bbmriportal.eu/ (accessed 20 January 2011).

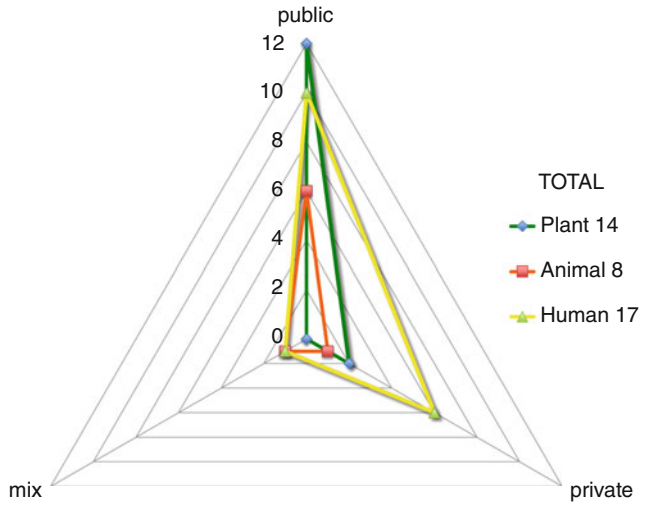

Fig. 15.2 Public/Private/Mix by type $n = 31$

15.3 Types of Research and Materials Kept

The following list shows the types of materials that the biobanks in the selection are interested in collecting, storing, sequencing, etc.:

- Plant materials
  - These biobanks' activities range from seed collection and storage (such as at the Royal Botanical Gardens, Kew and the Nordic Genetic Resource Centre) with the aim of cataloguing and preserving biodiversity, to crop productivity, and forestry. Many engage in DNA extraction, sample archiving and historical documentation, as well as database maintenance, sample acquisition, plant and seed viability, rejuvenation, evaluation and distribution of plant seeds. Some focus on plant genes, biological material relating to plants, and fungi to obtain DNA samples for DNA barcoding. Others look to plant material, usually young leaves, for samples of plant genomic DNA, as well as some for moss mutants, transgenic lines and ecotypes filamentous fungi, yeasts, plasmids, phages and plant cells.
- Animals and other non-human lifeforms that are not plants
  - These biobanks range from the supply of non-human primate animal models for immune-based disorders, to those that collect and manage tissue, blood, DNA, somatic and germ cells, and semen from mammals, birds, amphibians, and reptiles, including endangered species. Others focus on food production, such as aquaculture and livestock development. Microorganisms, bacteria as well as cell lines of different species tissues, gametes, and other viable cells.

- Human
  - The few biobanks that contain human material in this survey are varied in their approach, to a general "any human materials" approach, to those that focus on brain tissue or other specialised collections, such as DNA samples or matching human B-lymphoblastoid cell lines. Samples of some include collections of human urine, blood, saliva, or establishment of cell lines of fibroblasts, amniocytes and chorionic villous cells from appropriate tissue. Some look to stem cells, human cells, disease related cells, cultured cell lines, and cord blood (stem cell rich blood).

15.4 Agreements Utilised

The exchange or supply of biological materials is usually accompanied by a Material Transfer Agreement, which may be considered a licence or contract governing the use of the biological materials, ranging from the type of exploitation to the term of use of the material.[8] Surprisingly, only two of the biobanks use the Standard Material Transfer Agreement (STMA).[9] The International Treaty on Plant Genetic Resources for Food and Agriculture was adopted in 2001,[10] and the Food and Agriculture Organisation of the United Nations went on to form an expert group to develop a Standard Material Transfer Agreement. However, many of the surveyed sites use their own agreements.[11] Human biobanks typically have a more stringent MTA, even though they may be very straightforward.[12]

15.5 Cost of Accessing Accession

Cost of obtaining an accession varies greatly. Most of the biobanks surveyed indicate that they would only take the cost of actually accessing the materials, namely reimbursement for retrieval and transport, etc., or else, the fee is negotiable on a case-to-case basis. The range was from zero charge, to the highest being in the range of $11,000 per accession.[13]

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[8] Further information can be found *infra* in the chapter of Thomas Margoni "The Role of Material Transfer Agreements in Genetics Databases and Bio-banks".

[9] The full STMA is at http://planttreaty.org/ (accessed 20 January 2011).

[10] The Treaty came into force 29 June 2004 and, as of 25 January 2011, has 127 members.

[11] Such as http://arabidopsis.info/docs/slat.pdf (accessed 20 January 2011).

[12] Such as http://www.tau.ac.il/medicine/NLGIP/order.htm (accessed 20 January 2011).

[13] Riken Bioresource Centre lists the charge for a 15K cDNA clone set at Yen 906,300 (around $11,000 per set) for a non-profit organization, and double that for a for profit organization. See http://www.brc.riken.jp/ (accessed 20 Jan 2011).

15.6 IP Policy and Access

The majority (22 of the 31) of the biobanks disclosed their intellectual property policies on their websites. The remainder did not make any information available online. Most of the biobanks have the policy that the supply of materials does not change any of the intellectual property rights that already subsist in the accession, i.e., the biological materials, and those covered by the material transfer agreements. Other downstream rights from the use of the materials are typically covered by the material transfer agreement. There are almost as many intellectual property statements as there are disclosing biobanks, and they range from giving up all downstream rights to very restrictive use. Some examples are given below. Two follow the International Treaty on Plant Genetic Resources for Food and Agriculture (IT-PGRFA), and it is worth repeating the salient points of Article 12, that the parties to the treaty should facilitate access to plants "genetic resources" for food and agriculture under the terms of the treaty, including legal or other measures to enable this,[14] and:

12.3, such access[15] shall be provided in accordance with the conditions below:

(a) Access shall be provided solely for the purpose of utilisation and conservation for research, breeding and training for food and agriculture, provided that such purpose does not include chemical, pharmaceutical and/or other non-food/feed industrial uses. In the case of multiple-use crops (food and non-food), their importance for food security should be the determinant for their inclusion in the Multilateral System and availability for facilitated access;
(b) Access shall be accorded expeditiously, without the need to track individual accessions and free of charge, or, when a fee is charged, it shall not exceed the minimal cost involved;
(c) All available passport data and, subject to applicable law, any other associated available non-confidential descriptive information, shall be made available with the plant genetic resources for food and agriculture provided;
(d) Recipients shall not claim any intellectual property or other rights that limit the facilitated access to the plant genetic resources for food and agriculture, or their genetic parts or components, in the form received from the Multilateral System;
(e) Access to plant genetic resources for food and agriculture under development, including material being developed by farmers, shall be at the discretion of its developer, during the period of its development;
(f) Access to plant genetic resources for food and agriculture protected by intellectual and other property rights shall be consistent with relevant international agreements, and with relevant national laws.

[14] *International Treaty on Plant Genetic Resources for Food and Agriculture,* 3 November 2001, 2400 UNTS, Arts. 12.1-12.2.

[15] *Ibid*., Art. 11.

The section is designed to support the purpose of the treaty to share agricultural materials wherever possible, treating them as part of the common heritage. Another biobank states that in addition to developing their intellectual property terms in line with this treaty, the terms of the United Nations Convention on Biological Diversity[16] has also been embodied in their policies.

It is perhaps natural that many biobanks do not use this treaty as a template as it is designed for crops and agriculture. For example, the seed bank of Kew Gardens is clearly a great deal broader than only crops and agriculture, although their research and accessions will no doubt prove useful for the same. Their policy provides specific guidelines[17]:

1. Material should only be used for scientific research, education, conservation and the development of botanic gardens;
2. Recipient should not sell, distribute or use for profit or any other commercial application;
3. The benefits arising from their use of the Material shall be fairly and equally distributed;
4. Acknowledgment of Kew, as supplier, in all written or electronic reports and publications resulting from use of the Material;
5. Copyright in all information or data... supplied with the Material is owned by Kew.

Similarly, the Missouri Botanical Garden has its own policy guidelines[18]:

1. "all requests to pass either material provided by the Garden or extracted DNA to third parties must be approved, via a material transfer agreement, by the Curator of the Herbarium;
2. acknowledge both the Missouri Botanical Garden and each individual collector of material provided in each publication in which the data is used;
3. provide the Garden with reprints from all resultant publications;
4. publish jointly with Garden staff members or their foreign collaborators whenever appropriate;
5. register GenBank/EMBL[19] accession number".

Overall, there are almost as many policies on intellectual property as there are biobanks. Even within a single biobank, the intellectual property rights associated with a particular sample will depend entirely on the provenance of the material, and any agreements that were made in the creation of the accession.

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[16] *Convention on Biological Diversity,* 5June 1992, 1760 UNTS.

[17] The Royal Botanical Gardens, Kew for intellectual property in their MTA. It also stipulates that they comply with the Convention on Biological Diversity. See http://data.kew.org/dnabank/MTA.html (accessed 22 January 2011).

[18] Missouri Botanical Garden at http://www.wlbcenter.org/dna_banking.htm (accessed 22 January 2011).

[19] This refers to the publically available annotated genetic sequence database held by the National Institute of Health in the United States of America, http://www.ncbi.nlm.nih.gov/genbank/, and the European Molecular Biology Laboratory that is supported by European Bioinformatics Institute, see http://www.ebi.ac.uk/embl/ (accessed 22 January 2011).

15.7 An Example of a Biobank's Activities

The Indian subcontinent is second in the world for types of genera and types of families of both animal and plant material.[20] There is a huge amount of material in the region that is only known in the locality and much to be studied. However, many species are under threat, for example there are only about 400 Asiatic lions and 1000 Asiatic leopards remaining in the region. These particular species are very interesting examples of the issues facing wildlife in many parts of the world. They are under threat of extinction not because they ran out of evolutionary potential, but because human intervention has been killing them off either directly or through the destruction of habitat. There are other species that have become extinct recently in India, such as the white rhinoceros.

The Centre for Cellular & Molecular Biology (CCMB), with the support of the Government of India set up as its first annex a unique laboratory that would work towards the conservation of various endangered species through research on their reproductive biology. The Laboratory for the Conservation of Endangered Species (LaCONES, CCMB-ANNEX-1) was thus established in Hyderabad, India, and formally opened in 2007. LaCONES's purpose was stated as[21]:

1. "Monitoring of genetic variation through DNA fingerprinting;
2. Cryo-preservation of semen, eggs and embryos of endangered species;
3. Semen analysis to study the semen quality for selecting animals for breeding purposes;
4. Determination of the time of ovulation to achieve successful intra-uterine insemination;
5. Standardisation of artificial insemination for wild animals;
6. In vitro fertilisation (IVF) and embryo transfer;
7. Establishment of cell bank and cloning for rare animals".

As a biobank, it houses embryos, semen, and eggs of endangered species using their cryogenic facilities. This is a difficult task, not only due to the technologies involved, but also on a practical basis as some of these species are large and dangerous, such as the Indian leopard. For example, in order to perform *in vitro* fertilisation of a leopard, the semen must first be collected, which is achieved using electrical stimulation of a sedated male, and then a fertile female needs to be identified and eggs collected. *In vitro* fertilisation, and embryo transfer is also carried out on site. It is anticipated that the gene bank and cell bank housed at LaCONES will be able to provide the materials to prevent the extinction of highly

[20] From The Royal Botanical Gardens, Kew research, graphically represented at http:// www.kew.org/news/families-and-genera-map.htm (accessed 24 January 2011).

[21] Abdul Kalam, "President of India Dr A.P.J. Abdul Kalam dedicates LaCONES to the Nation" National Institute of Science Communication and Information Resources (CSIR) News, New Delhi, VOL 57 NO 4 28 FEBRUARY 2007.

endangered species in India. LaCONES is focusing on big cats, deer, nonhuman primates, and birds. Although a recently established research facility, much work has been achieved, such as the discovery that the endangered Indian Blackbuck may provide competent oocytes from postmortem recovery.[22]

The institute has already done a great deal of work, and background research, to understand the issues surrounding the preservation of species, as well as collecting samples from rare species. An example is the study of the follicular dynamics in the Indian Blackbuck. Researchers have completed, and perfected, artificial insemination techniques and this has led to the birth of a fawn. They have also completed phylogenetic studies showing different varieties in Indian deer species and their relationships.

LaCONES is engaged in the impact that habitat fragmentation has on the reproductive ability and genetic variation in big cats. They have also developed an analysis of excreta to monitor the reproductive functions of big cats. In the past, to determine if a big cat was in heat, you would have had to try to catch the animal, which upsets their fertility cycles and of course is dangerous.

The activities described above may be seen as typical biobank activities with predicted outcomes, that is, collecting specimens and data along with associated research. However, in addition to those biobank activities originally anticipated, there have been other research outcomes at LaCONES, and undoubtedly other biobanks institutions. For example, although it is well known that law enforcement agencies use on-site forensic crime scene investigation techniques, including DNA analysis, it is little known that LaCONES has utilised similar processes to solve animal smuggling cases. A large database of DNA signatures, including those of rare and endangered species has been developed. LaCONES has used the animal DNA database, akin to the databanks for human DNA profiling used by law enforcement agencies, to solve over 100 cases referred to them by investigating agencies and wildlife curators. For example, a recent case involved the seizure of 1,500 tortoises in Kuala Lumpur, which were half-starved. It was unclear from where these tortoises had been taken. LaCONES used their animal signature-databases to identify that the tortoises that had come from South India. This information was then used to repatriate them to the originating area.[23] In addition to being biobanks, many institutions are also research centres that will continue to provide advancements over and above their main purpose as a resource for biological materials and data.

[22] Sambasiva et al. (2010), p. 623.

[23] Shivaji and Gaur (2010), p. 86: “Ideally, the rescued tortoises should be repatriated to their original populations both to avoid mixing genetically distinct populations and potential outbreeding depression as well as increase the likelihood of successful reestablishment. Such a study was carried out for the identification and subsequent repatriation of rescued Star tortoises to their original geographical locations in the wild. A large number of the rescued star tortoises were genotyped using microsatellite and mitochondrial DNA markers”.

