Xenotransplantation

Ethical, Regulatory, and Social Aspects

Daniel J. Hurst
Luz Padilla
Wayne D. Paris
Editors

Springer

Xenotransplantation

Daniel J. Hurst • Luz Padilla
Wayne D. Paris
Editors

Xenotransplantation

Ethical, Regulatory, and Social Aspects

Springer

Editors
Daniel J. Hurst
Department of Family Medicine
Rowan-Virtua School of Osteopathic Medicine
Stratford, NJ, USA

Wayne D. Paris
Department of Social Work (Emeritus)
Abilene Christian University
Abilene, TX, USA

Luz Padilla
Department of Epidemiology
University of Alabama at Birmingham
Birmingham, AL, USA

ISBN 978-3-031-29070-1 ISBN 978-3-031-29071-8 (eBook)
https://doi.org/10.1007/978-3-031-29071-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Working with exceptional colleagues (Luz, Wayne, David, and innumerable others) on xenotransplantation has been a tremendous pleasure–one that I will not soon forget. As Antonio expressed in Shakespeare's Twelfth Night:
"I can no other answer make but thanks, and thanks; and ever thanks."

Daniel J. Hurst (Cherry Hill, New Jersey, USA)

Collaborating with Daniel, Wayne, and other authors has been an honor, but most of all, it is a great privilege to call most of our collaborators friends. To families and individuals who are racing against time in need of an organ, and lastly, to my husband and children.

Luz Padilla (Birmingham, Alabama, USA)

Given this book is the final work of my professional career, I would like to express my appreciation to the innumerable colleagues, students, and patients who have shared my odyssey. Special appreciation is reserved for David KC Cooper for his guidance, support, and patience over the

past 30+ years. I can only hope my work reflects his dedication to teaching, research, and advancement of clinical knowledge. And finally, to Luz and Daniel, without whom none of the XTx work would have been accomplished. Both of you have been exemplary colleagues, the best I have ever had the opportunity to collaborate with. Every day of our partnership has been a gratifying experience.

Wayne D. Paris (Abilene, Texas, USA)

Foreword

It is a great privilege for me to have the opportunity to contribute a Foreword to this important book.

Xenotransplantation (or cross-species transplantation)—specifically the transplantation of genetically-engineered pig organs, tissues, or cells into human recipients—has been a major research interest of mine for almost 40 years [1]. The gene-edited pig heart transplant carried out by my colleagues at the University of Maryland on January 7, 2022 (and approved by the US Food and Drug Administration on compassionate grounds) suggests that we are at last becoming close to formal clinical trials of xenotransplantation, after which I hope pig organ transplantation will be established as a routine option for patients with end-stage organ failure.

You might ask, 'Why is the pig the chosen animal source of organs for transplantation into humans?' If we can successfully overcome the immunological barriers, the pig offers many advantages (Table 1). Furthermore, xenotransplantation has many advantages over the transplantation of organs from deceased humans (Table 2)

Progress has been slow because the problems we faced were complex and difficult to overcome [2]. You may argue that, after more than 35 years—half a lifetime—of research, we should have made more rapid progress. But the late Claus Hammer, who was both a surgeon and a veterinary surgeon, pointed out that humans and pigs have been evolving apart for 80 million years, and so what we have been trying to do is to "outwit evolution." It is therefore perhaps not surprising that it has proven so difficult. Whenever one hurdle was successfully surmounted, another appeared. We likened it to peeling an onion—when one layer had been successfully peeled, yet another layer presented itself (and, as with peeling onions, the process was sometimes accompanied by tears).

The problems we faced differed in nature and magnitude from those surmounted by the pioneers in the transplantation of human organs (allotransplantation) 70 years ago. The barriers to xenotransplantation were predominantly related to the vigorous and immediate innate immune response that resulted in graft destruction within minutes. They involved the detrimental effects of human antibody binding to the pig organ (leading to complement activation), molecular incompatibilities between the pig and primate coagulation-anticoagulation systems, and the development of a systemic inflammatory response to the graft. Luckily, the fortuitous introduction of methods of gene-editing in pigs enabled most of these barriers to be overcome. As a result, and of great importance, xenotransplantation offers us, for the first time in

Table 1 The advantages and disadvantages of the pig as a potential source of organs and cells for humans

Availability	Unlimited, and whenever required
Breeding potential	Good
Period to reproductive maturity	4–8 months
Length of pregnancy	114 ± 2 days
Number of offspring	5–12
Growth	Rapid (adult human size within 6 months)[a]
Size of organs for all ages of humans	Adequate
Anatomical similarity to humans	Close
Physiological similarity to humans	Close
Relationship of immune system to humans	Distant
Knowledge of tissue typing	Considerable (in selected herds)
Necessity for blood type compatibility with humans	ABO-blood type compatibility can be assured
Experience with genetic engineering	Considerable
Risk of transfer of infection (xenozoonosis)	Low
Availability of designated pathogen-free pigs	Yes
Cost of maintenance	Under the biosecure designated pathogen-free conditions required by the national regulatory authorities, e.g., the US Food and Drug Administration, the costs will be significant
Public opinion	Supportive

[a] Breeds of various miniature pigs reach a maximum weight of approximately 10–50% of the weight of domestic pigs

Table 2 Potential advantages of pig organ xenotransplantation over human allotransplantation (if the immunological challenges can be successfully overcome)

1. Unlimited supply of 'donor' organs.
2. Organs available electively, i.e., whenever required. (Patients with end-stage organ failure will be able to receive a transplant immediately, without any need for such supportive therapies as dialysis, mechanical circulatory support, or intensive care.)
3. Avoids the detrimental effects of brain death on the donor organs (which can cause structural injury to an organ and/or early metabolic dysfunction after transplantation).
4. The 'donors' will be free of all potentially infectious microorganisms (and of endogenous retroviruses, if necessary).
5. 'Borderline' transplant candidates, i.e., those with health problems that may be detrimental to prolonged patient survival after organ transplantation, e.g., poorly-controlled diabetes, severe peripheral or cerebral vascular disease, will be more acceptable (as they will no longer be competing for scarce organs with other potential transplant candidates).
6. Avoids the cultural barriers to deceased human organ donation that is present in several countries, e.g., Japan.

the 70 years history of organ transplantation, the possibility of *modifying the donor*, rather than just treating the recipient. This new concept holds immense potential and promise for the future.

After the initial innate immune response. there then followed the adaptive immune response—T and B cell responses to the graft—similar to that seen after uncomplicated human organ transplantation. The conventional immunosuppressive therapy that is largely successful in allotransplantation was found to be inadequate in xenotransplantation. However, again fortuitously, the introduction of novel immunosuppressive agents that block the CD40/CD154 T cell co-stimulation pathway successfully suppressed the all-important T cell response to a pig xenograft.

While these immunological problems were being investigated, attention was also being paid to the risk of transferring a pathogenic microorganism with the graft from the pig to the human recipient and, of more concern, the possibility of its transfer from the patient to the community at large. In other words, is xenotransplantation going to prove safe, not only for the recipient of the graft, but also for those with whom he or she comes into close contact? This question will not be finally answered until clinical trials are undertaken, though expert opinion is that, if the organ-source pigs are bred and housed in a clean, biosecure environment, and monitoring for infectious microorganisms in both the pig and patient is intensive, the risks are probably small.

The above considerations, particularly the matter of the safety of xenotransplantation, raised numerous ethical, social, and regulatory questions, and it is in this present book that these topics are discussed in some detail. One could argue that there is some risk in nearly every major innovation in medicine, but xenotransplantation (inasmuch as it potentially impacts the community and not just the patient) is perhaps associated with rather more than in most advances. It is partly for this reason that the publication of this book is so timely and valuable.

When contemplating what I should write in this Foreword, I re-read a paper I had written in 1996 entitled ‘Ethical aspects of xenotransplantation of current importance’ [3] The topics I addressed in it were numerous and included the potential risks of xenotransplantation, the ethics of the use of animals, public attitudes to xenotransplantation, ‘profit’ motives (both financial and academic), conflicts of interest, informed consent, who should monitor the clinical trials, and the ethics of health care financing, among other considerations. I found it of considerable interest to realize how the aspects I covered then remain discussed and to some extent unresolved today, more than 25 years later. The contributors to this book expand on many of these topics and provide us with current thinking in this regard. For example, they draw attention to the requirement that the patient will be required to commit to life-long monitoring and follow-up even if the pig graft is removed, which is different from almost all previous clinical trials.