15.8 Conclusions on Biobank Activities

One of the issues is the property rights attached to biobank held materials. Of the 31 sites providing information, the majority posted online that they retained rights over the materials, all intellectual property rights, researchers objected to research institutions or scientific studies. All had material transfer agreements of various sorts; most of them being special purpose transfer agreements and no generic MTA was used. Interestingly none used the open science MTA. Most retained rights over material but some plant biobanks followed IT-GRFA or similarly aligned policies.

Perhaps before we suggest models of how to access biobanks and the materials therein, it would be advantageous to take a serious and comprehensive survey of the current systems being used by biobanks worldwide, and identify the best practices, which vary depending on the type of accessions that they provide. Most biobanks have already developed their own accession systems with their own models, technology, and intellectual property and material transfer agreements in place. It is unlikely that simply postulating new norms of accessing accessions based on theoretical analysis will introduce any significant change to their operation unless there is a very good reason to do so.

This brief report on the sample survey has revealed several interesting issues that need to be addressed for both current use of biobanks and future accessibility. It is not surprising that there are divergent approaches depending on whether the materials are human or non-human, as naturally there is much more regulation, ethical constraints, and to some extent, research money that comes with human subject research.[24] However, when it comes to other lifeforms there is still a great divergence between how biobanks manage their material accessions, whether it is use of a physical sample, or access to the data. Due to the norms set by funding agencies, the trend is that the latter is more open. Indeed, many funding agencies mandate that genomic data is placed in a public database as a stipulation of providing funding to researchers.[25] It is disappointing that, under half of the biobanks originally identified had any useful information online that related to their intellectual property rights or MTAs, or other activities.

Finally, another issue that has received little attention is the spin-off research done by some biobanks, including LaCONES and Kew Gardens. Whether they are developing new techniques for investigating the current state of species, their fertility, or developing new storage protocols, future research should address

[24] There are many hundreds of articles on research involving human materials' biobanks.

[25] For example, the Welcome Trust Foundation in the United Kingdom states, "It was agreed that all human genomic sequence information, generated by centres funded for large-scale human sequencing, should be freely available and in the public domain in order to encourage research and development, and to maximise its benefit to society". http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTD002751.htm (accessed 11 July 2012); The National Science Foundation in the US makes this a condition of receiving funding. The conditions are described in greater detail in "Research General Terms and Conditions" which can be found at http://www.nsf.gov/pubs/policydocs/rtc/termsidebyside_june11.pdf (accessed 11 July 2012).

these issues as biobanks, and especially their databases, become more common and better understood.

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Chapter 16
Conveying Information, Generating Trust: The Role of Certifications in Biobanking

Matteo Ferrari

Abstract The ability to communicate sound and reliable information is an imperative in modern societies. Markets flourish, thanks to the knowledge players are able to acquire and use; consumers base their purchasing decisions on the information they receive from producers and media; contractual counterparties are selected according to the expertise and knowledge they are able to show. Does the law take part in this process, facilitating the transmission of reliable information? The answer is obviously yes. On legal tool by which information is validated and transmitted is certification. Certifications are rapidly spreading as a flexible and effective way to disseminate knowledge: in turn, the disseminated data are characterized by a high degree of reliability and seem to be able to generate a bond of trust between the parties involved in the information exchange. Nowadays more and more private certification schemes are used in lieu of public controls, sparing resources and allowing for a higher degree of flexibility in the inspection process. We are shifting from a system where trust was generated by public institutions to one in which trust is the result of an activity carried out by private operators. The biobanks' sector is no exception to these dynamics. The promising developments for the aetiopathogenesis and the treatment of diseases which can derive from sharing of data between biobanks determine the need to generate an environment characterized by mutual trust, thus facilitating the circulation of such data. This is especially true if we consider that biobanks can operate not only according to different standards and procedures, but also within different cultures which can influence the way such standards and procedures, *per se* similar, are implemented. In this article, I will deal more in detail with some of the points I have raised. In particular, in the first part of the paper I will describe the notion of certification, trying to provide an initial taxonomy in terms of functions and types;

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the second part will focus on how certification bodies can be made accountable for the services they provide; in the third part attention will be shifted to the biobanks' context, adapting the general features of certifications described so far to the peculiar aspects characterizing biobanks. Finally, I will explore some of the possible benefits and problems that certifications can generate for the biobank domain.

16.1 Introduction

There are many means through which the law can intervene. In this paper, I will focus on one of them, which is gaining more and more importance despite the fact that legal scholars have devoted scarce attention to it so far. The reference is to certifications, (legal) tools by which information is validated and transmitted. Certifications are rapidly spreading as a flexible and effective way to disseminate knowledge. In turn, the disseminated data are characterised by a high degree of reliability and seem to be able to generate a bond of trust between the parties involved in the information exchange. Trust plays a pivotal role in modern contexts, but in a different manner with respect to what has occurred in the past. The break-up of the direct ties which kept together the subjects operating within a community have posed the need to re-create, in a somewhat artificial way, a relationship based on mutual trust. Certifications can contribute to this process, grounding trust not on a direct, geographically contingent relationship, but on a legal mechanism.[1]

This is not the only reason for the increasing success of certifications. In recent times, their proliferation has also been due to the progressive delegation of inspection duties from public to private subjects. Up to a few decades ago, the duty to inspect that goods and services were complying with given standards laid almost exclusively upon public institutions, which were thus enjoying a nearly monopolistic position in attaching a "label" of reliability and trustworthiness to such products/services. Nowadays more and more private certification schemes are used in lieu of public controls, sparing resources and allowing for a higher degree of flexibility in the inspection process. In other terms, we are shifting from a system where trust was generated by public institutions to one in which trust is the result of an activity carried out by private operators.

The biobanks' sector is no exception to these dynamics.[2] The promising developments for the aetiopathogenesis and the treatment of diseases which can derive from sharing of data between biobanks determine the need to generate an

[1] On the relationship between certifications and trust, see Benedetti (2006), p. 7. On the importance of public trust in biobanking, see Levitt and Weldon (2005), p. 311.

[2] I will not venture in defining biobanks or in analysing their regulation. For a first introduction to the subject and for further bibliographic references see, in addition to the contributions contained in this book, Gottweis and Petersen (2008), Elger et al. (2008), Kaye and Stranger (2009), and Dierickx and Borry (2009). For the Italian experience see Macilotti et al. (2008), p. 102; Macilotti (2008), p. 222; Id. 2009, p. 153.

environment characterised by mutual trust, thus facilitating the circulation of such data. This is especially true if we consider that biobanks can operate not only according to different standards and procedures, but also within different cultures which can influence the way such standards and procedures, *per se* similar, are implemented. These dissimilarities, despite the fact that they depend on the content of the norms or the way they are applied, can impair that environment of shared trust I mentioned above. On the other hand, trust is a feeling which should imbue not only the networking between biobanks. It plays a direct and fundamental bearing also on the relationship between biobanks and public institutions, as well as citizens at large. In this regard, we should distinguish between two categories of citizens: the donors of the biological materials, who have a direct interest in controlling the management of the biobank where their samples are stored, and taxpayers, who are interested in checking how their money is spent. Of course, the degree of trust which needs to be generated will vary depending on which category we consider. In addition, we should also take into consideration that, in a world of scarce resources, public institutions willing to invest money in biobanking have to make some kind of selection: a process that, for being virtuous, must rely on some objective factors which show that the potential beneficiaries are trustworthy.

In the following pages, I will deal more in detail with some of the points I have raised. In particular, in the first part of the paper, I will describe the notion of certification by trying to provide an initial taxonomy in terms of functions and types. In the second part, I will focus on how certification bodies can be made accountable for the services they provide. In the third part, the attention will be shifted to the biobanks' context by adapting the general features of certifications described so far to the peculiar aspects characterising biobanks. Finally, I will explore some of the possible benefits and problems that certifications can generate for the biobank domain.

16.2 The Notion of Certification

We can get a first clue on what a certification is by analysing its etymology. The term is derive from the Latin *certum facere*, which means to make certain; but it is by looking at the origin of the word *certum* that we are able to better grasp the notion of certification. Indeed, *certum* derives from the verb *cernere*, which means to select. In other words, by certifying, we select some products or services according to given characteristics they have (and that other products/services, even if apparently similar, do not have). Since the selection is carried out by verifying the presence of given characteristics in a product/service, eventually those who perform the certification activity provide information that the product/service has such given characteristics.

Therefore, certifications can be conceived as legal devices aimed at transmitting a particular form of information: a piece of information which has been selected and validated by a third party (the certification body) and which, because of this validation, has acquired a status of trustworthiness. At the same time, by transmitting these validated data, certifications contribute to filling the information asymmetries which might exist between those providing the data and those receiving them.[3] The concept of information asymmetry is self-explanatory to a large extent. What is interesting to note here is the fact that such asymmetries can further undermine the existence of a trust-based relationship. If I do not know which rules a subject applies, the procedures she follows, which expertise the operators working for her have, etc., I will probably be reluctant to trust her and/or I might adopt precautionary measures which can be cumbersome and inefficient. Providing such information can be a first answer to these problems: an answer which can be nonetheless insufficient if we are not able to control the reliability of the data received. Here, a host of new problems arises: controlling the information might be expensive; those interested in receiving it might lack the expertise necessary to distinguish the data which are reliable from those which are not, while those providing it might be in a situation of conflict of interest; there might be a multiplication of costs if we have to control the information every time we enter into contact with the counterparty; and some data can be controlled only by intruding heavily on the productive or administrative processes implemented by the subjects retaining the data. All these problems help to understand why certifications are performed by third-party, independent bodies: they have a specific expertise, are not in a conflict of interest with the parties to whom they provide their service and can apply economies of scale to the certification process.

As mentioned before, certifications select products/services according to given characteristics they possess. The specification of such characteristics is usually carried out by reference to standards: indeed, certifications and standards live in symbiotic status. What a certification body does is to verify the conformity of a subject's activity to the standards for which the certification is sought.[4] Thus, standards play a pivotal role in the certification process: they represent the benchmark against which a product or a service can be certified, as well as they determine the characteristics such a product/service must have.[5] This means that, thanks to the certification process, third parties can trust the fact that a product/service abides by standards which makes it attractive.

[3] Jahn et al. (2005), p. 53. See also Poncibò (2007), p. 656; Gentili (2000), p. 59.

[4] Point no. 12 of Art. 2 of the Reg. (EC) 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products offers a definition of conformity assessment (which is the core of a certification) as "the process demonstrating whether specified requirements relating to a product, process, service, system, person or body have been fulfilled".

[5] The relationship between standards and certifications with specific regard to biobanking is sketched in Betsou et al. (2007), p. 221. See also, in general, Ancora (2000) and Smorto (2003), p. 205.

At the operational level, certifications are carried out through an initial inspection which is aimed at checking whether the standards are fulfilled or not. The source of the duties and rights the certifier has in performing her service is placed in the contract signed between the certifier and the subject seeking the certification. After the first inspection, the certifier performs periodical audits in order to control that the subject keeps complying with the standards. The frequency of these subsequent audits depends on the nature of the activity to be controlled and on the number and seriousness of non-compliances found during the previous inspections.[6] The certification body has the duty to conduct the inspection in an independent and professional way, through careful controls.

The contents of the inspection depend also on the type of certification. In this regard, it is possible to distinguish between two forms of certification: product certifications and process certifications. In the first case the certification body tests the final product (or service), checking whether it complies with the required standards. The inspection is usually carried out on a randomly chosen sample of products. In the case of process certifications, attention is shifted to the processes implemented by the firm seeking the certification, in order to assess if they are consistent with the required standards. This does not mean that the product is completely unrelated to this type of certification. In most cases, a process which abides by the required standards will lead to products with specific characteristics. Nonetheless, the modalities through which the certification activity is carried out are different from those characterising product certifications.

The division between product and process certifications is not the only taxonomy we can envisage. Another interesting classification centres on the difference between mandatory and voluntary certifications. The first are certifications which are required by the law before putting into commerce a product/service: a good example is offered by the CE mark, which must accompany many products marketed in Europe and can be affixed only after the product has been certified by an authorised certifier.[7] The latter are certifications which a subject can decide to adopt without any formal imposition. Market pressures or other factors[8] can force her to certify her activities but, in fact, the law does not impose certification. This is the case for social accountability certifications, such as the SA8000, which verifies compliance with ethical standards related, for example, to working conditions.

A third taxonomy can be drawn by referring to those who benefit from the information encapsulated in the certification. So far, I have generically referred to third parties as recipients of the certification: but, of course, parties can be different,

[6] In other words, the frequency of the periodical audits depends on a risk analysis of the activities carried out by the subject applying for the certification.

[7] In cases where the risks posed by the products are low, the producer can self-certify her products, filling in a declaration of conformity. On the CE marks see in general Decision 768/2008/EC of the European Parliament and of the Council of 9 July 2008 on a common framework for the marketing of products.

[8] To give an example, sometimes firms are required to be certified in order to get access to some benefits, such as loans and tax discounts, or to enter into a contract with a public body.

with dissimilar needs and abilities in understanding the information they receive. It is thus possible to distinguish between B2B[9] and B2C[10] certifications: in other words, between certifications mainly addressed to professional operators and certifications mainly addressed to laymen. An example of the first is offered by the ISO 9000 certification of quality management systems; a form of B2C certification is represented by the certification of organic foodstuffs.

In building a certification scheme that can meet the needs of the biobank sector, we have to take into consideration all the factors I mentioned so far: if we want to certify the final product (the sample tissue) or the process through which the tissues are collected, handled and stored; if we prefer a voluntary rather than a mandatory scheme; who are the recipients of the information encapsulated in the certification; who is setting the standards used in the certification process and how these standards are framed; how large are the information asymmetries between the parties; to what extent we need an environment characterised by mutual trust in order to have biobanks work efficiently. Before dealing with these critical questions, we should look closer at the pivot of the entire certification process: the certification body. Indeed, if the final goal of any certification is to provide data which have been verified by a third-party, independent body, we cannot refrain from asking how we are guaranteed that these bodies are really independent.

16.3 Quis Custodiet Ipsos Custodes?

To explore the mechanisms through which certification bodies maintain their independence towards the subjects they certify means to deal with the problem of how to make these bodies accountable. Only when a subject is subjected to some kind of sanction if she does not fulfil her duties she will have an incentive to effectively comply with what she is required to do. The essence of accountability is placed exactly in the dynamic revolving around the threat of a sanction and the (resulting) incentive to perform the tasks assigned. Accountability can be realised through a host of different means: usually legal systems implement a variety of them in order to increase the efficiency of the overall accountability system. Certifications follow the same path. If we look at the accountability mechanisms to which certification bodies are subject we note that they range from administrative checks to civil liability, from market controls to criminal sanctions. I will provide a brief overview of the main mechanisms put in place, subdividing them in three areas: accreditation, liability and market-based controls.

[9] Business to business.

[10] Business to consumers.

Accreditation is the process by which a certification body is authorised to perform certification activities.[11] It should be noted that accreditation is a form of certification in itself since, in order to be authorised, the certifier must comply with given standards that guarantee its independence and professionalism. In addition to this, the certifier can also be required to possess other characteristics which do not relate to specific standards but which are, nonetheless, deemed important. The standards vary depending on the activities the certification bodies carry out. Nonetheless, their common core is represented by norms which require acting in a professional and independent manner. In most of the cases, the certifier's certifier is a body in which all the stakeholders involved in the certifications are represented: it can be either private or public.[12] The accreditation process is regulated in Europe by Regulation 765/2008,[13] which establishes "the organization and operation of accreditation of conformity assessment bodies performing conformity assessment activities" (Art. 1, par. 1). Even if the regulation refers to the concept of conformity assessment, this concept matches the idea of certification as I have specified it above: therefore, paraphrasing Art. 1, par. 1, Regulation 765/2008 establishes "the organization and operation of certification bodies performing certification activities". Here, I do not have space to go into detail as to the accreditation process. It is sufficient to remember that each Member State must have only one accreditation body and that all the national accreditation bodies must submit themselves to peer evaluation by the other national bodies. Usually the national accreditation body cannot directly authorise the certifier. What it does is to certify that the certifier complies with the required standards: then, the competent Ministry or Department, taking into account this certificate, authorises the subject to perform certification activities.

Also, the certification bodies operating in the biobanking field must undergo an accreditation process. This is expressly recognised by the Organization for Economic Co-operation and Development which, at point 7 of its Guidance for the Operation of Biological Research Centres (BRCs), provides that BRCs[14] must be

[11] For the distinction between certification and accreditation with specific regard to biobanking, see Betsou et al. (2007), p. 223, footnote 2.

[12] For example, in Italy the body in charge of the accreditation of the certification bodies is Accredia, a non-profit private association whose members are public bodies, unions of producers and consumers, associations representing certification bodies. The same type of body has been created in the UK: the United Kingdom Accreditation Service is a non-profit private company.

[13] Articles 3–14 of the Regulation (EC) 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products offers a definition of conformity assessment.

[14] BRCs can be considered as biobanks from a functional point of view. Nonetheless, some legal systems distinguish between "simple" biobanks, which are not certified, and BRCs, which are certified. In other words, the distinction between the two lies in the presence or absence of a certification. Such a distinction is for example adopted by the Italian legal system, in particular in the Art. 2 of the Ministerial Decree of May 15, 2006.

certified by a certification body recognised by the government or through a certification procedure administered directly by the government.[15] If we look at national experiences, Italy has enacted specific norms to regulate the accreditation of biobank certifiers.[16] These have to be pre-emptively authorised by the Ministry of Economic Development, which will grant such authorisation only if the certification body shows that it abides by standards of professionalism and independence.[17] The authorisation is granted for a limited time (4 years) and must be renewed: in addition, the certifier is subject to periodical audits aimed at verifying that the requirements are still met. When it is established that such requirements are no longer present, the authorisation can be revoked or suspended, depending on the seriousness of the violation discovered.[18] Through the combination of ex ante and ex post controls, the accreditation process is able to select the certification bodies which maintain over time enough expertise and independence to provide a reliable service. At the same time, sanctions such as the revocation and suspension of the authorisation, as well as the need to periodically renew the accreditation, are a first incentive for the certifiers to operate according to the required standards.

Nonetheless, this is not the only incentive certification bodies face. Another important mechanism to make them accountable is the liability they can incur if they violate the norms they should abide by. Behind the term liability, there are varieties of different tools: even the revocation and suspension of the authorisation we mentioned before can be conceived as a form of (administrative) liability. I will focus

[15] OECD (2004). Art. 6, par. 1, of the Dir. 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, provides that biobanks must be authorised, accredited, designated or licensed by a *competent authority*. The notion of competent authority is not specified: it is anyway possible to imagine that a Member State can delegate the task of accrediting a biobank to a private certification body.

[16] Ministerial Decree of May 15, 2006, articles 3–8. See also Linee guida per la certificazione delle biobanche [Guidelines for the certification of biobanks], 19 Aprile 2006, by the Comitato Nazionale per la Biosicurezza e le Biotecnologie (2008), pp. 9–10. See also Macilotti (2008), p. 224.

[17] The standards which are mentioned are the UNI CEI EN 45012 (General requirements for bodies operating assessment and certification/registration of quality systems), the UNI CEI EN ISO/IEC 17020 (General criteria for the operation of various types of bodies performing inspection), the ISO 9001 2000 (Quality management systems). Except for the ISO/IEC 17020, the other standards have been subsequently updated (ISO 9001 2000, updated in the ISO 9001 2008) or replaced with new ones (EN 45012, replaced by the ISO/IEC 17021 2006). It is not clear who should verify the conformity with the abovementioned standards. On one hand, the Decree of 2006 mentions the Ministry for Economic Development as the sole subject in charge of the authorisation process; on the other, European Regulation 765/2008 establishes that the accreditation of certification bodies must be performed by the national accreditation body which, in Italy, is Accredia. European legislation seems thus to provide that at least part of the accreditation process (i.e. the assessment of the conformity of the certification body with the required standards) must be carried out by a subject different from the Ministry for Economic Development.

[18] In particular, if the certifier does not meet the requirements set in the standard ISO/IEC 17020, the authorisation will be revoked. If it does not meet the requirements established in the standard EN 45012 the authorisation will be suspended for a maximum period of 30 days.

my attention on two forms of liability which play a pivotal role in modern societies: criminal liability and civil liability.

First, certification bodies[19] and the people who act on their behalf can be criminally liable if they are corrupted in order to certify a subject who does not comply with the required standards. This is clearly the case when there has been a delegation of inspection duties from public bodies to private certifiers, i.e. when there is what I called a mandatory certification: indeed, the certifier is acting as a public functionary. Nonetheless, criminal liability can come into play even when the certification is not mandatory *per se*, but is a pre-requisite to having some public benefits such as public funds, or for contracting with public bodies.

Second, if the certifier acts with negligence in performing her service, causing damage either to her contractual counter-party or to third parties, she will have to compensate the victim who suffered the damage. Here we have to distinguish between contractual liability and tort liability. The first occurs when the damage is suffered by the subject who enters into a contract with the certifier, asking for the certification. In all other cases, i.e. when the damage is suffered by someone who is not part of the certification contract, the liability will be in tort. The nature of the damages which can be suffered because of a negligent certification is manifold, ranging from health damages to pure economic losses. With specific regard to the (negligent) certification of biobanks, health damages and pure economic losses would probably play a residual role. On the other hand, considering also what I wrote before with regard to the link existing between certifications and trust, the type of damages which is more interesting to mention concerns those occurring because of a loss of reputation. Let us consider the case in which several biobanks form a consortium requiring, as a pre-requisite before entering it, to be certified according to given standards. The certification becomes an instrument by which the other biobanks know that they can trust the incoming biobank. But what if it is found (and made available to the public) that the incoming biobank does not operate according to the required standards despite the fact it has been certified? The entire consortium can suffer a loss of reputation if one of its members acts negligently. This is not the place to analyse in detail the problems which are raised by an action brought by the consortium (and/or the other virtuous biobanks) against the certifier. Nonetheless, it is worth noting that such a possibility exists and perfectly fits in the trust-based rationale behind certification that I stressed a few pages above.

The final mechanism to make certification bodies accountable is offered by the market. Competition and reputation, two factors that are closely intertwined, play a pivotal role in any type of market and represent two of the main indexes through which markets select actors. Of course, these mechanisms work to a large extent in an independent way with respect to the law: nevertheless, legal rules can have an impact on them, either facilitating or hampering their operation. I will focus on one aspect which can be considered as a sort of pre-requisite with respect to the role

[19] In Italy, under the d. lgs. 231/2001, criminal liability can be extended to companies, associations and the like in specific cases and for specific crimes, among which are bribery and corruption.

norms are able to play in making the functioning of the market smoother. Indeed, the first condition for establishing a market is to have competition: this implies that it would be preferable to have a multiplicity of certification bodies competing one with the other in offering their service. It is evident that a certifier acting as a monopolist would frustrate any virtuous selection based on competition and reputation. In addition, reputation is often based on comparison. One firm is better than another due to a set of features it has and that the competitor does not: a comparison which would be impossible if, again, there is only one, monopolistic certifier. These points may seem, and are indeed, obvious: nonetheless, it is important to stress them since many times we witness cases where the authorisation process for certifiers is *de facto* designed or implemented in such a way as to create a monopoly.[20] This risk should be slight in the biobank sector, where we can imagine (at least) a European market for certifications. However, the concrete realisation of such a market will depend on the policies that the single national States will implement in authorising certification bodies to operate within their territories, since the accreditation procedures are eventually determined on a national level. In this sense, if the goal is to create a European biobank network, it would seem appropriate also to harmonise the accreditation process for certification bodies through the enactment of more intrusive and detailed norms than the scanty references contained in the guidelines currently in place.

16.4 Using Certifications in the Biobank Context

An enquiry into the possible uses of certification schemes for biobanks must begin with the analysis of the needs of the sector and on how certifications can meet them. The starting point is a simple consideration: in order to better exploit the economies of scale that also characterise the research sector, allowing for a more efficient use of financial resources, as well as for a better partition of scientific and technical competences, biobanks will be increasingly asked to operate within national and international networks.[21] As it has been stated, "Experts widely recognised the need to improve collaboration and networking among the numerous existing biobanks, as well as new initiatives in Europe (and world-wide). Efficient organisation of these resources through the development, for example, of an infrastructure would potentially facilitate financial sustainability and greatly contribute to the rapid progress of research and development of better diagnostic and therapeutic approaches. [. . .] It has been widely recognised by all stakeholders that in order to accelerate scientific

[20] This is the case, for example, for some types of mandatory certifications used in the food sector. In Italy, the (mandatory) certification of wines bearing a geographical indication can be performed only by one certifier authorised for each specific indication. This means that wine producers wishing to use a specific geographical indication face a monopoly, having no other choice than to resort to the sole certifier who has been authorised by the Ministry of Agriculture.

[21] See Shickle and Griffin (2009), p. 1.

discovery it will be critical to improve biobank quality, interoperability and sustainability".[22] There are already initiatives aimed at building international biobank networks, such as the one promoted by the OECD.[23] On the other hand, the creation of such networks requires taking into account a few elements which, as I mentioned above, have a direct bearing on certifications.

Firstly, there is a need for uniformity.[24] The interoperability among biobanks implies the creation of a common ground on which all the players share rules, practices and goals. In this regard, there are two aspects which come into play: on one hand, the establishment of common standards, with which all participants to the network should comply; on the other, a uniform application of such standards. Certifications intervene with regard to this second aspect, checking if the participants abide by the required standards.[25] The enactment of the standards is a pre-requisite for the operation of the certification: the latter, nonetheless, assures that a uniform application is given to them. In this sense certifiers can be conceived as a sort of ex ante courts which decide, before any dispute arises, whether or not the interpretation and application of the standards implemented by the subject seeking the certification is correct. In other words, certifications represent a form of ex ante control and, like all the forms of ex ante controls, encourage harmonisation and uniformity.

Secondly, there is a need for reliability. Reliability is the cause and the effect of trust: and, as mentioned several times before, the latter plays a pivotal role in building and maintaining any kind of network. Biobanks are no exception: if the goal is to foster interoperability between biobanks, such interaction requires an environment characterised by mutual trust. This can be partly created through the

[22] See Zika et al. (2010), pp. 143–144. DG Research Directorate for Health Research, PHOEBE and BBMRI (2008), reports that, "[...] real progress in unravelling the causes of disease and developing translational applications will derive from pooling and harmonizing resources across the EU. This requires biobank interoperability" (p. 1).

[23] See the cooperation promoted by the OECD Directorate for Science, Technology and Industry "Towards a global biological research centre network", of which a brief summary is available at http://www.oecd.org/document/51/0,3746,en_2649_34537_33791027_1_1_1_1,00.html. At the national level, in Spain "the Spanish Ministry of Science and Innovation [...], through the Instituto de Salud Carlos III [...] has decided to create and develop a network of hospital banks ($n = 52$) to which other biobanks ($n = 11$) have been associated": Spanish Network Biobank Network—Strategic Plan December 2010, 6, available at http://www.redbiobancos.es/Pages%5CDocs%5CPlan_estrategico_ING.pdf. Nonetheless, among the weaknesses reported in the Strategic Plan there is also the "lack of standardization of the data associated with biological samples" (p. 15) and, on a global level, the "lack of international standards for certification and/or accreditation specific for biobanks" (p. 16).

[24] For a discussion of the preliminary issues concerning the creation of a uniform regulatory system, see Kaye (2006), p. 245. See also Indech (2000), p. 343; Betsou et al. (2007); Carter et al. (2011), p. 247.