The transplantation of pig organs into patients, like the transplantation of human organs before it, will impact society in numerous ways, and so the attitudes of members of the community towards it, particularly of those with strongly-held religious beliefs, is of great importance. My impression is that the Maryland pig heart transplant in a patient was generally well-received by the public and media, suggesting

that there will be support for this new form of therapy once it is introduced into routine clinical practice. The editors of this book have been very active in assessing public and professional (doctors and nurses) attitudes to xenotransplantation and, in this volume, provide us with the benefit of their investigations and experience.

Particularly in view of the potential for the transfer of an infectious microorganism from the organ-source pig to the patient and community, the judicious regulation of xenotransplantation by national authorities is a matter of great importance. Nevertheless, the authorities have to tread a narrow line. Although they must ensure the safety of the procedure, they must not delay its introduction unnecessarily as so many very sick patients are likely to benefit from it. The regulatory aspects of clinical xenotransplantation are complex and differ slightly between the countries that have given consideration to the topic. Fortunately, the editors have called on experts to provide us with overviews of how national or international authorities are proposing to regulate this new form of therapy.

Of one point there can be no doubt, and that is that we are far advanced today in our knowledge and experience of xenotransplantation than were the pioneers of allotransplantation. When I had the privilege to meet with one of the very early pioneers of kidney transplantation, French surgeon René Küss, then in his nineties, he described to me the primitive conditions when he performed his first human kidney transplants in 1951. He and a colleague from another Parisian hospital would go to the local prison where a criminal was due to be guillotined and would wait outside the execution room. The headless body would be brought out and placed on the floor. On their knees, the surgeons would open the abdomen and remove the kidneys, the surgical field illuminated by the light from a single lamp bulb. Without the use of any form of cold storage of the organ, they would each transport one kidney to their respective hospitals and transplant it into the waiting patients. There was no form of immunosuppressive therapy whatsoever. It is no wonder that the results of these pioneering efforts were so poor.

Compare these efforts with what we have already learned about xenotransplantation in the experimental laboratory today and from 70 years of experience with clinical organ allotransplantation. Our understanding of the fundamental immunobiological problems of xenotransplantation, and how they can be overcome, is vastly superior to that of allotransplantation by surgeons in the 1950s. With the knowledge and technology available to us today, our first clinical attempts of pig organ transplantation should be far more successful than the first allotransplants.

I firmly believe we are at a stage when it is ethically justified to initiate small, well-controlled clinical trials of gene-edited pig kidney or heart transplantation under the cautious oversight of the national regulatory authorities. We shall learn much more from this initial clinical experience than we shall by continuing solely in the laboratory, although continuing preclinical studies will provide further experience from which we can undoubtedly benefit. I will always remember the words of one of my early mentors in cardiac transplantation, Christiaan Barnard, the South African surgeon who carried out the world's first human heart transplant: "You cannot stay in the laboratory forever," he told me. If future patients are to benefit as soon as possible, we need to consider this advice today.

This book provides us with much information and expert opinion that will help us take that momentous step of moving from the laboratory to the clinic, I am sure you, the reader. will acquire much food for thought from the pages of this book.

References

1. Cooper DKC. The long and winding road to clinical xenotransplantation: a personal journey. Eur Surg Res. 2022; doi:10.1159/000525757. Online ahead of print.
2. Cooper DKC. (editor) Recollections of pioneers in xenotransplantation research. Nova Science Publishers, New York, 2018.
3. Cooper DKC. Ethical aspects of xenotransplantation of current importance. Xenotransplantation. 1996;3:264–74.

David K. C. Cooper
Center for Transplantation Sciences, Department of Surgery,
Massachusetts General Hospital/Harvard Medical School,
Boston, MA, USA

Preface

In mid-2018, Dr. Wayne Paris stepped off the airplane as he arrived at Birmingham's Shuttlesworth Airport in Alabama. The city of Birmingham is not all that different from Paris' hometown and institution in Abilene, Texas, and he was excited to spend a year-long sabbatical at The University of Alabama at Birmingham (UAB) developing and advancing a familiar field of interest to him—pig-to-human organ transplantation or Xenotransplantation.

While many multidisciplinary collaborations in academia surge for various reasons, the particular relationship between the three editors of this book—who hold different training and were on various career trajectories—surged from a shared passion, intrigue, stubbornness, privilege, and joy of pursuing their professional interests. How their paths crossed and coincided into the field of xenotransplantation begins in 1979 when Paris graduated with his master's degree in Social Work from the University of Oklahoma. Prior to moving into academia in 2004, Paris worked as a Clinical Transplant Social Worker (LCSW) for 25 years in medicine and organ transplantation at the Nazih Zuhdi Transplantation Institute at Integris Baptist Medical Center in Oklahoma City, Oklahoma. His clinical experience was primarily in heart, lung, and liver transplantation. In addition to his clinical work, Paris had an extensive clinical outcome research and publication practice, and presented at numerous national and international medical and social work conferences. He was active in several social work and medical societies and regularly served on national and international social work and medical meeting abstract and grant review committees during that time.

In 2004, Paris accepted an Assistant Professor position at the School of Social Work at Southern Illinois University Carbondale (SIUC). He taught across the curriculum in the undergraduate program from 2004 to 2010. While at SIUC, Paris completed his PhD in Social Work from the University of Huddersfield, Yorkshire, United Kingdom in 2006, a doctoral program that specialized in clinical outcomes research.

In 2010, Paris was recruited to serve as Graduate Program Director of the Masters of Science in Social Work at the School of Social Work at Abilene Christian University (Abilene, Texas). He served in that capacity for 5 years and directed one of the few accredited social work programs in the United States that requires a graduate thesis. After stepping down as Graduate Program Director in 2015, he reconnected with his mentor David K.C. Cooper, MD, PhD, FRCS. Dr. Cooper at

that time was Co-Director of the Xenotransplant Program in the Department of Surgery at UAB and an internationally recognized leader in xenotransplant research who was making scientific progress in preparation for pig-to-human kidney clinical trials. Some final preparations for those trials recommended that, in addition to biological advancements, the development and conducting of psychosocial research about the public's willingness to consider the procedure. This would be in line with recommendations from the World Health Organization, International Xenotransplantation Association, and United States Food and Drug Administration to secure local, "relevant opinions."

Dr. Luz Padilla obtained her medical degree from the University of Guadalajara in Mexico. Her interest in disease prevention through evidence-based research led her to pursue a Master's of Science in Public Health in Epidemiology in 2014 at UAB. She became faculty at UAB in 2016 and was appointed Director of Surgical Research of the Pediatric and Congenital Heart Center at UAB and Children's of Alabama.

Dr. Daniel Hurst was, at the time, Clinical Assistant Professor at UAB teaching undergraduate bioethics, working in clinical ethics, and leading the research for the Cahaba-UAB Family Medicine Residency Program. Hurst's training is multidisciplinary, holding two graduate degrees in theology, a MSc in Global Health and Infectious Diseases from The University of Edinburgh, and PhD in healthcare ethics from Duquesne University.

In early January 2019, Hurst, Padilla, and Paris gathered in Padilla's office at UAB. Hurst and Paris had met just a few days earlier over coffee at the hospital's Starbucks, introduced by a mutual friend who knew they had similar interests in bioethics. Gathered in Padilla's office that day, what began to coalesce was the beginning of a multidisciplinary (medical, social, and ethical) group devoted to studying the ethical and social implications of xenotransplantation. Since then, the three editors have had multiple publications, research studies, and now this book in hopes to make a contribution and be better prepared as xenotransplantation makes its way to clinical trials. The editors feel fortunate to have important figures in xenotransplantation agree to collaborate and contribute their expertise in this book, and we hope the book, at least in some small way, can advance the field.

Stratford, NJ, USA — Daniel J. Hurst
Birmingham, AL, USA — Luz Padilla
Abilene, TX, USA — Wayne D. Paris

Contents

Introduction

1

Daniel J. Hurst, Luz Padilla, and Wayne D. Paris

Overview

There is an acute need to address the organ shortage today. Stated bluntly, the demand for human organ transplantation greatly exceeds the available supply from both living and deceased donors. Policy solutions, such as presumed consent, have been attempted in different jurisdictions globally with varying results. Iran has turned to a paid kidney donation model. However, much of the world is hesitant to take such steps and the impact of how these steps affect supply are inconclusive. Alternative sources of organs are needed, and xenotransplantation—the cross-species transplantation of organs—is one potential solution.