[25] As I have noted above, the controls related to the compliance with the standards performed by the certification body are also aimed at transmitting validated information about the subjects who have been certified and, namely, about the fact that these subjects have the features embodied in (or required by) the standards they apply.

promotion of uniformity; nevertheless, trust is something which goes beyond the mere uniforming process. Indeed, trust is a feeling which is built upon repeated interactions and cross-checks based also on assessments coming from external observers. Certifications, with their periodical audits and thanks to the independence status certification bodies enjoy, can contribute to trigger the dynamics I mentioned, providing a verifiable benchmark. However, reliability does not have to be interpreted as an element which should characterise only the networking among biobanks. It plays an important role even with respect to the relation between biobanks and citizens. I have already mentioned that we should distinguish donors, public institutions and taxpayers: the degree of trust and reliance that these three categories imply is of course different, stronger for the former than for the latter. Nonetheless, the mechanism governing these hypotheses works in a similar way: the willingness to donate samples, as well as the support granted for financing initiatives, will always depend on the perception the subjects involved have of the fairness, professionalism and reliability of biobanks.[26] Again, certifications can offer their own contribution. Citizens could show a preference for those biobanks which have been certified, associating them with a higher degree of reliability and professionalism: in other words, trusting them more. In turn, this could lead to a stronger willingness to donate samples or to invest resources on behalf of the biobanks which have been certified. From a different, but complementary perspective, certifications can be conceived as a marketing tool: by transmitting valuable information about the qualities of a given biobank, they render it more competitive than other, non-certified biobanks. Here is the core of the certification's notion: making the selection process easier on behalf of other biobanks which want to build some kind of networking; of public institutions which are willing to invest resources; and of citizens, who have to decide whether to donate a sample or if public money is spent in a reasonable way.

Thirdly, there is a need for flexibility. Biobanking is a developing activity which cannot be considered to have yet reached its full maturity and potential. Therefore, we should be cautious in imposing burdens which could curb its development. On the other hand, not all biobanks are at the same level and for some of them it might be more feasible to bear additional costs than for others. The costs I am referring to are related, for example, to the implementation of management systems or to particular procedures of sample collection and storage. The recourse to certifications can provide some flexibility in tracing the governing structure for biobanks. Of course, this will depend on the types of certifications we choose: for example, preferring mandatory forms of certifications is not very different from imposing a burden through a statutory norm. Choosing voluntary certifications may be preferable for a sector which is taking its first steps, possibly coupled with a set of incentives aimed at promoting the adoption of such (voluntary) certifications, a point I will come back to later. The flexibility implied in the option of choosing between different (voluntary) certifications allows biobanks to devote resources to

[26] See Levitt and Weldon (2005), p. 311.

those sectors (management systems, procedures for sample collection, storage of tissues, etc.) they consider strategic for their future. Even the complexity of the standards can vary depending on the certification which is sought: there are standards which are more sophisticated than others. The choice between the possible alternatives will be dictated by the trade-off between the costs that complying with complex standards entails and the benefits deriving from the implementation of more reliable and detailed rules.

The final need I wish to point out relates to accountability. I have already dealt with this aspect earlier: here it is sufficient to remember that accountability plays a pivotal role in building trust. The need for trust in the biobanking field is self-evident in many respects: the data which are handled in these structures render them particularly sensitive, requiring an environment with a high degree of trust before their retention and use are consented. If the donor knows that her data will be employed according to reliable procedures, she will be more likely to give consent. In a similar vein, a biobank which is asked to transmit information about its repository and/or researches by a fellow biobank will be more willing to do so when it knows the latter works according to shared, responsible and validated standards. Certifications are tools which are perfectly fit for this purpose, either if we consider the biobank-donor relationship or the relationship among fellow biobanks.

16.5 On the Possible Uses of Certifications in the Biobanking Context

In the final part I will try to answer three questions which seem, to me, to play an important role in delineating the future relationship between biobanks and certifications. In this way, I will also seek to summarise some of the points I raised above.

The first, basic question is the following: are certifications a possible solution for some of the needs of the biobank field or do they entail the risk of creating additional problems and costs? The answer, as often happens, depends on a variety of elements. It cannot be denied that certifications might represent an additional burden for biobanks, in terms of economic costs, human resources, and restructuring of internal procedures. Thus, if preference is accorded to a certification scheme characterised by rigidity and closeness, the burdens will grow exponentially. In addition, biobanks do not represent a homogeneous category: rather, they differ as to their needs, their internal organisation, the services offered, the resources they have. Also at this regard, the way the burdens impact on biobanks will vary depending on the specific biobank we consider. Going back to the question I asked, certifications can be a solution insofar as they are conceived in such a manner as to (1) minimise the costs which they invariably imply and (2) be flexibly adapted to the features and needs of single biobanks. The other two questions can be in some way considered spin-offs of these two basic considerations.

The second issue concerns the type of approach which should be adopted in building the general framework governing biobanks' certification. Should we prefer a market-based or a government-run scheme for certifications? Examples of both types can easily be found: for example, in Japan government-controlled certifications are used for some industrial products,[27] while the certification of organic agricultural products is usually performed by a host of certification bodies in competition with one another.[28] The actual trend, anyway, is clearly favouring a market-based approach: the shift of inspection duties from the public to the private sector witnesses the growing success that the idea of market has in the certification domain. Moreover, as I noted before, a market approach allows for a higher degree of accountability than one based on a monopolistic operator, as well as for a higher degree of flexibility. The need for accountability and trust, the increasing dismissal of public-run certification schemes, the necessity of flexibility are all elements that seem to favour a market-based approach. The real challenge will be to build a truly competitive market, avoiding the risk of monopoly and/or of local protective measures preventing access to outside operators. Other branches of the law and, most notably, anti-trust law, as well as the regulations governing the free movement of services,[29] can help in promoting a competitive market. At the same time, it is also important to consider the economic viability of a market in which a variety of biobanks' certifiers compete. Here, the size of a market seems to play a major role: the larger (European or international) the market, the higher the chance of having many actors competing in an economically sustainable way.

The third and last question revolves around the dichotomy between voluntary and mandatory certifications. In the taxonomy I outlined earlier, the distinction between these two types plays a pivotal role. Should we prefer a voluntary or a mandatory scheme of certification? On one hand, requiring mandatory certifications can increase the level of reliability of the entire biobank system: if all the biobanks have to operate according to given standards, those who enter into contact with any biobank will be sure that such standards are observed. On the other hand, voluntary certifications allows for a higher degree of flexibility: biobanks can choose whether, and according to which standards, to certify their activities, taking into consideration their needs, resources and goals. The problem is, thus, seeking to balance these two poles: reliability and flexibility. Too much flexibility can undermine reliability; vice versa, too much reliability can stiffen the system, compromising flexibility.

The dilemma can nonetheless be overcome by imagining a solution which takes into consideration incentives. Through a careful use of incentives it is possible to balance reliability and flexibility, providing biobanks with enough stimuli to adopt

[27] Ramseyer (1996), p. 1823.

[28] This is the case, for example, in Europe, where Regulation 834/2007 establishes the norms governing the certification of agricultural produce.

[29] In Europe, see Art. 49 of the Treaty on the Functioning of the European Union and the Directive 123/2006 on services in the internal market.

certifications, at the same time without imposing them. Two forms of incentives can be put in place: public and private. Moreover, both can take different forms. The first may consist of direct money subsidies, granted to biobanks which obtain a certification, or of tax benefits, making some of the certification expenses sustained deductible; they may also be framed as a requisite for working with public institutions such as, for example, public research centres and hospitals, or to obtain research grants. As for private incentives, they may be shaped as a pre-requisite to enter into a contractual relation, in a consortium or in any other type of network formed by private subjects[30]; as a condition for receiving funds from private bodies, such as charity trusts; as a requirement for having an article published in a scientific journal[31]; we might also imagine them as a contractual imposition by the donors to the biobank before giving their consent to the use or storage of their sample.[32]

The catalogue of the incentives must be enlarged beyond the private/public divide: there is indeed a third category in which what I call market incentives can be included. These are incentives that, as a matter of fact, already urge biobanks to certify their activities. For example, certification of the management system usually leads to a better internal organisation which, in turn, should save resources and make the biobank more competitive: therefore, the biobank has an incentive in adopting it. Certifications can also convey information as to the ethical commitment of the subject or enhance her reputation: again, all elements which make biobanks more competitive and constitute incentives.[33]

An incentive-based certification system does not only help balance flexibility with reliability, but it can also improve the reactivity of the whole system. Firstly, both private and public subjects can concur in setting priorities and arranging a congruent ensemble of incentives: the result is likely to advance pluralism. Indeed, the concurrence between public and private actors allows a variety of interests to surface, at the same time permitting a rapid realignment of the system with the goals which are thought to be central. Secondly, the catalogue of incentives which can be put in place is open and can be enriched through innovative solutions: the same co-existence of private and public actors can trigger a sort of competitive dynamics in developing new incentive mechanisms.

[30] This case is not functionally different from the case I mentioned before in which a public institution requires biobanks to be certified before cooperating with them.

[31] The point has been sensibly raised by Matteo Macilotti, who pointed out that a defective conservation of the tissues or other misconducts in managing them can undermine the reliability of the scientific experiments conducted on such tissues and, potentially, lead to disputable conclusions. In order to avoid this type of problem, scientific journals might require the researchers submitting an article to prove that both the biobank from which the tissues used in the experiment came, and the laboratory where the experiment was conducted, were certified.

[32] It seems to me that this option is more theoretical than practical: what it is more likely to happen is that donors will be more willing to give their samples to biobanks which are *de facto* certified, regardless of the existence of an express contractual clause imposing the certification.

[33] For competitiveness I mean here the ability of a biobank to attract donors, funds and other resources, as well as to participate in networks.

A final caveat should be spelled out as to the relationship between private certifications (and standards) and mandatory norms. Certifications are not a substitute for mandatory norms: rather, they are something operating in addition to them. Indeed, they serve different functions: the goal of mandatory norms is to set a minimum, common level of measures which cannot be bypassed.[34] On the contrary, certifications aim at raising the protection offered above those measures which form the common level I was referring to before. Thus, certifications cannot depart from, or be in contrast to, mandatory norms: they have to work in synergy with them, filling those interstices left unregulated or which are regulated in a different way at the international level.[35] In the biobanks domain these interstices are not few and do not concern residual aspects, especially if we look at the international dimension of biobanking regulation. This is the reason why certifications are bound to play an important role in the future, one of increasing expansion; the success of this expansion will depend, among other things, on the factors I highlighted before.

16.6 Conclusion

In the near future, biobanks will be required more and more to coordinate their activities with those performed by fellow biobanks, exchanging data and sharing results. At the same time, they will also be asked to reassure public institutions and citizens that what they do is done in an efficient way, avoiding waste of resources and respecting the rights of those involved in the biobanking activities. Both these questions point to the need to build an environment of mutual trust, where different operators (or simple bystanders) can work knowing that their partners act according to shared and reliable rules. In turn, this requires thinking of legal tools which can contribute to building such an environment.

While significant attention has been focused on developing common standards for regulating biobanks' activities,[36] far less attention has been devoted to how such standards will be implemented. There is no doubt that creating common standards is the first, necessary step to building that environment, imbued with trust, which I evoked repeatedly. Only the presence of shared rules allows players to predict how

[34] For example, Art. 7 of the Dir. 23/2004, regulating inspections and control measures, cannot be neglected because periodical audits are carried out by certification bodies or because other control measures have been applied according to given private standards.

[35] For example, "Significant variability emerged with regards to privacy and data protection requirements among biobanks in Europe. Although informed consent for approval of biobank-based research is almost ubiquitously required, the actual consent requirements and related procedures vary widely among biobanks, depending on the national laws and guidelines applied": Zika et al. (2010), p. 143.

[36] See for example Betsou et al. (2007), where most of the article is devoted to creating ISO-compatible standards for biobanks. The same can be said with regard to the initiatives promoted by national or international bodies: see for example the Guidance for the Operation of Biological Research Centres, cit., published by the OECD, or the Italian Linee guida per la certificazione delle biobanche, 2006, cit., and Linee guida per il riconoscimento/accreditamento, 2008, cit.

they have to act and how others will act,[37] a basic condition for trusting others. Nonetheless, wondering what will be the means through which these common rules will be applied and how effective and efficient it will be does not seem a trivial question.

Certifications are a tool which can provide some of the answers to the questions raised above. If properly conceived, they are able to convey information about the reliability and trustworthiness of the activities carried out by biobanks, allowing for a higher degree of flexibility and efficiency than public regulation. However, it would be misleading to imagine making recourse exclusively to certifications in order to create (or strengthen) trust. Certifications should come along with other initiatives, such as private or public information campaigns on biobanks. The same notion, goals and functioning mechanisms of certifications should be the subject of initiatives aimed at advertising them. If we want certifications to be able to convey reliable information and to generate trust, operators and citizens should be aware of what a certification is.

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[37] Levitt and Weldon (2005), p. 320: "A 'gift relationship', embodying solidarity and trust, requires the establishment of a mutual relationship with obligations and expectations on both sides. This is the sort of evidence that people need in order to place their trust well".

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Part III
Biobanks: The Perspective of Biobanker's

Chapter 17
Scientific and Managerial Premises and Unresolved Issues in Tumour Biobanking Activities

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Abstract Research biobanks are organisations that collect and preserve human biological materials, according to ethical and legal rules, in order to supply researchers with high quality human specimens for scientific purposes, accompanied by as much data as possible. Disease-oriented biobanks are aimed at collecting biomaterials pertaining to specific pathological conditions, and among them are tumour biobanks. High-quality biobanking relies on several aspects, which include long-term funding, appropriate ethical and legal framework, active involvement of patients and the medical community, quality of samples and of the corresponding data, proper regulation of the procedures for distributing biomaterials, appropriate Information Technology (IT) infrastructure, networking in a national and international environment. In this essay we will focus our attention on some of these aspects, describing, in particular, the workflow and organisation of a specific type of biobank: the tumour biobank. Our analysis is based on the experience developed in the recently established *Trentino Biobank* (TBB), which is a paradigmatic biobanking project in Italy.