This book comes at an opportune time when recent studies on xenotransplantation have been performed in the United States in 2021 and 2022. More studies and even formal clinical trials are set to begin. Because of this, the need for clarity regarding ethical, regulatory, and social issues is imperative.

This book seeks to fill a gap in the literature on ethical, regulatory, and social implications of xenotransplantation. Leading thinkers on these issues globally have been sought and contributed to this work with the hope of providing some clarity to

D. J. Hurst (✉)
Department of Family Medicine, Rowan-Virtua School of Osteopathic Medicine, Stratford, NJ, USA
e-mail: hurst@rowan.edu

L. Padilla
Departments of Epidemiology and Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: lpadilla@uabmc.edu

W. D. Paris
School of Social Work, Abilene Christian University, Abilene, TX, USA
e-mail: wayne.paris@acu.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_1

pressing questions and further the conversation. To this end, the book proceeds in four parts, each of which is briefly described here.

In Part I: Ethical Aspects, many of the ethical aspects of xenotransplantation are covered. The ethical aspects of xenotransplantation have been enumerated by many authors for at least the past three decades. As we move closer to clinical trials, addressing these issues have become more pressing. Trevor Stammers begins the section with a chapter on allotransplantation ethics. In order to understand some of the issues present in xenotransplantation it is important to have a grounding in the larger field of transplant ethics, which Stammers provides. Mariachiara Tallachini discusses the role of public involvement in xenotransplantation and *why* the public's involvement is important. Following this, Potter and White provide a clinical ethics chapter, which is the only publication to date that takes this focus in regard to xenotransplantation. Pediatric ethics issues are then discussed by Padilla, Maxwell, and Hurst. In Chap. 6, Hurst discusses some philosophical intricacies of xenotransplantation and participant informed consent. Martine Rothblatt, chairperson and CEO of United Therapeutics, writes of geoethical concerns in Chap. 7. Lastly, the section concludes with a chapter on animal ethics by Tanja Opriessnig and Patrick Halbur.

Part II on regulatory aspects covers laws and regulations that will have to take place before xenotransplantation occurs in various parts of the world. Although many countries are involved and/or are interested in advancing or adopting xenotransplantation, it finds itself in different stages across the world. The requirements and expectations for its outcomes and use hold different implications based on varying country laws and the need to be socially and culturally sensitive to the population of each country. Part II describes the regulations, laws and the history of the considerations that have taken place in the United States, Europe, Japan and China.

Part III: Religious Aspects examines xenotransplantation through the lens of various religious traditions. Hurst and colleagues begin the section with a chapter on Protestant and Catholic viewpoints, presenting a summary of the empirical and theological writings from Protestantism and Catholicism toward xenotransplantation. Sunni and Shia Islam have distinct chapters in order to parse differences in how the two branches of Islam think through xenotransplantation. Bedzow provides insight on how Judaism may approach xenotransplantation. The section closes with a chapter on Hinduism.

As the experimental work in xenotransplantation moves closer to clinical trials and perhaps to clinical application as a therapeutic option, the question of the social factors associated with it have become more pertinent and in need of closer examination. This is the purpose of Part IV: Social Aspects. In allotransplantation the most important social question has always been how to deal with the inadequate number of donors compared to those in need of a donor organ. The psychosocial assessment of the potential transplant candidate has figured prominently. Patient follow-up was important, but not as critical as making sure the patient accepted for transplantation was the best candidate that would maximize the use of a scarce societal resource. This does not suggest that candidate assessment will be any less important with xenotransplantation, but rather that it is only one part of a much

more complex process. A process will entail who receives a xenograft, the number of times the patient may be transplanted, how the choice of human versus pig source influences the selection process, and the individual patient, family and social milieu reaction to a non-human donor.

In an attempt to explore the numerous avenues associated with this complex process, we have attempted to present the latest knowledge and understanding about what may be involved from a broad definition of what *social* really means. The works included do not focus solely on psychosocial factors as classically defined, but rather encompasses a broader, more inclusive consideration of the term. The book raises social concerns not only related to the individual but also societal concerns such as forced isolation and the possibility of zoonosis.

Our hope is that this edited volume provides a comprehensive viewpoint on the ethical, regulatory, and social implications of xenotransplantation. Some of the issues discussed in this context are perennial issues that have been discussed over the past several decades, while other content we believe is completely novel to this volume. Many of the chapters are written by recognized researchers and practitioners in their fields who are privy to the most up-to-date information. Since this is a rapidly moving field, we are also cognizant that what may be the most up-to-date information at time of press may quickly be surpassed. This is likely to be true of the regulatory environments in which xenotransplantation will be tested in trials and become a clinical option, whereas we believe the remainder of the content will remain relevant for much longer.

Part I

Ethical Aspects

Allotransplantation Ethics

2

Trevor Stammers

Introduction

The pioneering and subsequent development of organ transplantation was one of the greatest advances in medicine of the late twentieth century. A glance at the World Health Organization's Global Observatory on Donation and Transplant's homepage readily demonstrates the worldwide reach of transplantation medicine. Their statistics for 2019 showed that globally, 153,863 organs were transplanted that year, marking a 4.8% increase compared with the previous year [1]. There was an average of 17.5 organs an hour transplanted in 2019.

The story of organ donation is however far more than just statistics. It results in people's lives being saved and transformed. Such uplifting and inspiring human elements of transplantation are clearly evident in the moving 2007 memoir, *The Power of Two* [2]. This and the subsequent film based on it, tell the remarkable story of Japanese twin-sisters, Anabel Stenzel and Isabel Stenzel Byrnes, born with cystic fibrosis. Their "survival through miraculous double lung transplants, and improbable emergence as authors, athletes and global advocates for organ donation" [3] is a radiant testament to the life-transforming benefits of organ transplantation. There is however a correspondingly sobering side to this personal human story in terms of the potential and actual costs to those donating organs in the case of living donation, and to donors' relatives in deceased donation. Maylis de Kerangal's novel *Mend The Living* [4], graphically illustrates the bewilderment and emotional trauma of parents approached about giving consent for organ donation from their son, who has been determined to be brain dead following a road crash. There is pain too when transplants fail or recipients die from complications of the surgery and aftercare. Furthermore, the transplant recipient remains under medical follow up indefinitely and so in one sense, still remains a patient even following successful surgery.

T. Stammers (✉)
Scottish Council on Human Bioethics, Edinburgh, Scotland, UK
e-mail: tgstammers@doctors.org.uk

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_2

The statistics at the start of this chapter also tell a troubling story when placed in their wider context. Despite so many thousands of transplants carried out, they only meet a fraction of the need, even in countries with advanced healthcare systems let alone those with no coordinated system of organ allocation. The threat of death from organ failure also drives a heinous trade in trafficked organs which generally exploits and harms the 'donor' and undermines trust in transplantation medicine generally. It is estimated that 1 in 10 kidney transplants worldwide is of a trafficked organ [5].

The latest global statistics are even more disturbing. They show 129,681 transplants (15 per hour) were carried out, representing a 17.6% decrease in numbers of organs transplanted in 2020 compared with 2019 [6]. This is because of the global effects of the COVID-19 pandemic crippling health care systems, making hospital admission unsafe for healthy live donors, and making deceased donation more difficult because of the pressures on operating theatres and critical care units. The numbers on the waiting list for transplants also fell in many countries though, because many on the list also died during the pandemic. In the United Kingdom (UK) for example the waiting list decreased from 6138 to 4256 yet there were fewer transplants for 2020–2021 than the previous year. Though overall global transplant activity fell by around a third, there were considerable global disparities in how badly individual nations were affected. A paper comparing 22 different countries showed for example, that while transplant activity in Argentina during the pandemic fell by almost 61%, in Austria the decrease was only just over 10% [7].

All of this illustrates why there is a continuing pressure to increase the availability of organs for allotransplantation and to invest in finding possible alternatives such as bioprinting of organs or xenotransplantation. This chapter however will give a broad overview of some the ways in which allotransplantation is either being currently expanded or may be in the near future.