17.1 Introduction

The availability of ever more powerful and less expensive technology to analyse biomolecular alterations, and the rapid development of increasingly reliable IT tools to analyse these data, will surely bring about an incredible increase in

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knowledge, which will translate into better healthcare.[1] For example, knowing the precise gene alterations responsible for a specific type of cancer will help to produce new drugs tailored to interact with these specific mutations. Gene alterations may also become useful biomarkers for early diagnosis, especially if these can be detected in body fluid such as blood or urine. In this perspective, human biospecimens are an invaluable source of information for medical research, especially in the oncological setting.[2] No research can be carried out on the nature of cancer or on the mechanisms which are deregulated in cancerous cells without analysing human biospecimens. Therefore, the availability of human biospecimens may represent a rare limiting step in future development of new diagnostic and therapeutic tools. To achieve these accomplishments, the scientific community needs biospecimens, which meet extreme high levels of quality. They must also be accurately annotated. This means that all biospecimens must be collected and stored according to protocols which allow optimal preservation of the intrinsic molecular composition, and that each sample must be associated with demographical (sex, age, ethnical group, life style, smoking, etc.), pathological (organ and tumour type, stage, histological aggressiveness, etc), clinical (familiarity, therapeutic interventions, relapses, etc.), and survival data.

Biospecimens are not only a source of knowledge, but can also be a source of profits for the pharmaceutical/biotechnological industry, as several important patents can be produced starting from this kind of material. The availability of biospecimens has indeed been directly linked to the economic development of the biotechnological industry.[3] This aspect of biobanking opens a series of new problems concerning the property of the tissues and the regulation of the possible economical benefits deriving from their use.

High-quality biobanking relies on several aspects, which include long-term funding, appropriate ethical and legal framework,[4] active involvement of patients and the medical community, quality of samples and of the corresponding data, proper regulation of the procedures for distributing biomaterials, appropriate Information Technology (IT) infrastructure, and networking in a national and international environment.

In this essay, we will focus our attention on some of these aspects, describing, in particular, the workflow and organisation of a specific type of biobank: the tumour biobank. Our analysis is based on the experience developed in the recently established *Trentino Biobank* (TBB), which is a paradigmatic biobanking project in Italy.

[1] Roden et al. (2008), p. 362.

[2] Riegman et al. (2008), p. 213; Oosterhuis et al. (2003), p. 73.

[3] Von Walcke-Wulffen (2009); EuroCryo Saar, November 2009.

[4] Macilotti et al. (2008), p. 86.

17.2 Biobank Organisation: The Example of the TBB

We recently established the TBB[5] which supports research by collecting and storing leftover fragments of surgically removed tumour samples.[6] Tissue fragments are stored as formalin-fixed paraffin-embedded and cryopreserved samples, with high quality standards. TBB has an IT system for the management of biological samples and clinical data,[7] and guarantees that biological samples and corresponding data are collected and stored with the patient's consent, in compliance with ethical and legal provisions. Samples are provided to Research Institutes only within the framework of peer-reviewed high-quality research projects approved by a Scientific and an Ethical Committee.

High quality, efficient biobank management relies on an internal organisation governed by appropriate distribution of the work. The TBB staffs include the biobank manager, the quality manager, and the biological material manager. The *biobank manager* is responsible for coordinating and verifying the proper operation of the biobank and for managing budget issues. He has decision-making authority over all the activities carried out, and is therefore responsible for their proper functioning. The *quality manager* is responsible for identifying patients who could donate biological material, explaining the aims of TBB to patients and obtaining their informed consent, performing quality controls on biomaterials and data, and ensuring ongoing update of the standard operating procedures. The *biological material manager* is responsible for collecting the material from the operating theatre, delivering it to the pathologist for macroscopic evaluation, storing the material in suitable vials and ensuring their proper storage and cryopreservation, recording the collected materials in the biobank software, and monitoring the efficiency and maintenance of the cryopreservation systems. An important role in TBB's activities is carried out by the Scientific Committee and the Ethical Committee. The *Scientific Committee* is a body within the TBB which evaluates if a specific research project has the scientific requirements for using biomaterials stored in the TBB. The *Ethical Committee* is external to TBB and provides opinion regarding ethical issues that could arise in the course of the TBB's activities. The committee is also responsible for approving research projects that involve the use of biomaterials stored in the TBB, if these projects have not already been approved by a National Ethics Committee or if the applicant is located in a foreign country. All materials are provided to researchers according to a specific material transfer agreement procedure.

[5] *Trentino Biobank*, is founded by the Provincial Health Authorities of Trento and by the Fondazione Cassa di Risparmio di Trento e Rovereto, and is a functional structure of the Surgical Pathology Unit of the S. Chiara Hospital of Trento; www.tissuebank.it.

[6] Barbareschi et al. (2008), p. 139.

[7] Galvagni et al. (2008); p. 116.

17.3 Biobank Workflow

TBB collects leftover tissues and bodily fluids of patients affected by cancer who undergo surgical resection in our Hospital. Following surgical excision, all human tumour biospecimens are routinely examined and processed for diagnostic and staging purposes in the Unit of Surgical Pathology. Therefore, TBB's activities are strictly integrated into the workflow of the diagnostic activities. The biomaterial samples for biobanking are collected under the full responsibility of the surgical pathologist, who evaluates the feasibility of storing certain aliquots of the surgical specimens, without interfering with the diagnostic process (e.g. very small lesions are not sampled). The samples collected for TBB are leftover tissues, hence, redundant for diagnostic purposes. Biomaterials are collected according to internationally recognised procedures.[8] According to these procedures, the biomaterial manager freezes, stores, and identifies each sample in vials or cryomolds with a specific bar code, which is different from the diagnostic identification code of the surgical specimen. The −80 °C freezers and liquid nitrogen tanks are located in a special storage area with controlled access, in keeping with Italian rules for the collection of genetic material. Each specimen is appropriately recorded in the biobank database in which the material type, storage methods and the associated identification code are specified. By means of this coding, the specimens and the associated information are managed anonymously in order to prevent the disclosure of personal data or their use by unauthorised persons. Pathological and clinical data are then automatically added in the course of time as they become available. This is made possible through direct integration of the TBB database with the IT management systems of the departments of Surgical Pathology and Medical Oncology of the S. Chiara Hospital in Trento. The TBB IT database automatically imports a minimal pathological and clinical dataset, but both systems can be further queried to obtain additional information that may be necessary.

17.4 Informed Consent

Italian legislation provides for the need to obtain a specific informed consent for using human samples for scientific research. This prescription finds some obstacles in common practice. Indeed, it is impossible to know/foresee all possible future uses of human tissue, and unlimited consent would not adequately guarantee

[8] IARC Working Group Reports (2008); Morente et al. (2006), p. 2684; ISBER (2008), Mager et al. (2007), p. 828.

patients' rights.[9] To overcome these obstacles, TTB has elaborated a specific two-step information strategy. The first step consists in the provision of some main categories of research (such as breast cancer research, colon cancer research, etc.) that are used to narrow the consent. Therefore, when a patient gives his/her consent, he/she does not consent to research in general, but he/she consents only to the use of his/her tissue within a specific category of research. As a second step, patients must also be adequately informed that (a) their biomaterials will be used only in scientific research projects that respect human dignity and have been approved by an Ethical Committee; (b) the specimens and the related data may be used exclusively for scientific research purposes and never for direct profit purposes; (c) the data are managed in coded form and processed in compliance with Legislative Decree 196 of 2003, as well as with the Authorisation for processing genetic data issued by the Italian Data Protection Authority; (d) only the TBB staff can connect the identity of the donors with their samples and data; (e) researchers will receive only coded samples and data; (f) donors may give notice at any time that they have changed their minds regarding their statement and can withdraw their consent at any time; if the donors revoke their consent, the biospecimens are destroyed; (g) donors can know at any time the current use of their stored samples and data, in other words, since it is not possible to assure the patient's rights to be fully informed about the future specific research which will be conducted on their tissues, the TBB guarantees the patient the right to inquire about it; and (h) donors may access the documentation concerning their biological specimens and all related documentation produced by the Ethical Committee. Patients can also decide if they want to be contacted in the future if relevant information about their health is found during a research project and whether they want this information be shared with their family.

The aims of TBB are described to the patient by qualified personnel, who deliver an informational brochure and explain all the points of the informed consent. The authorisations/restrictions decided by the patients in the informed consent are recorded in the TBB database.

In our experience, with more than 700 patients, all agreed to donate their materials to TBB. Frequently, patients, although in a very difficult personal and psychological situation due to their discovery of being affected by cancer, would positively accept the donation of their samples (some examples of patients' reactions are reported in Table 17.1).

However, a significant percentage of patients (18 %) did not want to be contacted again if important medical information surfaced that could be of benefit to their own health or their relatives'; 8.8 % of patients didn't agree to sharing clinical and genetic data with relatives, and 0.6 % denied providing biomaterials by private companies for industrial research.

[9] Petrini (2010a), p. 217; Petrini (2010b), p. 1040; Hansson (2010); 340: c2335; Hansson et al. (2006), p. 266.

Table 17.1 Paradigmatic consideration from some patients during the administration of the IC

1.	*54-year-old man with lymphoma: he provided his consent, saying that, having always worked as volunteer in charities,* ***he considered his participation in the biobank as another form of volunteering***
2.	*50-year-old woman with breast cancer: she told us she was in total agreement with all the initiatives related to research (fundraising, information, etc.) and that the gift of her biomaterial for research purposes was a further contribution to the development of science and that* ***this made her feel involved in "something" important for the future***
3.	*42-year-old man, researcher at the University: he stated that he was not able to fully understand the real meaning of storing tissue for research, as this topic was beyond his scientific knowledge, but* ***he trusted TBB to take care of the biospecimen, as TBB is part of the Hospital where he decided to be cured***
4.	*63-year-old woman, with pancreatic cancer: she stated that* ***the idea of doing something useful for helping future human beings was a relief to her present suffering***

17.5 Quality Control of Biospecimens

Regular control of the quality of biomaterials is of the utmost importance in biobanking.[10] The purpose of quality control is not just evaluating the integrity of the biomaterials, but also taking corrective measures if the controls detect any irregularity. The factors that determine the quality of the material can be divided into intrinsic and extrinsic. The *intrinsic factors* are closely linked to the type of material and can pertain to the type and character of the lesion (e.g. admixture of benign and tumour tissue in the collected sample, amount of non viable cells), and the surgical procedure (the integrity of the biochemical component may be affected by the length of the surgical procedure, the so-called period of warm ischemia). Corrective measures cannot be performed in relation to these factors as they pertain to intrinsic characteristics of the material/procedure. To ensure the quality of the material in terms of intrinsic factors, the only element that is crucial for correct storage is careful gross evaluation by the pathologist who takes the sample, with subsequent histomorphological evaluation of the samples before processing. The *extrinsic factors* pertain both to the handling of the material and to the storage method. These factors depend largely on the operator and, as such, corrective measures can be followed based on the results obtained from the quality controls performed on the biomaterial. The most important critical point is the time between surgical removal and when it is frozen (so-called cold ischemia), which should be as short as possible and accurately recorded and handled by the pathologist. Quality controls of the TBB's biomaterials are performed periodically at random on 1 % of the material stored by analysing qualitatively and quantitatively the total amount of RNA extracted. RNA is extracted according to a verified procedure, and the RNA integrity is evaluated using the bioanalyser equipment, which provides a numerical

[10] Carter and Betsou (2011), p. 157; Yuille et al. (2010), p. 65.

value (RIN value) ranging from 1 to 10. Samples with RIN values above 6 are considered optimal for gene expression analysis.[11]

The quality of pathological and clinical data is also important and requires continuous updating and assessment by qualified personnel. The TBB personnel performs weekly monitoring of the proper entry of pathological and clinical data in the TBB software and, when discrepancies are found, the data imported are changed under the supervision of the TBB manager. Moreover, the IT system periodically provides backup of all biomaterial and pathological data.

17.6 Unresolved Issues

Several unresolved issue still exists, especially concerning regulations and laws that are incompletely codified and vary from country to country. One of these unresolved issues concerns the possible use of biomaterials stored in the archives of the Units of Surgical Pathology. The historical collections contains millions of samples of well annotated surgically removed human tissues, which have been stored for a prolonged period. In several Institutions, these archives contain samples even from the beginning of the last century. Therefore, these archives are an enormous source of accurately annotated human tissues, which can provide invaluable information about human diseases.[12] However, in most instances, these samples have been (and still are) collected only for diagnostic purposes without specific consent from the patients to the use of the biospecimens for research. How can these materials be used in research? Obtaining informed consent for these historical collections is almost impossible as many patients are already deceased and it is unfeasible to contact living patients. Can we use these specimens and their corresponding data in research protocols, provided they are included in a biobank that acts as a third party between patients and researchers? In this case, should we use completely anonymised samples or could it be possible to use coded samples? Or, could we hypothesize a "drop-off" system, where biobanks, following adequate public information about the specific research project (e.g. on hospital websites, newspapers, etc.) can include these materials within their files and offer them to researchers, unless the patient opts not to adhere to the research project?

A biobank not only stores samples, but may also manipulate them, obtaining sub-products, such as nucleic acids, proteins, etc. or even analytical data, such as gene sequencing, and gene expression profiles. From collected biospecimens, it is also possible to obtain cell lines (primary cultures, immortalised cell lines, etc.) or even produce xenograft, by implanting tumour cells in recipient animals.[13] These options open a large horizon of possibilities but also raise new unresolved issues.

[11] Muyal et al. (2009), p. 9; Strand et al. (2007), p. 38; Mathot et al. (2011), p. 547.

[12] Riegman and van Veen (2011), p. 357.

[13] Stanta et al. (2011), p. 149.

Xenograft could be used to exploit in vivo drug trials, reducing the need for human testing, or could be used for the same patient to select the most active drug against their tumour. These activities open broad fields of interest in biobanking activities, but also need accurate regulation.

Another problem concerns the possible use of the biomaterials stored in research biobanks for diagnostic purposes: if a patient agrees to store his/her biospecimen for research, there is always the possibility that in the future the same sample could become of diagnostic significance (e.g. for the investigation of a specific marker which can drive new therapeutic approaches). Therefore, it would be wise to spare an aliquot of the sample for this purpose. Should this become standard practice in biobanking? To what degree do diagnostic and research biobanks differ as entities?

Finally, in our model, the biobank is a third party between patients and researchers. However, frequently, biospecimens are collected by people who are also directly involved in research. And indeed, this is the most frequent situation in practice. How can we assure that the biobank really acts as a third party, if the same people collecting biomaterials are also involved in research on the same specimens?

In summary, biobanking is of the utmost importance for medical research and its proper regulation as a third party between patients and researchers is fundamental.

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Chapter 18
The Italian Prototype Networks of Research Biobanks

Giuliano D'Agnolo* and Elena Bravo**

Abstract Research-based biobanks will create new synergies between industry and public research structures, strengthening the competitiveness of our country for health industries. In addition to the ultimate objective of prevention and treatment of complex diseases, the short-term benefit will come from the development of new and more powerful diagnostic agents. In fact, molecular diagnostics, a new discipline based on "-omics" technologies, a powerful tool to understand diseases and assist individuals at risk, is one of the fastest growing segments in the healthcare industry. In order to collect the socio-economic benefits summarised above, many European countries, have underway, or are planning, large, well organised biobanks. However, the existing samples collection, resources, technologies and expertise have been developed under different ethical and legal landscapes across

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Europe. The existing collections suffer from fragmentation, variable access rules and the lack of commonly applied standards. This lack of standardization prevents the effective use of biological samples and data from different biobanks, which is a prerequisite to achieve sufficient statistical power for genomics research in humans. By initiating the Biobanking and Biomolecular Research Infrastructure (BBMRI) [All Member States and the Commission agreed on a shared vision of how the European Research Area (ERA) should develop by 2020 (http://ec.europa.eu/research/era/index_en.htm). This vision was adopted by the Council of Ministers in December 2008, and implemented for the needed infrastructures by ESFRI, the European Strategy Forum on Research Infrastructures, a already existing strategic instrument with the task of developing the scientific integration of Europe and to strengthen its international outreach. Since it was formed in 2002, at the behest of the European Council, ESFRI has witnessed significant advances towards unity and international impact in the field of research infrastructures. The publication of the first Roadmap for pan-European research infrastructures in 2006, and its update in 2008 (http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri) was a key contributing factor, and several projects are now in the realization phase like BBMRI (http://www.bbmri.eu/). BBMRI is a large scale project building a research infrastructure structured as a federated network of biological resources centres including all types of biobanks: disease oriented, population-based biobanks, biomolecular-resources; it includes all fields of medical research: rare diseases, cancer, complex diseases, etc.] on February 1st, 2008, Europe addressed the need to: harmonise standards for sample collection, storage and analysis; harmonise data collection and database infrastructure; provide ethical and legal guidance; develop a sustainable funding model for biobanks. This article describes some of the aspects of this European infrastructure.

18.1 Introduction

Many common diseases like Alzheimer, asthma, arthritis, cancer, cardiovascular diseases, diabetes, hypertension, obesity, Parkinson and psychiatric diseases, are due to complex conditions that not only cause personal suffering, but also represent a burden for society in terms of health care costs and economic productivity. Complete treatment of these diseases remains elusive because they do not originate from a single cause but are the result of a large number of effects, often additives, stemming from a genetic predisposition, lifestyle, and the environment. These diseases are estimated to be, in our country, about 70 % of all diseases, with a mortality approaching 80 %. The availability of biological tests for a more precise classification would make their treatment faster and cheaper, would decrease the incidence of side effects of their treatment, and would lead to more effective clinical trials and the development of new strategies for prevention and health promotion. The study of complex multifactor diseases requires a comparison of a large number of samples obtained from affected and unaffected individuals.

Collections of biological materials, or biobanks, along with clinical information associated with the samples, are, therefore, an indispensable tool to elucidate the molecular mechanisms and causal pathways, whether genetic or environmental, to translate biomedical research into health care improvements. Chronic illnesses, characterised by slow progression, are a direct and indirect burden for the economy of our country. As research-based biobanks will lead to direct improvements in treatment and prevention of diseases, a significant economic impact in terms of reducing health costs and increased productivity of a healthier population has to be expected.

Research-based biobanks will create new synergies between industry and public research structures, strengthening the competitiveness of our country for health industries. In addition to the ultimate objective of prevention and treatment of complex diseases, the short-term benefit will come from the development of new and more powerful diagnostic agents. In fact, molecular diagnostics, a new discipline based on "-omics" technologies, a powerful tool to understand diseases and assist individuals at risk, is one of the fastest growing segments in the healthcare industry.

In order to collect the socio-economic benefits summarised above, many European countries, have underway, or are planning, large, well organised biobanks. However, the existing samples collection, resources, technologies, and expertise have been developed under different ethical and legal landscapes across Europe. The existing collections suffer from fragmentation, variable access rules, and the lack of commonly applied standards. This lack of standardisation prevents the effective use of biological samples and data from different biobanks, which is a prerequisite to achieve sufficient statistical power for genomics research in humans. By initiating the Biobanking and Biomolecular Research Infrastructure (BBMRI)[1] on 1 February 2008, Europe addressed the need to:

- Harmonise standards for sample collection, storage and analysis;
- Harmonise data collection and database infrastructure;
- Provide ethical and legal guidance; and
- Develop a sustainable funding model for biobanks.

[1] All Member States and the Commission agreed on a shared vision of how the European Research Area (ERA) should develop by 2020 (http://ec.europa.eu/research/era/index_en.htm). This vision was adopted by the Council of Ministers in December 2008, and implemented for the needed infrastructures by ESFRI, the European Strategy Forum on Research Infrastructures, an already existing strategic instrument with the task of developing the scientific integration of Europe and to strengthen its international outreach. Since it was formed in 2002, at the behest of the European Council, ESFRI has witnessed significant advances towards unity and international impact in the field of research infrastructures. The publication of the first Roadmap for pan-European research infrastructures in 2006, and its update in 2008 (http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri) was a key contributing factor, and several projects are now in the realisation phase like BBMRI (http://www.bbmri.eu/). BBMRI is a large scale project building a research infrastructure structured as a federated network of biological resources centres including all types of biobanks: disease oriented, population-based biobanks, biomolecular-resources; it includes all fields of medical research: rare diseases, cancer, complex diseases etc.

BBMRI will be: "a distributed research infrastructure with operational units in most if not all European Member States. BBMRI will be implemented under the ERIC (European Research Infrastructure Consortium)[2] legal entity. A headquarter is foreseen in one Member State which will coordinate the National Hubs, established in the participating Member States. The headquarter will provide a common access portal to resources available in Member states, as well as appropriate facilities and expertise. The National Hubs are also established under the ERIC legal entity and will link the national scientific community (e.g., universities, hospitals, research institutions, resource centres) to BBMRI-ERIC".[3] BBMRI will have a distributed hub and a spoke architecture.

18.2 The Legal Framework

Biobanks depend on people's willingness to contribute samples for both research and storage. Public support is thus essential in securing the long-term viability of biobanks and rests on the assumption that the complex issues surrounding biobanks are managed appropriately by the responsible authorities. In this process, different stakeholders are involved, not least the general public. Knowledge of the public perspective, and of factors that influence their willingness to donate tissue samples, may inform the governance of biobanks and the design of information and consent procedures.

The public's willingness to contribute to future research is, according to the observations made by the directors of the biological repositories of the Italian comprehensive cancer centres, relatively high.[4] However, the Italian Authority on Data Protection and Privacy has issued an authorisation that limits the conservation of biological samples only for the time strictly necessary to carry out the research for which the appropriate informed consent has been obtained.[5] In subsequent opinions, the Authority has always confirmed the necessity of obtaining from the donor a restricted informed consent specific for the objective of the research proposed at the time of the sample collection.

[2] Council Regulation (EC) No 723/2009 of 25 June 2009 provided a common legal framework for a European Research Infrastructure Consortium (ERIC). ERIC is a legal entity with legal personality and full legal capacity recognised in all EU Member States. Its basic internal structure is very flexible leaving the members to define the statutes, case by case, membership rights and obligations, the bodies of the ERIC and their competence.

[3] See http://www.bbmri.eu/index.php/national-hubs.

[4] Alleanza Contro il Cancro (http://www.alleanzacontroilcancro.it/) associates the Italian comprehensive cancer centres in order to harmonise research on cancer, within Italy, and with the European programmes, by creating an exchange of information and cooperation among the leading European cancer institutes in order to create a European alliance on cancer. Alleanza Contro il Cancro has established a network of its biological repositories (http://www.iss.it/ribo/index.php?lang=2).

[5] Garante per la protezione dei dati personali (2007).

These opinions rise, for those working with biological materials, the problem of establishing the limits and with which methods it is licit to preserve samples beyond the time necessary to achieve the aim for which the samples were collected, and if it is legitimate to use samples also for purposes that are different form those initially identified. In fact, it happens often that collections of biological samples are preserved, by scientific research institutes, for future new studies.

In order to contribute to solve these problems, the National Bioethics Committee (CNB) and the National Committee for Biosafety, Biotechnology and Life Sciences (CNBBSV) predisposed specific guidelines for harmonising the informed consent used to collect biological samples for research purposes.[6] Many studies highlight the fact that people generally want to control whether their samples are used for research purposes, while the majority of them, as already mentioned, is happy to donate their samples. The model of informed consent proposed by the two Committees respects this request, by both informing donors about the future use of the biological material and the information derived from it, as well as by guaranteeing that the correct procedures are adopted in order to protect personal data. The model achieves the right balance between social interest and the protection of personal information. In 2006, the CNB had already stressed the potential social role of the biobanks by suggesting that, "In addition to the individual rights and privacy the biobank can become the instrument of a new solidarity between groups and between generations based on voluntary sharing of samples and information, building a common resource which must be based on democratic norms".[7]

In the absence of a formal legal discipline, the Committees suggest that the samples belong to the donor with the general formula of "concession of use", or are considered as "explicit and irreversible donation", with regard to the choice made in writing by the donor, with the provision that the donation of biological samples for research cannot have any lucrative purposes. The Committees propose also that the local Ethics Committee could allow the use of preserved samples when such use does not affect any interest of untraceable donors.

A strong cultural stimulus to the development of quality collections of biological samples was given by CNBBSV, under the impetus of its President Prof. Leonardo Santi, both by drafting specific guidelines on the accreditation and the quality certification of biobanks and by the organisation of numerous courses, across Italy, on such topics.[8] The guidelines had the objective of overcoming the fragmentation of the spontaneous collections, usually realised by researchers.

[6] The CNB and the CNBBSV, which are advisory bodies to the Prime Minister Office, have published jointly the "Guidelines for the collection of biological samples for research: informed consent" (http://www.governo.it/biotecnologie/documenti.html).

[7] National Bioethics Committee (2006).

[8] National Committee for Biosafety, Biotechnology and Life Sciences (2007).

18.3 The Italian Situation Before the Inception of BBMRI

In the scenario described above, several institutions have organised their collections, according to internationally shared rules or established thematic networks that shared sample and data to strengthen the instruments available to researchers.

The full potential of the opportunities offered by large infrastructures services and tools was deployed by some very important networks.

18.3.1 Disease-Oriented Biobanks

The Telethon Genetic Biobank Network was founded by 7 Biobanks supported by Telethon Foundation, whose purpose is to collect, preserve and offer to the scientific community, and to Telethon-funded investigators in particular, biological samples and related clinical data from individuals affected by genetic diseases, their relatives and/or from healthy control individuals. At present, the Network is constituted of eight biobanks and two biobanks in 1-year pre-admission period.[9] The aim of the Network is to coordinate and manage the biobanks' activities in order to enhance synergy and to provide scientists with an effective service. Samples are made available only to qualified professionals who are associated with recognised research or medical organisations engaged in health-related research or health care, provided that an adequate portion of those samples is safeguarded to the patients' advantage.

VAS,[10] Vascular Independent Research and Education European Organization, is a European Scientific no profit Association whose mission is to contribute to the development of Angiology/Vascular Medicine, in multi-centre co-operation amongst clinicians and researchers throughout Europe and Worldwide. VAS, coordinated by Prof. Mariella Catalano of the University of Milano, is collecting and distributing biological samples among different groups distributed in 23 European countries.

In 2004, the Ministry of Health financed the organisation of a network of tumour biobanks, under the leadership of Dr. Angelo Paradiso. At the very beginning, only seven comprehensive cancer centres part of the *Istituti di Ricovero e Cura a Carattere Scientifico* (IRCCS)[11] joined together in order to harmonise the procedures for collection, characterisation and long-term preservation of cells and tissues. These

[9] Telethon Genetic Biobanks Network (http://www.biobanknetwork.org).

[10] VAS (http://www.vas-int.org/sito/home.php?arg=1).

[11] IRCCS are 42 research oriented hospitals supervised and financed by the Ministry of Health.

IRCCS belong to the already mentioned association *Alleanza Contro il Cancro*. This embryonic organisation has grown and now encompasses other institutions and University hospitals.

The Istituto Nazionale per la Ricerca sul Cancro di Genova was the first Italian institution to organise, in 1994, thanks to the foresight of its director Prof. Leonardo Santi, existing biobanking activities in a single Biological Resource Centre.[12] The Centre has extensive collections of tumour tissue, hereditary tumours, cancer of the respiratory tract, lymphoproliferative disorders, urological tumours,[13] human B lymphoblastoid cell lines and the interlab cell line collection (ICLC).[14]

The *Centro Nazionale per le Risorse Biologiche*,[15] a non-profit consortium of biotechnological Italian Institutes of excellence, has organised the first regional network by linking the disease-oriented biobanks of the Liguria region.