Living Donations

Donations of non-vital organs from voluntary donors are essential to any transplant program. Living donations have significant advantages for recipients as, unlike deceased donation, there is no risk of deterioration of the organ if there are delays between the death of the donor and implantation into the recipient. In developed healthcare systems there is little risk to the donor either. The risk of death with 3 months after kidney donation (which is by the far the commonest solid organ transplanted) is less than 1 in 3,000 for example [8]. There is of course a slightly greater risk of end-stage renal diseases eventually developing in the donor as a result of having only one kidney but this remains low at 1 in 100 over a lifetime [9]. With liver lobe donations, the operative risk of death at 1 in 588 operations is higher than that for kidneys, but there are fewer long-term adverse consequences [10]. However, taking into account the total number of years lost as a result of each donation, live kidney donation accounts for more than liver donation [11].

In the early days of kidney transplantation, hopes ran high that improvements in organ preservation, immunosuppression and tissue typing would eventually make the results from transplants of deceased organs as good as those from living donors [12]. However living donation overall still leads to better outcomes than deceased donation and therefore remains an essential element of transplant services worldwide with increasing effort being put into increasing the numbers of such donations. In the United States (US) in 2019, living donors comprised 37.7% of all kidney donors [13], and a new record of the total number of living donors was also set at 3797 [14]. In the UK, up to 2019–2020, living donors accounted for 40% of all donors before the COVID-19 pandemic hit [15]. Global figures for living kidney donors in 2019 are comparable at 37.3% of all kidney donors [16].

The COVID-19 pandemic hit transplantation rates badly. A large part of the problem was that living donation became very unsafe for potential donors because of the high risk of acquiring the virus in hospital. In the UK, living donations in 2020–2021 fell to just 444 from 1058 the previous year. Living donations in the US fell by 27% as of August 11th 2020, compared to the same point in 2019 [17]. Ninety percent of all US transplant programs reported at least a halving of the number of living donor evaluations during the pandemic [18]. Since 2021 developed health care systems have restored their transplantation rates back to pre-pandemic levels and various schemes to increase the number of living donors that have been re-implemented.

Methods of Increasing Living Donation

In 1954 the first successful kidney transplant was carried out in the US between male twins who were immunologically compatible [19]. For many years thereafter the only transplants carried out were from living donors who were close relatives of the recipient. As understanding of the mechanisms of immune rejection of transplanted organs increased, immunosuppression became increasingly safe and effective thus enabling expansion of both living and deceased donations. There have been three principal ways in which increasing the number of living donations has been achieved—relaxation of the safety criteria to enable more living donors, the introduction of donor incentives, and broadening the range of potential recipients from living donors.

Relaxation of Criteria to Become a Living Donor

With the increasing importance from the 1980s onwards of respecting patient autonomy within medical practice [20], the priority of wherever possible, respecting the request to be a living donor has received increasing attention. During the 2000s previous restrictions arising from such factors as age, weight, adverse family history, smoking, obesity, diabetes, hypertension and heart disease have been relaxed to permit more donors without compromising safety [21]. With regard to age for

example, the UK has no upper age limit for living donations and Canada's oldest living donor to date was 92 years old at the time of donation [22]. Most US programs have no upper age limit for eligibility though there are still strict criteria on donations from young children. Attitudes have changed to allow patients to donate who for example had progressive debilitating diseases such as multiple sclerosis or chronic respiratory problems or even specific types of cancer such as some brain tumours, which were not considered to be transmissible to organ recipients [23].

Incentivizing Donors

Though the risk to living donors is small, the inconvenience and costs involved, especially in travel and time off work, may be considerable. It is not surprising therefore that many countries offer some form of reimbursement of costs to living donors. Even in 2009, a survey of 40 countries showed that reimbursement of living donors occurred in 21 countries and was legally specified in 16 of them [24]. The UK [25, 26], New Zealand [27] and Canada [28] for example all offer some reimbursement of costs to living donors. A recent study of reimbursement of expenses for living donors covering 109 countries showed an overall positive effect and concluded such programmes "may be an effective approach to alleviate the kidney shortage worldwide" [29]. Although introducing such initiatives was more effective in relatively less developed economies and countrywide introduction was recommended as in the US, no significant improvement on donor rates had been found at individual state level [30].

A few countries, notably Iran [31], and Saudi Arabia [32] have offered financial incentives to become living donors rather than just paying compensation for expenses and lost income. However, there is considerable doubt about the effects of introducing financial incentives rather than reimbursed expenses in countries with different political systems from these countries [33]. Other countries such as Israel [34] and Singapore [35] have introduced medical incentives such as awarding points to prioritize living donors for a transplant should they require one themselves. The introduction of incentivized systems however risks decreasing the number of altruistic unpaid donors on whom the system depends. Once the public perceives their altruism is no longer valued by a state, the number of living donations may decrease.

Broadening the Range of Potential Donors

With the exponential rise of digital communications and use of social media, it is now very easy to broaden outreach by and to potential recipients in ways not previously possible. Use of the internet to find a donor is legal in many countries and has been widely taken up in the US, despite concerns of a "transplant beauty contest" where the eventual recipient is not the one most in need but the one with the best online publicity profile [36]. In 2004, MatchingDonors.com was one of the first websites launched to match donor and recipients and it generally has over 15,000 potential donors registered on it at any one time [37].

The Human Tissue Authority, the UK's regulating agency for transplantation, issues guidance for people interested in becoming live donors [38], which includes the fact that is it illegal to seek financial reward for donating an organ and that potential donors should not use sites which charge a fee for potential recipients to register. Both Facebook [39] and Twitter [40] are also increasingly used to locate living donors.

Though there are obviously complex ethical issues linked with the use of social media, they are here to stay and rather than seeking to dissociate from them, transplant authorities should seek to cooperate with them and indeed utilize them, too, to the benefit of donors and recipients alike [41].

Deceased Donations

Though living donations form a large minority of total donations, the global transplantation system relies on deceased donations which form the majority source of organs overall. Deceased donations have a number of advantages over living donations. Vital organs, most commonly the heart, cannot come from living donors,[1] and whereas usually only one organ is removed from a living donor, multiple organs, including both kidneys rather than just one, are removed from deceased donors, who can therefore save more than one life through donation. In the UK, though deceased donors comprised 60% of all donors in 2019 [42], during the pandemic this percentage rose to nearly 73% for 2020, because of the disproportionate decline in living donations. In the US, 2019 was a record year for deceased donation with a total of 11,870 (62% of total donations) [14]. In contrast to the UK, the number of deceased donations rose in the US by 6% to over 12,500 donations [43]. Globally, the figures for 2020 show the total number of kidney transplants was 80,912, of which 62.7% were from deceased donors [44].

Types of Deceased Donation

Unlike living donations, deceased donations are classified into two different categories: donation after circulatory death[2] and donation after brain death.[3] The proportion of donations from each category varies from one nation to another. Part of the reason for this is that there are still ongoing medical and philosophical debates about the diagnosis and nature of brain death (see for example: [45]), even decades after the concept was first formulated. Some countries for religious and cultural reasons do not accept brain death as being an acceptable criterion for organ removal. In Singapore for example, deceased organ donors remain low at 7–9 per million

[1] Except in the rare circumstances of 'domino donations'.

[2] Previously referred to as donation after cardiac death or 'non-heart-beating' donors.

[3] Previously referred to as 'beating-heart' donors.

population annually compared to many other developed countries, mostly because of concerns about brain death [46].

Though some ethicists take the view that morally "Dead bodies don't matter" [47], they clearly do matter to the loved ones of the deceased and it is essential to ensure that people are actually dead rather than just being 'as good as dead' in the eyes of some, before organs are removed. Though there are a large number of ethical issues raised by deceased donation, the primary areas targeted to increase deceased donations are making it easier to obtain consent and extending the scope of those who are considered dead.