Some large disease-oriented collections are stored by public research institutions at BioRep, a private biorepository service provider, associate member of BBMRI.

A Biological Resource Centre for cellular therapy and biobanking has been developed, more recently, by Paolo Rebulla, at the Foundation IRCCS Ospedale Maggiore Policlinico Mangiagalli e Regina Elena.[16] Rebulla has implemented a comprehensive project to collect, store and distribute biological samples made available by donation or through diagnostic and therapeutic procedures and research programs carried out within the foundation.[17]

18.3.2 Population Biobanks

Population based biobanks were built as a tool of specific epidemiological programmes. In the early 1980s, the World Health Organization (WHO) established the MONICA (Multinational Monitoring of trends and determinants in Cardiovascular disease) in many Centres around the world to monitor trends in cardiovascular diseases, and to relate them to risk factor changes in the population over a 10-year period. In Italy, the areas involved in the project were located in the North, in Brianza and Friuli. The participating Centre, the Istituto superiore di sanità (ISS), collected more than 20,000 biological samples from the people enrolled in the

[12] Centro per le risorse biologiche dell'Istituto Nazionale per la Ricerca sul Cancro di Genova (http://www.istge.it/crb/english.htm).

[13] European Collection for Biomedical Research (ECBR) (http://ml570.istge.it/ecbr/ecbrsite.html).

[14] ICLC is a core facility of IST, directed by Barbara Parodi. It offers a service of storage, quality control and distribution worldwide of certified human and animal cell lines, mainly of tumour origin. It belongs to the European network of Biological Resource Centres (BRCs) CABRI, and it has the role of International Deposit Authority (IDA) for patent purposes (http://www.iclc.it).

[15] http://www.cnrb.it.

[16] http://www.biorep.it.

[17] Rebulla et al. (2008).

project.[18] The samples are still collected and used for further analysis under the supervision of Dr. Simona Giampaoli.[19] Later MONICA has evolved in a new project called MORGAM (Monica Risk, Genetics, Archiving and Monograph).[20] The project is a multinational collaborative study exploring the relationships between the development of cardiovascular diseases, their classic and genetic risk factors and biomarkers.

GenomEUtwin (full title: Genome-wide analyses of European twin and population cohorts to identify genes predisposing to common diseases) is an international project, whose main objective is to identify genetic polymorphisms involved in stature and in body mass index, and in complex diseases such as migraine, stroke and cardiovascular diseases.[21] The Genetic Epidemiology unit, of the National Centre for Epidemiology, Surveillance and Health promotion of the ISS, has collected, so far, biological materials (blood, buffy coat, serum plasma and DNA) from 2,500 twins.

The University of Bologna, under the project GEnetics of Healthy Ageing (GEHA),[22] has collected sample from 1,500 individuals surviving to extreme ages, in order to identify "longevity genes" in humans.[23]

To better understand the equilibrium between genetics and environment, and its consequences on cardiovascular and cancer disease, the Moli-sani project[26] has collected biological samples from 25,000 people, stored at the Università Cattolica di Campobasso. All clinical and laboratory results, obtained by the project, are being given back in the hands of participants, so they are able to discuss with their General Practitioner the best way to prevent such diseases. Donors will be contacted every 3 years to check their health, the assumption of drugs, and lifestyle changes. A thorough clinical investigation will be carried out on the ones who are going to get sick.[24]

18.4 Italian Biobanks After the Adoption of BMMRI: The Organisation of Regional Networks

The long-term objectives of BMMRI were adopted with enthusiasm by the Italian biobanks. At present, 40 biobanks, and the number is growing, are associated to the European infrastructure both as individual organisations and as thematic networks.

[18] Menotti et al. (1989).

[19] Urbinati et al. (2010).

[20] http://www.ktl.fi/morgam/.

[21] http://www.genomeeutwin.org. Quintana Trias (2003).

[22] http://www.geha.unibo.it.

[23] Capri et al. (2006).

[24] http://www.moli-sani.org.

The CNBBSV represented Italian researchers in the early stages of the preparatory phase of BBMRI. This participation strengthens the evidence in favour of the integration of existing biobanks and networks. For this purpose, the CNBBSV issued an opinion outlining the necessity of the adoption of appropriate programmatic procedures by the regional authorities.[25] Most Italian biobanks are located in institutions that not only perform research but also provide health care to patients. Since health care is paid by the regional authorities, they also take the burden of paying for the hidden costs of biobanks. The average cost of a biobank was evaluated, in a European survey, by Georges Dagher of Inserm,[26] to be 440,000 euro/year including personnel salaries.

The CNBBSVs' opinion recommended that, "... for banks established for research purposes a legislative measure is required which, as for organ transplants and blood transfusions, stipulates that biological samples, collected by the biobank should be in the public domain. This implies that local banks should be placed in a national network and a public institution, with functions similar to the UK Human Tissue Authority, must control the operation of the biobank and must assure to citizens the traceability of their samples. Such an act should include: (a) a provision stipulating that the biological samples supplied are community assets; (b) regional authorities should officially recognise biobanks and the regional networks should be linked to a national network; (c) one public institution should be responsible of the national network and should act as a guarantor for citizens with regard to traceability of their samples and the ethics of research for which their samples are going to be used; (d) the development of a standardised informed consent; (e) special provisions for historical collections, developed before the practice of informed consent was adopted".

On 25 March 2009, the Italian Government and the Regional Authorities adopted a common decision on the definition of a biobank as a "service unit, located within public or private health facilities. not directly for profit, aimed to the collection, processing, preservation, storage and distribution of human biological material for diagnostic investigation, research and therapeutic use".[27] The same co-decision has earmarked EUR 15 million for the Regional Authorities in implementing three types of collections and precisely cord blood biobanks,

[25] Donati (2010).

[26] Personal communication (http://www.bbmri.eu/index.php/workpackages/wp-7).

[27] Accordo tra il Governo, le Regioni e le Province autonome di Trento e Bolzano sulle linee progettuali per l'utilizzo da parte delle Regioni delle risorse vincolate, ai sensi dell'articolo 1, commi 34 e 34bis, della legge 23 dicembre 1996, n. 662, per la realizzazione degli obiettivi di carattere prioritario e di rilievo nazionale per l'anno 2009. Accordo ai sensi dell'articolo 1, comma 34bis, della legge 23 dicembre 1996, n. 662. http://www.statoregioni.it/testo_print.asp?idprov=6801&iddoc=21445&tipoDoc=2. Other biobank activities of mutual interest between the National Government and The Regional Authorities are described in http://www.ccm-network.it/.

devoted exclusively to transplant activities, and two types of biobanks for research, muscle-skeletal biobanks, and oncology biobanks.

The Regional Authorities have implemented the co-decision in different ways.

The Provincial Health Authorities (Azienda Provinciale per i Servizi Sanitari) of the Autonomous Province of Trento has established the Trentino Biobank, at the Operative Unit of Surgical Pathology of the S. Chiara Hospital of Trento.[28] Trentino Biobank is in charge of the collection and storage of human biological materials for scientific research purposes. Stored biomaterials include surgically removed tissue specimens and blood samples and/or other biological fluid samples, such as urine, saliva, etc. Biomaterials are either stored in special cryopreservation systems (freezers at −80 °C and liquid nitrogen tanks) or embedded in paraffin after formalin fixation. The Trentino Biobank has a state of the art procedure for researcher willing to have access to the stored samples.

In Tuscany, several institutions joined together in 2003 to form the Foundation Farmacogenomic FiorGen, a no-profit organisation of social utility.[29] One of the partners of the FiorGen Foundation is CERM of the University of Florence, which stored a large number of urine samples of healthy and celiac individuals.[30] CERM is an associate partner of BBMRI since the beginning, interested in maintaining in quality-controlled conditions a variety of samples, to be analysed with NMR spectroscopy.

CERM, therefore, was instrumental in the realisation of a centre for biological resources. FiorGen took advantage of the expertise, brought by CERM through BBMRI, and built a new facility the da Vinci European Biobank (daVEB).[31] DaVEB is now a main repository, storing 27 diverse collections for several research groups, operating in the Florence's area, and acts as a centralised IT infrastructure for other groups working at the Universities of Siena and Pisa. It is fast becoming a regional hub.

Regione Liguria,[32] adopting the guidelines of the CNBBSV, has formally recognised the biobanks, which, in its territory, collect and distribute and samples for research by (a) acknowledging that the donation of organs and tissues, both for research and for diagnostic use, have high social and economic value; (b) addressing the need to establish a network of biobanks which form part of the project BBMRI.[36] Regione Liguria has recognised the following biobanks as relevant for the regional health system:

[28] http://www.tissuebank.it.

[29] http://www.fiorgen.net.

[30] http://www.cerm.unifi.it/home.

[31] https://www.davincieuropeanbiobank.org.

[32] Deliberazione delle giunta regionale n. 34 del 22 gennaio 2010. Riconoscimento delle Biobanche per diagnosi ricerca in Regione Liguria. Bollettino Ufficiale della Regione Liguria Anno XLI, n. 7 del 17 febbraio 2010.

- Galliera Genetic Bank (GGB)[33] of the Human Genetic Laboratory at Galliera Hospital in Genoa, which started its activity in 1983. Several cases of human genetic diseases have been collected from the linked laboratory and from many other centres throughout Italy. To date, the bank stores IL-2 activated lymphocytes, EBV transformed B cell lines, parted lymphocytes, fibroblast cell cultures, amniotic fluid cell lines, trophoblast cells, chorionic villi, tissue samples, and DNAs of subjects affected by different genetic diseases.
- The IRCCS Giannina Gaslini that, as a Paediatric Biological Resources Centre, stores biological material from patients suffering from genetic illnesses.[34]
- The Cell factory and Biobank of the Istituto Nazionale per la Ricerca sul Cancro di Genova.[14]
- The Genoa Tissue Bank (GTB)[35] is the bank of Pathological Anatomy at the University of Genoa, Hospital San Martino. It is a service unit distributing cancer materials and the related non-neoplastic counterpart to public or private institutions.
- The Biologica Resources Centre of the Istituto Nazionale per la Ricerca sul Cancro di Genova.

Both the biobanks of Galliera and Gaslini Hospitals are members of the Telethon Foundation network, while the Cell factory and Biobank of the Istituto Nazionale per la Ricerca sul Cancro di Genova[14] is a member of the Alleanza Contro il Cancro network.

Another initiative on biobanks derived from the collaboration of the Ministry of Health and the Regional Authorities, through the CCM, the Italian acronym for the National Centre for Disease Prevention and Control. Its task is to liaise between the Ministry of Health and the Regional Governments in the fields of public health surveillance, prevention, and prompt response to emergencies.

In 2010, the CCM issued a call for proposals, directed to public health institutions, to build a national network of population based biobanks.[36] The winner of the call was the Istituto superiore di sanità with a project "Construction of the Italian hub of the population biobanks". The network is under construction and is composed of several biobanks already mentioned and the Institute of Medical Genetics of the European Academy of Bolzano (EURAC)[37] which, under the supervision of Dr. Pramstaller, will collect samples from 15,000 individuals living in the Venosta Valley of Bolzano Province.

[33] http://www.ggb.galliera.it.

[34] http://www.gaslini.org/.

[35] http://www.arsliguria.it/index.php?option=com_content&task=view&id=2734&Itemid=221.

[36] http://www.ccm-network.it/.

[37] http://www.eurac.edu/en/research/institutes/geneticmedicine/default.html.

18.5 Italian Biobanks After the Adoption of BMMRI: The Organisation of Prototype Networks

The BBMRI, in June 2009, made a call for planning a prototype network based on the most advanced population-based and disease-oriented biobanks.[38] After the implementation of the ERIC[2] legal entity, the prototype should be scaled up to the fully working infrastructure. Among the key features of the prototype is the requirement that it should be based on national prototype networks organised as hubs of thematic biobanks.[39] To respond to the call, the ISS and the CNBBSV jointly discussed with the biobanks and the existing networks the organisation of the Italian prototypes. The ISS and the CNBBSV were able, in October 2009, to obtain the participation of six Italian prototypes in the European one. These are:

- Italian network of Genetic isolates (INGI)
  Coordinator: Prof. Paolo Gasparini – Università di Trieste
  Aims: to reconstruct the general picture on the molecular bases of complex and quantitative traits of our country by establishing a network of studies on genetic isolates. A mixed population will be reconstructed from isolated/minorities ones.
  Number of participants: seven research groups.
- BBMRI-Multispecialty Hospital Biobank prototype (MHBp)
  Coordinator: Prof. Paolo Rebulla – Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano
  Aims: operational model of hospital networked biobanking connected with a national hub. A core cryostorage facility can be used by all hospital specialties and departments, thus, supporting at reduced costs a global program of biobanking research.
  Number of participants: four Italian research groups.
- Network of Italian Pathology Biobanks (NIPB)
  Coordinator: Prof. Giorgio Stanta – Azienda Ospedaliera Universitaria di Trieste
  Aims: to improve the availability of histological classified human tissues for translational research and validation and standardisation of diagnostic, prognostic, and therapy predictive biomarkers.
  Number of participants: nine Italian research groups.
- Italian Network of Oncological Biobanks (RIBBO)[40]
  Coordinators: Dott. Giovanni Migliaccio – ISS, Dott. Angelo Paradiso – IRCCS Ospedale Oncologico, Bari
  Aims: to contribute to the standardisation of technical procedures for handling oncological samples as well as to the harmonisation of legal and ethical issues linked to the sample collection.

[38] BBMRI News 24 July 2009 Issue 2.

[39] http://www.bbmri-prototype.eu/.

[40] The Rete Italiana delle Biobanche Oncologiche (RIBBO) is the natural evolution of the already mentioned initiative undertaken by Alleanza Contro il Cancro (http://www.iss.it/ribo/).

Number of participants: 19 Italian institutions.