Increasing Consent Rates for Deceased Donation

It is generally agreed that the wishes of the deceased regarding donation should be respected but in order to be respected, they should ideally be expressed in a verifiable form [48]. In countries which operate an opt-in system, where individuals must expressly indicate their wish to donate, efforts to increase deceased donation focus on encouraging donors to sign up and increasing ways to do so. The over 50% increase in transplants in the UK, a decade after implementation of the recommendations of the 2008 Donation Task Force [49], shows how effective such strategies can be. However, the UK along with many other countries, most notably Spain with record levels of donors per million population [50], now operate on an opt-out basis [51]. Here, unless individuals actively take steps to indicate unwillingness to donate, it is assumed they are willing, though in most countries the consent of relatives is sought and rarely over-ruled. However, some ethicists recommend relatives' wishes should never be allowed to prevent donation [52].

Expanding Categories of the Dead

The 'dead donor' rule (DDR), the ethical principle which stipulates that "(vital) organs be only removed from dead patients" [53], has been increasingly questioned as the demand for organs worldwide has increased. Various suggestions have been put forward to modify the criteria for both donation after circulatory death [54] and donation after brain death [55] so that increasing numbers in both groups could fulfil the DDR, whilst others have suggested that the DDR be abandoned altogether [56] in order to maximise organ retrieval from those for example with persistent disorders of consciousness (PDOC). The claim is made that causing the death of such patients is not morally wrong. "What matters is not when a patient dies but whether their death constitutes some further harm" [57]. Whilst indeed it may not matter to the patient, it certainly may matter to their relatives and to the general public whose trust in transplantation could be undermined [58, 59].

Conclusions

To date no country in the world, with exception of Iran, has managed to completely meet the demand within its population for organs. In a post-pandemic world, the situation for most countries has already been substantially worsened in the short term. In the long term, adverse health consequences of the pandemic continue to take their toll, especially in terms of renal and respiratory damage, which in turn could increase the need for organs. Even if trust in in the transplantation system is not undermined by future ill-considered moves to expand the pool of both living and deceased donors, possible sources of organ replacement other than allotransplants will need to be explored. Alongside bioprinted organs, implantable biorobotic organs, and organs grown in vitro or in chimeras, xenotransplantation has an important place in research for such alternatives.

References

1. World Health Organization, Global Observatory on Donation and Transplant, 2019. Data. http://www.transplant-observatory.org/wp-content/uploads/2021/06/GODT2019-data_web_updated-June-2021.pdf
2. Byrnes IS, Stenzel A. The power of two: a twin triumph over cystic fibrosis. Missouri: University of Missouri Press; 2007.
3. Anonymous. Plot summary of The Power of Two movie The Power of Two (2011) - Plot Summary-IMDb.
4. de Kerangal M. Mend the living. London: Maclehose Press; 2016.
5. Stammers T. Organ trafficking: why do healthcare workers engage in it? Camb Q Healthc Ethics. 2022;31(3):368–78.
6. Global observatory on donation and transplant, Statistics for 2020. http://www.transplant-observatory.org/
7. Aubert O, Yoo D, Zielinski D, et al. COVID-19 pandemic and worldwide organ transplantation: a population-based study. Lancet Public Health. 2021;6(10):e709–19.
8. Segev DL, Muzaale AD, Caffo BS, Mehta SH, Singer AL, Taranto SE, Montgomery RA. Perioperative mortality and long-term survival following live kidney donation. JAMA. 2010;303(10):959–66.
9. Muzaale AD, Massie AB, Wang M-C, Montgomery RA, McBride MA, Wainright JL, Segev DL. Risk of end-stage renal disease following live kidney donation. JAMA. 2014;311(6):579–86.
10. Muzaale AD, Dagher NN, Montgomery RA, et al. Estimates of early death, acute liver failure, and long-term mortality among live liver donors. Gastroenterology. 2012;142:273–80.
11. Kiberd BA, Tennankore KK. Lifetime risks of kidney donation: a medical decision analysis. BMJ Open. 2017;7:e016490.
12. Thomas E. Starzl, ethical problems in organ transplantation. Ann Intern Med. 1967;67(3):32–6.
13. Health Resources and Services Administration. 2019. Data. https://data.hrsa.gov/topics/health-systems/organ-donation
14. US Organ Procurement and Transplantation Network Organ donation again sets record in 2019. https://optn.transplant.hrsa.gov/news/organ-donation-again-sets-record-in-2019/
15. NHS Organ and Tissue Donation and Transplantation Activity Report 2020–21. Fig 2.2, p 5. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/23461/activity-report-2020-2021.pdf

16. World Health Organization. Global Observatory on Donation and Transplantation 2021. http://www.transplant-observatory.org/wp-content/uploads/2021/06/GODT2019-data_web_updated-June-2021.pdf. Slide 2.
17. United Network for Organ Sharing (UNOS) COVID-19 and solid organ transplant. https://unos.org/covid/
18. Lentine KL, et al. Survey of US living kidney donation and transplantation practices in the COVID-19 Era. Kidney Int Rep. 2020;5:1894–905.
19. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantations of human kidneys between identical twins. JAMA. 1956;160:277–82.
20. Stammers T. The evolution of autonomy. The New Bioethics. 2015;21(2):155–63.
21. Mandelbrot DA, Pavlakis M, Danovitch GM, et al. The medical evaluation of living kidney donors: a survey of US transplant centers. Am J Transplant. 2007;7(10):2333–43.
22. Canadian Blood Services. Can I be a donor if I am older? https://www.blood.ca/en/organs-tissues/deceased-donation/am-i-eligible
23. Rakké YS, Zuidema WC, Hilhorst MT, et al. Seriously ill patients as living unspecified kidney donors: rationale and justification. Transplantation. 2015;99:232–5.
24. Sickand M, Cuerden MS, Klarenbach SW, Ojo AO, Parikh CR, Boudville N, Garg AX. Donor nephrectomy outcomes research network. Reimbursing live organ donors for incurred non-medical expenses: a global perspective on policies and programs. Am J Transplant. 2009;12:2825–36.
25. National Kidney Federation, Reimbursement of living donor expenses. https://www.kidney.org.uk/reimbursement-of-living-donor-exp
26. NHS England 2018. Commissioning policy: reimbursement of expenses for living donors. https://www.england.nhs.uk/wp-content/uploads/2018/08/Policy-Reimbursement-of-Expenses-for-Living-Donors-Updated-August-2018.pdf
27. Manatu Hauora (Ministry of Health), New Zealand, Compensation for Live Organ Donors. https://www.health.govt.nz/our-work/hospitals-and-specialist-care/organ-donation-and-transplantation/compensation-live-organ-donors#:~:text=About%20the%20Compensation%20for%20Live%20Donors%20Act&text=The%20Act%3A,of%20up%20to%2012%20weeks
28. Kidney Foundation, Living Donor Expense Reimbursement Program. https://kidney.ca/Support/Programs-Services/living-organ-donor-reimbursement-program#:~:text=The%20Living%20Organ%20Donor%20Expense,far%20away%20from%20the%20recipient
29. Siddique AB, Apte V, Fry-Revere S, Jin Y, Koizumi N. The impact of country reimbursement programmes on living kidney donations. BMJ Glob Health. 2020;5(8):e002596.
30. Chatterjee P, Venkataramani AS, Vijayan A, et al. The effect of state policies on organ donation and transplantation in the United States. JAMA Intern Med. 2015;175:1323.
31. Ghods AJ. Organ transplantation in Iran. Saudi J Kidney Dis Transpl. 2007;18:648–55.
32. Al Sebayel M, Alenazi AM, Sabbagh R, et al. Donor organ shortage crisis: a case study review of a financial incentive-based system. Transplant Proc. 2014;46(6):2030–5.
33. Fisher JS, Butt Z, Friedewald J, et al. Between scylla and charybdis: charting an ethical course for research into financial incentives for living kidney donation. Am J Transplant. 2015;15(5):1180–6.
34. Ashkenazi T, Lavee L, Mor E. Organ donation in Israel-achievements and challenges. Transplantation. 2015;99:265–6.
35. Iyer TK. Kidneys for transplant–"opting out" law in Singapore. Forensic Sci Int. 1987;35:131–40.
36. Kluge E-HW. Designated organ donation: private choice in social context. Hast Cent Rep. 1989;19:10–6.
37. Matching Donors. https://matchingdonors.com/life/. Accessed 31 Oct 2022. There were 15645 potential donors listed.

38. Human Tissue Authority. https://www.hta.gov.uk/guidance-public/living-organ-donation/living-organ-donation-matching-websites-and-social-media
39. Cameron AM, Massie AB, Alexander CE, et al. Social media and organ donor registration: the Facebook effect. Am J Transplant. 2013;13:2059–65.
40. Ruck JM, Henderson ML, Eno AK, et al. Use of twitter in communicating living solid organ donation information to the public: an exploratory study of living donors and transplant professionals. Clin Transpl. 2019;33(1):e13447.
41. Moorlock G, Draper H. Empathy, social media, and directed altruistic living organ donation. Bioethics. 2018;32:289–97.
42. NHS Blood and Transplant 2021. Organ and Tissue Donation and Transplantation Activity Report 2020/21. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/23461/activity-report-2020-2021.pdf. Accessed 9 Sept 2021. There were 1580 deceased donors and 1058 living donors in 2019.
43. Association of Organ Procurement Organizations New Data Shows 2020 is Record Year for Organ Donation and Transplant. https://aopo.org/2020-record-year-for-organ-donation-and-transplant/#:~:text=More%20than%2012%2C500%20people%20donated,%2Dover%2Dyear%20growth%20rate
44. Global Observatory on Donation and Transplantation. http://www.transplant-observatory.org/countkidney/
45. Terunuma Y, Mathis BJ. Cultural sensitivity in brain death determination: a necessity in end-of-life decisions in Japan. BMC Med Ethics. 2021;22(1):58.
46. Kwek TK, Lew TWK, et al. The transplantable organ shortage in Singapore–has implementation of presumed consent to organ donation made a difference? Ann Acad Med Singap. 2009;38:346–53.
47. Harris J. Consent and end of life decisions. J Med Ethics. 2003;29:10–5.
48. Vincent A, Logan L. Consent for organ donation. Br J Anaesth. 2012;108(Suppl. 1):i80–7.
49. Organ Donation Task Force Working Together to Save Lives 2011. https://bts.org.uk/wp-content/uploads/2016/09/The-Organ-Donation-Taskforce-Implementation-Programmes-Final-Report-2011.pdf
50. In 2019 Spain had a donor rate of 49.6 donors per million, the highest in Europe. https://www.lamoncloa.gob.es/lang/en/gobierno/news/Paginas/2020/20200907organ-donation.aspx
51. NHS Blood and Transplant. What is the opt out system in England? https://www.organdonation.nhs.uk/helping-you-to-decide/about-organ-donation/faq/what-is-the-opt-out-system/
52. Shaw D. We should not let families stop organ donation from their dead relatives. Br Med J. 2012;345:33.
53. Robertson J. Relaxing the death standard for organ donation in pediatric situations. In: Mathieu D, editor. Organ substitution technology: ethical, legal, and public policy issues. Boulder: Westview Press; 1988. p. 69.
54. Boucek MM, Mashburn C, Dunn SM, et al. Pediatric heart transplantation after declaration of cardiocirculatory death. N Engl J Med. 2008;359(7):709–14.
55. Lazaridis C, Blumenthal-Barby JS. Organ donation beyond brain death: donors as ends and maximal utility. Am J Bioeth. 2015;15(8):17–9.
56. Rodríguez-Arias D, Smith MJ, Lazar NM. Donation after circulatory death: burying the dead donor rule. Am J Bioeth. 2011;11(8):36–43.
57. Smith AP. Abandoning the dead donor rule. [published online ahead of print, 2022 Oct 3]. J Med Ethics. 2022; medethics-2021-108049.
58. Woien S. Donation after cardiac death: an alternative solution to burying the dead donor rule. Am J Bioeth. 2011;11(8):54–6.
59. Stammers T. The ethics of global organ acquisition Chapter 3. Bloomsbury; 2023

Xenotransplantation: The Role of Public Involvement

3

Mariachiara Tallacchini

Introduction

Public involvement, namely including the general public, for health regulations and policies has gained momentum and has been deemed increasingly relevant in the past few decades in most democratic societies. This chapter illustrates the meaning and the evolution of public involvement in xenotransplantation (XTx) from a science policy perspective—that is, how scientific knowledge and normative requirements merge in decision-making—and with an interest for the current changes as to how democratic societies think of themselves [1]. Xenotransplantation represents a unique case as debates about the role of the public, from people's attitudes to citizen consultations, have been extensive and controversial. The chapter starts by briefly considering the role of the public in transplantation technologies in order to highlight that, while sharing a public health dimension, transplants and xenotransplants seem to look at the public for different purposes. In transplantation, the public has been considered crucial to support organ donation; in xenotransplantation, public involvement has gained momentum and then has become an international regulatory requirement as a strategy both to assess the acceptability of its risks and to better legitimize its implementation. As xenotransplantation carries potential risks of spreading xenozoonotic pathogens, its regulation involves traditional medical principles as well as environmental and public health approaches, such as the precautionary principle, which will be explained further in this chapter.

The chapter proceeds with an analysis of how "the public" has become relevant in the recent regulatory history of xenotransplantation. More precisely, different publics have been taken into account by making them the object of surveys and interviews where their positions are quantified; but they have been also addressed as

M. Tallacchini (✉)
Department of Legal Studies, Università Cattolica S.C., Piacenza, Italy
e-mail: mariachiara.tallacchini@unicatt.it

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_3

subjects of deliberative interactions—with a special reference to the public consultations that took place in Canada and Australia at the turn of the millennium.

The overall knowledge and experience that has been acquired through all these theoretical and practical exercises has the potential to provide new ways of collaboration among citizens, scientists, and institutions. Also, from this perspective, transplantation and xenotransplantation can be looked at in a continuum as to public involvement, because they share the necessity of connecting individual and public health. The COVID-19 experience has added new insights to these forms of interactions in terms of using knowledge and sharing uncertainties responsibly, revealing the need for a more deeply committed citizenship from all parts of society.

Individual and Public Health in Transplantation Technologies

The contemporary history of transplantation of human organs, including its first surgical successes and increasing promises in the mid-twentieth century, seemed to suggest that transplants would become a viable therapy for a large population of patients. However, somehow paradoxically, despite their achievements, transplantation medical technologies and policies have had to face some major obstacles since their beginnings. On the one hand, successful campaigns to create social acceptance of donation—including acceptance of the concept of brain death [2]—and to forge a culture of human awareness and solidarity have not always achieved optimal results. On the other hand, even with more refined organ donation programs, the shortage of available, adequate, and compatible organs to be transplanted has been persistent and perhaps structural.

Indeed, as the former point is concerned, several well-organized donation campaigns all over the world have turned out to be capable of increasing organ availability—with the case of Spain becoming paramount [3, 4]—by combining a variety of medical and policy measures, including legal measures, financial incentives, expanding donors, and education.

More inclusive criteria for donors with potentially suboptimal organs depend on a complex set of technical factors and medical decisions, and financial incentives have remained somehow marginal, due to their potential ambiguities. Legal measures have been considered as one of the most relevant steps to be taken. In order to promote donations, legislations have either asked their citizens to provide express informed consent to donation in case of death (opt-in systems) or presumed their consent if individuals do not explicitly disagree (opt-out systems). Providing legal certainty to support transplant policies has definitely helped [5, 6] However, even in regulatory contexts where consent to donation is provided in advance, still medical personnel keep consulting with families and close contacts before proceeding. As the Spanish experience has shown, public confidence is not simply related to legislation encouraging donation, but is connected to the broader dimension of trust towards institutions [4, 7].

This is why increased attention has been paid to education processes raising knowledge and awareness in school programs [8, 6]. Education is deemed essential

as organ shortage represents an "inadequate societal response to organ donation" [6]. Indeed, the comparison between public attitudes and organ availability has consistently shown that, while the results of interviews and surveys reveal high levels of support to transplantation, the actual organ supply remains significantly lower [8]. This is why, according to some scholars, the educational message should introduce conceptual changes in encouraging organ donation. An efficient revision in transplant and organ donation education programs "may be a challenge to change the inadequate people's behavior" [6]. Citizens should be made aware that organ shortage is a health emergency, an "unjustifiable damage to public health" [8].

However, as said, also with optimized programs for organ donation the mismatch between the need for transplants and donor supply may remain. This can happen because: (1) some organs are more prone (like lungs) to be damaged due to trauma, disease or deterioration; (2) the rising prevalence of health problems, such as diabetes mellitus and obesity, can reduce the number of eligible donors; and (3) major public health problems, such as the COVID-19 pandemic, also have an impact on organs' safety [6].