- European Vascular Biobank (VAS)
  Coordinator: Prof. Mariella Catalano – University of Milano
  Aims: VAS is a European scientific no-profit association operating in the field of vascular disease and its prevention. The Biobank is centralised at the University of Milan.
  Number of participants: research groups in 23 European countries.
- Da Vinci European Biobank (daVEB)
  Coordinator Prof. Pierluigi Rossi Ferrini – University of Firenze
  Aims: to become a regional hub as a multicentre biobank with a centralised IT infrastructure and a main repository located at the Polo Scientifico (Scientific Campus) in Sesto Fiorentino.

The six networks have strong scientific links with European and international research groups and networks and are open to collaboration with new members.

The prototype will also contribute to:

- The production of templates for MTA, CDA, and common SOPs for efficient transnational exchange of samples and data that properly consider the applicable ethical and legal requirements;
- The production of common SOPs for scientific collaborations that properly consider the requirements of academia and industry;
- The application by the prototype of the OECD best practice guidelines and the WHO/IARC guidelines for biological resource centres.

In perspective, these concerted activities will allow the Italian community of "biobankers" to actively participate in the construction of the European infrastructure of biobanks and biomolecular resources, will strongly contribute to improve the quality of shared materials and data, will encourage the network to act as a partner to SMEs and Pharma companies in high quality clinical and experimental research programs, and will promote a better use of national and regional funding for biobanks.

The organisation of the Italian Network of Research Biobanks (INRB) can be seen at http://www.bbmri.de/wp3proto/.

18.6 The Building of the Italian Node of BBMRI-ERIC

The BBMRI-ERIC statutes, drafted by the members of the Working Package 1 of BBMRI, define the National Node as "an outpost of BBMRI-ERIC in a member State that interfaces with a national or regional network of biobanks and coordinates its activities with those of the pan-European infrastructure. Each National Node has a director, hereinafter referred to as 'National Coordinator'. The National Coordinator belongs to the Executive management of BBMRI-ERIC".

The creation of the Italian Node was facilitated by the initiatives of the CNBBSV, which funded at the ISS the implementation of an e-Infrastructure for collecting and organising the data on biological samples collected by biobanks.[41] The data catalogue will integrate relevant data from participating networks and biobanks according to a minimum data set developed by CNBBSV for the networks of disease biobanks, of population biobanks, and of infectious disease-oriented biobanks, the latter containing samples of infectious agents, as well as of the infected patients. In order to accelerate the translation of the collected data to the ISS central catalogue, the CNBBSV has published a call for proposals for the development of specific research networks on genetic biobanks, stem cell repositories, disease-oriented biobanks, tumour cells and tissue biobanks, and human pathogens biobanks. The winning networks will be funded by the CNBBSV with the provision that they have to organise their data and transfer them into the central catalogue according to the specifications issued by the ISS.

Prof. Ferruccio Fazio, Minister of Health, aware of all these initiatives and certain of the importance for the Italian researchers to participate in BBMRI, wrote to Prof. Enrico Garaci, President of the ISS "to undertake the necessary steps for the Constitution of the Italian National Node of BBMRI to coordinate the participation of the Biobanks so as to enable the Country to offer a significant contribution to the achievement of this important European infrastructure".

Dr. Elena Bravo was appointed as Coordinator of the National Node with the task of implementing the Minister of Health's instructions. She now faces the challenge of creating virtuous collaborations not only among scientists, but also among the Regional Authorities developing different models of regional networks.

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[41] Official Journal of the Italian Republic. Bando per la selezione di progetti finalizzati alla realizzazione di un programma pilota per la gestione in rete delle biobanche e dei Centri di Risorse Biologiche (CRB-Net). G.U. 5ª serie speciale n. 93 del 11 agosto 2008.

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Chapter 19
Governance of Biobanks for Cancer Research: Proposal for a Material Transfer Agreement

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Abstract In this article, we discuss some of the features and some of the open issues of a model for a Material Transfer Agreement (MTA) which could be used by biobanks for cancer research.

19.1 Introduction

Over the past decades, the perception of the role of scientific research in society has undergone a radical change. In the past, it was seen as a strictly public good. In the fifties, Jonas Salk did not patent his inactivated polio vaccine, which was injected into tens of millions of people around the world. This behaviour would seem very strange nowadays, as basic research is often seen as a patentable commodity.[1]

In the past, researchers have freely shared materials and information, and access to such material was considered essential to replicate published results. Together with peer review, replication was considered a pillar of scientific research assessment. What has probably changed is the fact that materials that were once considered useful only for basic research are often seen today as materials of potential commercial value. The gap between fundamental research and commercial

[1] Dove (2002).

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developments is now much narrower than before, and universities and research institutions encourage researchers to patent their findings and to rapidly transfer the results of their research to the private sector.[2]

Public funding tends to focus more and more on translational research, the pressure of rapidly translating results into products useful for the patients (from bench to bed) is growing and revenues from patents are becoming a significant item in the budget of most universities and public research centres. In this scenario, researchers often need to consult legal experts before exchanging biological samples with colleagues, as sharing of research material is now very often regulated by contracts called material transfer agreements.

19.2 Material Transfer Agreement

A Material Transfer Agreement (MTA) is a contract that governs the transfer of tangible research materials between two organisations, when the recipient intends to use it for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives. Biological materials, such as reagents, cell lines, plasmids, and vectors, are the most frequently transferred materials, but MTAs may also be used for other types of materials, such as chemical compounds and even some types of software. Three types of MTA are most common at academic institutions: transfer between academic or research institutions, from academia to industry and from industry to academia. Each calls for different terms and conditions.[3]

To encourage the process of sharing research biological materials between scientists in academic or not-for-profit research institutions, the National Institutes of Health and the Association of University Technology Managers developed, back in 1995, standard language to simplify material transfers between Universities and public research centres, issued as the Uniform Biological Material Transfer Agreement (UBMTA).[4] This model foresees no restriction other than the rule which prohibits the transfer of the material to third parties without approval or notification.

19.3 MTAs in Biobanks

In the context of biobanks, MTAs acquire additional requirements: biobanks of human tissues have evolved from small collections of pathological material—often based upon the initiative of single researchers and medical doctors and preserved

[2] Streitz and Bennett (2003).

[3] www.spo.berkeley.edu/guide/mtaquick.html. Accessed 25 June 2012.

[4] http://www.ott.nih.gov/newpages/UBMTA.pdf. Accessed 25 March 2012.

for specific projects—into structured Biological Resource Centres (BRC),[5] officially recognised institutions devoted to acquisition, quality control, processing, preservation and distribution of high-quality biomaterials for research.

When biological material of human origin is concerned, additional protection is required in MTAs so as to respect donor rights in terms of protection of personal data. Human material handling BRCs play a role of "custodians" of biological samples and related information belonging to the patients/donors. When providing their biological samples, the donors sign an agreement with the biobank (the informed consent) aimed at regulating the use of the donated material. Consequently, biobanks bear responsibility for a fair use of this material by the recipients.

In fact, fair access to the biological samples handled by biobanks is not an easy task and many actors bear rights on the material object of the transaction.

The first actor bearing rights on the material is the donor/patient. Indeed, the consent given by the patient who donates his or her biological sample to the biobank cannot be specific, as the aim of the biobank is not a single, well-defined research project, but an inevitably generic future use of well-characterised samples for biomarker discovery of specific diseases. If exhaustive information cannot be given by the biobank to the donor in terms of a detailed description of the research project that will make use of the donated material and information, the biobank should find other ways of making the donors aware of the use of the samples. For example, by publishing the ethical code of conduct and describing the ongoing projects on the biobank's website or by publishing brochures and newsletters to be distributed to the patients. The "donation" relies on trust: the patient is confident that the biobank will operate under an ethical code of conduct and will protect the donor's rights and will. The biobank is thus charged with the responsibility of assuring that this trust is well placed and that the will of the donor will be respected by all actors of the transfer of the material. By signing the biobank MTA, the recipient accepts to share this responsibility towards the donor. The donor should be protected as to privacy and confidentiality, and ethical use of samples and data should be assured through assessment of the projects by both a scientific committee and an independent ethical committee. The restrictions to use, as defined in the informed consent, should be strictly respected, and correct information on the use of samples should be given back to the biobank that will inform the donor of the results that could impact on his/her health. In this context, the biobank should be able to exercise the right of restricting the use of the material, by defining the range of specific experiments that can be performed, by restricting the rights of further distributing the material or its derivatives and by requiring feedback on the results of the research.

The second actor bearing rights on the material is the biobank itself. Policies of access and sharing of human bioresources and data have been developed over the years and biobanks are important in granting such access.[6] However, access can be

[5] OECD (2007).

[6] Kaye et al. (2009).

granted by biobanks if proper recognition of scientific contribution and long-term sustainability is assured, supported by the capacity for measuring their own resource use and impact. The lack of mechanisms to measure the impact of biobanks and the absence of recognition of the effort behind establishing and maintaining such resources is a major obstacle for sharing bioresources and data. In the context of EU projects, a Bioresource Research Impact Factor (BRIF) working group has been set up. The main objective of BRIF is to promote the sharing of bioresources by creating a link between their curators and the impact of the scientific research using them. A BRIF would make it possible to trace the quantitative use of a bioresource, the kind of research using it and the efforts of the people and institutions that construct it and make it available.[7]

The third actor bearing rights on the material is the researcher, i.e. the "recipient" of the biological samples. The researcher owns the results of the research, but the MTA usually restricts his/her rights over the material. For example, the user is often not allowed to transfer samples or information to third parties and he must commit himself to share with the biobank the results obtained through the use of the material and to acknowledge the origin of the material in all oral or written public disclosures of the research.

As to the profile of the recipient, usually biobanks do not foresee the direct transfer of the material to commercial companies, either because the donor did not allow such transfer or because the ethical committee does not agree that the biobank accepts a pharmaceutical or biotech company as customer. However, as recently published in an editorial in Nature, "Biobanks need pharma".[8] Europe leads the world in biobanking and the European Commission has recently funded the preparatory phase of the European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI).[9] The general public is sensitive to issues involving human biological material. Together with privacy and consent, a key issue is whether the pharmaceutical industry should get easy access to biobanks. In fact, the positive profile of the medical research community could be severely compromised if donors would perceive that the primary use of the tissue is to generate profit rather than to support research that will lead to improvements in the diagnosis and treatment of diseases. On the other hand, if biobank resources are fundamental to understanding the molecular basis of complex diseases, it is the pharmaceutical industries that will eventually develop the treatment to such diseases. To try to solve this problem, the BBMRI consortium has proposed the concept of "expert centres", research institutes of excellence linked to the BRCs, that would do all the molecular analyses on material requested for an approved study and provide data only to the industrial client. Donors' material would not move out of the biobanks, data would be stored for re-use in other studies and industry could not gain exclusive rights.

[7] Cambon-Thomsen et al. (2011).

[8] Editorials Nature (2009).

[9] See www.bbmri.eu. Accessed 25 March 2012.

19.4 Structure of a Biobank MTA

A number of international guidelines, projects, and organisations have developed standards for MTAs in the field of biobanks and Biological Resource Centres:

- The OECD Best practice guidelines for BRCs state that an MTA should be drawn up between BRC and the user so the user can be informed of his/her rights and duties relating to the biological material requested in relation to intellectual property rights,[10] consent, publication, result-reporting requirements, and quoting BRC accession number in publication;
- The P^3G (Public Population Project in Genomics) Ethics and Policymaking Core has drafted a document identifying core elements from the Sample and Data Access Policies of P^3G-member biobanks, "Samples and Data Access Agreements: Core Elements and Generic Clauses"[11]: important characteristics of an access agreement are brevity, clarity and simplicity, uniformity to ensure equality among investigators and less negotiation time;
- The European Culture Collections' Organization has defined and described the commonly agreed core content of an MTA to be used for the supply of samples from the biological material that ECCO holds in its public collections.[12]

The IST Biological Resource Centre (CRB-IST),[13] an Italian biobank for cancer research, has produced an MTA based upon its Policy on human biological material transfer. A Material request form, describing the project in detail, must be attached to the agreement, of which it represents an integral part. The following paragraphs are included and here described in brief:

1. Institutions covered
2. Administrative and medical responsibility
3. Appropriate permissions: approval of the research by an Ethical Committee
4. Information on the type and amount of material
5. Information on the use of the material: only for the purposes specified in the agreement
6. Custodianship, property, intellectual property: transfer of custodianship, not transfer of property nor intellectual property rights on the material and its derivatives
7. Responsibility: the samples are either coded or anonymised. Under no conditions will the material be used in human subjects
8. Safety: all material should be handled as potentially infectious

[10] OECD (2007).

[11] See www.p3gobservatory.org/repository/ethics.htm. Accessed 25 March 2012.

[12] www.eccosite.org. Accessed 25 March 2012.

[13] www.istge.it/crb/english.htm. Accessed 25 March 2012.

9. Use by Third Parties: the recipient shall not transfer human biological material (or any portion thereof) to third parties without the prior written consent of the biobank
10. Commercial human biological material utilisation: the recipient shall not sell any portion of the human biological material provided or products directly extracted from these tissues (e.g. protein, mRNA or DNA). Exemption may be agreed upon in cases where the material will be part of products intended for human diagnostic and/or treatment purposes. If the recipient desires to use or licence the material or modifications of the material for commercial purposes, the recipient agrees, in advance of such use, to negotiate in good faith with the biobank to establish the terms of a commercial licence
11. Research results, publications, acknowledgement of contribution: the recipient will share the results of the research by promptly sending a copy of any publication. In all oral or written public disclosures of the research the origin of the material will be acknowledged as follows: "We thank the biobank . . . for providing the samples"
12. Recovery of costs: the biobank does not sell human biological material, but may charge the recipient a fee to recover the costs of providing the service

This MTA could serve as the starting point of a common Uniform MTA for Italian biobanks, to be further discussed and amended in the working group of the Italian node of BBMRI and then offered as a core model to the biobanks of the Italian Regional and Thematic Networks of Research Biobanks participating in the European biobank infrastructure.

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Index

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