The paradox of human organ transplantation is that, while an increasing number of patients will survive and thrive long-term after organ transplantation, the limited number of organs available is reducing the percentage of patients that successfully complete transplant surgery. This unavoidable conclusion often represents the premise for considering xenotransplantation, even with their complex set of scientific, technical, and normative issues [9].

From the public involvement point of view, the two domains seem different. Transplantation remains within the traditional boundaries of medical ethics in terms of free and informed consent of the transplanted, and with close contacts and/or family involved on the donor's side. The public dimension of transplantation, aimed at encouraging donation, despite its implicit meaning of public acceptance, support, and commitment, as well as its public health implications, has never led to the forms of public involvement triggered by xenotransplantation regulation.

Xenotransplantation introduced a discontinuity and an anomaly in medical ethics as it resulted after WWII, namely centered on the rights and the autonomy of the individual, primarily expressed through informed consent [10]. Because of its potential for transmission of xenozoonotic infections, on the one hand, lack of information about unknown risks was making informed consent contradictory; on the other hand, these threats were calling for harmonizing individual and collective rights, thus challenging the individually-oriented paradigm for medical ethics. The uniqueness of xenotransplantation, at least when it started becoming an applicable technology potentially concerning a large number of patients, consisted in its involving not only the informed and consenting patients who are willing to accept the risks, but also their contacts and families, and eventually also the general public [11].

In the 2000s a group of bioethicists started reflecting on the widely unexplored ethical implications of pandemics and the prolonged bioethicists' negligent behaviors in looking at public health issues [12, 13, 14]. In order to highlight the situation, Michael Selgelid forged the word "pandethics" to refer to the ethical context where

the patient is both the victim and the vector of an infection [15]. Although Selgelid explored the context of (unexpected) outbreaks of infectious diseases, a medical technology with potential pandemic effects was not different. In the aftermath of the September 11, 2001 terrorist attacks against the United States by al-Qaeda members and the 2003 severe acute respiratory syndrome (SARS) outbreak that was first identified in China, Jay Fishman argued that "(m)eaningful distinctions do not exist for the medical community between epidemics caused by natural causes, new technologies or bioterrorism". He added, as a pragmatic more than a prophetical conclusion, that if we were to fail in coordinating better international reporting about infectious diseases, "we will always be a little bit too late. And with the next outbreak, we will, once again, be surprised" [16].

Therefore, xenotransplantation found itself at the crossroad between medical and public health regulatory issues. This intersection explains how it seemed relevant that the most directly impacted subjects (close contacts), but also society at large may have a say about the acceptability of this technology and its risks.

Risks, Precaution, and the Public: From the Environment to Health Technologies

A brief summary of the main passages and events that have accompanied and framed the rise and the expanding role of the "public" helps provide the context for understanding how this requirement has emerged in xenotransplantation regulation and has been considered as a source of democratic legitimacy and transparency.

Recognition that the public at large should be given a right to 'a say' about science and technology has been part of both scholarly reflection and science policy since the early 1970s in the environmental domain, and with the growing impact of techno-science in daily life. The involvement of specific fractions of the public was initially theorized and introduced in the United States with the National Environment Protection Act in 1969, while an industrial accident releasing dioxin in a chemical plant in Seveso (Italy) in 1976 triggered the 1980s European legislation on public information and participation [17].

In the mid-1970s public consultation was more widely proposed in relation to all technological domains within the context of the US Congress Office of Technology Assessment (OTA). Its first director, Joseph Coates, argued that public participation in technology assessment was essential for several reasons. First, it allows understanding the actual impacts of new technologies and their different forms of implementation. Second, it provides early awareness of failures and issues. Third, it prepares citizens for unexpected outcomes [18].

The issue of involving the public in the discussion also emerged in the context of the first two Asilomar conferences in 1974 on genetic engineering, where the term "public" was initially used (by bioethicist Alexander Capron) to refer to government and the law. During the same period, town meetings discussing the potential unintended release of genetically modified micro-organisms (MGMs), and directly launched by the scientific community, involved the population of Cambridge, Massachusetts [19].

In 1992 the Rio Declaration on Environment and Development internationally introduced the precautionary approach (and later "principle" in the European formulation of it [20]), stating that: "lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures" of prevention (Principle 15) [21]. The principle framed the idea that potential risks should be considered as actual risks in case of serious environmental threats. And, in 1996, the United Kingdom Nuffield Council of Bioethics, in a dedicated opinion that coincided with the 1996 draft Regulation on Xenotransplantation issued by the Food and Drug Administration (FDA) [22], for the first time connected xenotransplantation to the precautionary principle, thus extending its scope from the environment to health protection [23].

However, the implications of the precautionary principle remained open to a variety of interpretations, from calling for a moratorium to assessing public acceptance of risks. The former suggestion was taken up after a study in 1997 reported that human cells could be infected in vitro by porcine endogenous retroviruses (PERVs) [24]. In 1998 a group of leading xenotransplantation scientists in the US briefly called for a moratorium [25, 26], but later some of them shifted toward highlighting the need for public consultation [27]. In 1999 the Council of Europe, the institution in charge of human rights in the enlarged European context, also temporarily suggested a moratorium [28].

In the US regulation the precautionary principle was never favorably received—as precautionary measures have been mostly interpreted to refer to preventing actual risks [29]. The 2001 Public Health Service (PHS) Guidance on xenotransplantation quite marginally recognized that "public discourse on xenotransplantation research is critical and necessary" and that "public awareness and understanding of xenotransplantation is vital because the potential infectious disease risks posed by xenotransplantation extend beyond the individual patient to the public at large" [30]. The US never deemed necessary to launch a public consultation, even though the PHS Guidance was open to public comments, and public hearings with a limited participation from the public were held.

In Europe the meaning of the precautionary principle, extended to include all threats to human, animal, plant and environmental health, remained paternalistic as a "political responsibility" about the "high level of protection of citizens" [20].

In the past two decades, however, reflection on precaution has increasingly focused on the need not to stop emerging technologies, but to assess them carefully through an appropriate regulatory process, including public willingness and preparedness to accept potential risks when outweighed by substantial benefits.

Consulting Citizens on Xenotransplantation

At the beginning of the twenty-first century the US PHS Guidance set the regulatory conditions for the delicate passage from the preclinical to the clinical phase, thus normalizing and legitimizing xenotransplantation [31]. The US measures were rapidly followed by other countries, with different legal approaches towards experimenting with governance of emerging and controversial biomedical technologies.

The US approach primarily focused on mitigating the potential risks of infections. The major assumption was that the most likely potential form of infectious disease would be similar to the Human Immunodeficiency Virus (HIV) [30], a pathogen controllable through patients' responsible behavior. The guidance aims at protecting all involved subjects, but still relies only on patients' consent to inform their intimate contacts about potential risks [30, 32].

The Council of Europe (backed up by a favorable opinion from the European Commission) grounded its recommendations on the assumption of the worst case scenario of an airborne disease and suggested compulsory constraints for non-compliant patients and third parties (family and close contacts) (Article 21) [33]. According to the recommendation, patients and third parties should accept to "waive some fundamental rights" [34].

With a completely different approach, between 1999 and 2004, Canada and Australia equally interpreted the public health challenges posed by xenotransplantation severe enough to impact on the constitutional level of their societies and have the population contribute to the decision. Both governments went through extended forms of public consultation (through the mail, emails and the web, focus groups, and several town meetings) and translated the theoretical concept of scientific citizenship, namely citizens participating in science-based public policy, in operational terms. Later, in the mid-2000s, another participatory approach was endorsed by New Zealand, where the Maori population was consulted as a minority whose cultural values could matter in techno-scientific innovation.

Starting in 1999, the Canadian government launched an extensive public program on xenotransplantation, culminating in the release in 2001 of the report "Animal to-Human Transplantation: Should Canada Proceed? A Public Consultation on Xenotransplantation" [35]. The government was not primarily looking for approval, but was experimenting in strengthening democracy in health policy. The initiative shaped the role of citizens as "lay scientists", by providing them with the relevant information on xenotransplantation and waiting for their informed opinions. After a long and articulated process involving several deliberative experiences, citizens ended up by arguing that "Canada should not proceed" [35], thus challenging the so-called "knowledge deficit model" [36]. According to this model, uninformed people tend to disagree with science, while well-informed people tend to agree with it. Canadians reversed this theoretical assumption: having started with a favorable position towards xenotransplantation, the more they knew about its complexities and risks, the less ready they became in accepting it as a viable option. Though not opposed in principle, citizens argued that scientists and the health industry should more clearly demonstrate that benefits would outweigh risks, asking for continued public discussion on xenotransplantation.

In 2001, the Australian National Health and Medical Research Council (NHMRC) established a Working Party to provide advice on the scientific and normative aspects of xenotransplantation, to produce guidelines on clinical trials, and to consult with the community. In the next 2 years, an informed community discussion was organized [37, 38]. The Australian initiative was quite critical of the Draconian

safety measures introduced by other regulations, arguing that a challenging technology cannot primarily rely on patients' constraints and infringement of fundamental human rights: this does not correspond to sound science. Compulsory measures should not be used as a surrogate for scientific evidence of safety; therefore, "investigators should provide sufficient evidence of safety to show that there is no undue risk to the community if some participants choose to leave the trial" [37]. The final document suggested that Australian socially responsible scientists and citizens should cooperate to keep the community safe even if some patients may not comply with safety measures.

The results of both participatory exercises were disparate. After Canadians asked the government not to proceed with xenotransplantation, the government went back to a more science-based policy and set up an expert working group to further analyze the situation.

Australia accepted its citizens' concern about xenotransplantation, and in 2004 adopted a 5-year moratorium [39]. At the end of 2009, however, the Australian government expressed a favorable inclination toward proceeding with xeno-cell therapies, looking at the EU framework on Advanced Therapies [40] as a reassuring template that "risks, if appropriately regulated, are minimal and acceptable" [41].

In 2005 a more limited public consultation among the Maori population took place in New Zealand on the acceptability of a single clinical trial proposed by Living Cells Technology (LCT), a biotech company [42]. The trial concerned the implant of alginate encapsulated porcine islet cells into 8 type 1 diabetic patients [43]. Despite a long international controversy, the results of the consultation turned out favorable to xenotransplantation and to the proposed trial, also because the Maori felt that their opinion about innovative technologies had been taken into account by the government. Eventually, the New Zealand Minister of Health authorized the trial [44] that took place in 2009 [45].

The World Health Organization (WHO) attributed international recognition to these democratic experiences. Since the late 1990s the WHO had been very active in the field of xenotransplantation regulation [46]. In the early 2000s the increased threats of pandemics [47], and the risks of 'xeno-tourism' (patients traveling to countries where transplants can be easily performed without controls) [48] made the global situation more challenging. In 2004 the WHO warned against the absence of regulatory frameworks in countries where unauthorized experimentation could take place [49].

Finally, in 2008 the WHO Changsha Communiqué, following the first 'Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials' held in China, published a refined general framework and explicitly endorsed a democratic governance of xenotransplantation [50]. After having set the existence of effective regulatory frameworks as an essential condition to legitimately proceed with XTx, the WHO added that "the regulatory system should be transparent, must include scientific and ethical assessment and should involve the public" [50]. The Second and Third WHO Global Consultation of 2011 and 2018 have confirmed the same principles [51, 52].

Debating the Public Dimension: Publics or Citizens?

The roles of non-experts in contributing to public discussion in science policy has been at the core of philosophical, sociological, and political analysis in the past two decades [53, 54] and has been widely debated in the context of xenotransplantation. Xenotransplantation represents an outstanding case of how theories and techniques about making sense of the "public" have changed through time, and how diverse perspectives have fought against each other in order to have the specific attitudes of certain groups to represent the views of the general public.

The first inquiries about public feelings towards xenotransplantation are especially relevant in order to understand the evolution of the public's role. They began in the early 1990s, when the potential for genetic engineering of pigs to partially overcome the issue of hyperacute rejection of their cells and tissues made clinical trials more safely feasible and realistically close. In 1993 a US Gallup poll reported 51% acceptance among 6127 people asked through a telephone survey whether they would accept an animal organ if a human organ was not available [55]. Very quickly the issue of public response became highly debated and controversial. In 1995 and again in 1997 and 1998 [56, 57, 58] a group of Australian researchers, while recognizing the relevance of xenotransplantation, made the point that accurate and extensive analysis of public attitudes was "mandatory" to avoid replicating the problems already raised by human organ transplantation. According to the group, public attitudes "will undoubtedly determine whether or not xenotransplantation gains general acceptance" [58].

Through a questionnaire in Australian hospitals the researchers reported high rates of aversion to xenotransplantation among 1956 acute care nurses (only 19% in favor of animal organs) and also from a group of 113 patients with renal diseases or in dialysis waiting for a kidney transplants (42% willing to receive a nonhuman organ). The reasons for aversion were not specified and the interpretation of data remained open to different interpretations, with some authors arguing that 40% did not show aversion, but was a positive result [59]. The Australian data was not contested, but most researchers in the field reacted by providing their findings in support of xenotransplantation. The skepticism of Australian patients was immediately contrasted by a survey in the United Kingdom (UK) reporting the "scientific enthusiasm" (78% willing to receive a nonhuman organ) of 850 patients with renal failure [60]. The initial debate on public attitudes and its relevance for xenotransplantation to proceed suddenly became a war of numbers and regional attitudes (UK and US against Australia). In 1997, after evidence showed human cells infected in vitro with PERVs [24], quantitative analyses of xenotransplantation rapidly grew in scientific journals, where survey and attitude literature had already earned a relevant space that has constantly expanded since. The main purpose for these sociological approaches has been, and still is, measuring the strength of public support for xenotransplantation, and sometimes also providing implicit forms of advertisement to it. Here the "knowledge deficit model" is often assumed: namely, that the more knowledgeable, aware, and educated the public, the more willing they are to accept xenotransplantation [36].

Besides providing an understanding of public feelings (or perceptions, attitudes, etc.) towards the new technology, this vast literature also introduced a wide range of "publics" by constructing a variety of different relevant fractions of the population (nurses, students, people with religious beliefs, etc.) [61, 62, 63]. In fact, if initial consideration was primarily given to patients, their contacts, health personnel, and students in medicine, the focus has widened to include several stakeholders and non-stakeholders (individuals without a precise interest in the subject), including religious groups, non-Western countries, minorities, disadvantaged and under-represented communities [64]. Through the years, research on public attitudes has substantially changed both with an increased opening to multiple sociological approaches and a more complex vision of the public [65].

Moreover, new research methods have been framed that compare different ways of engaging lay-people and scientists, with individuals retrospectively reflecting on their initial positions and how these have changed through the participatory process [66].

Still, a divide seems to remain between these exercises and the forms of public consultation launched in Canada and Australia. The two different categories of research have been described as "one-way" and "two-way" communication: one aimed at collecting information from the public, the other providing room for dialogue and discussion between scientists and the public [36].

Though with subtleties, the former remains "descriptive"—or should remain as numbers may be used to express tendencies—the latter is meant to produce "normative" suggestions. Indeed, "How do specific fractions of the public perceive xenotransplantation?" and "What do citizens suggest when addressed as potential co-regulators?" highlight different ways of looking at how innovation should legitimately take place.

Publics can be seen as objects of research, with quantifiable positive and negative attitudes towards XTx; but they can also be empowered as subjects of decisions.

In the mid-2000s the "momentum" for large public involvement was over, but the Canadian and Australian participatory experiences continued, developing toward broader institutional forms of public involvement. Canada has kept working on providing opportunities for citizens to participate in decision-making processes, especially in the field of health. In doing so, Health Canada has clarified and codified the language of public involvement. According to the current Guidelines on Public Engagement, the term "public" refers to "any individual or unorganized group (…) that is interested in or affected by, or has the potential to be affected by, an issue, decision or action". The word "citizen" is not explicitly defined, but is subsumed in the term "Canadians". Also, two different ways of addressing the public are defined. First, "public engagement" refers to planned 'two-way' (bidirectional) discussions with all individuals, organizations, or groups affected by the decision-making. Second, "public opinion research" (POR) concerns the planned, 'one-way' systematic collection of opinion-based information of any target audience using quantitative or qualitative methods and techniques such as surveys or focus groups [67]. The two different categories of public involvements—the former based on dialogues, discussions, and fora; the latter based on expressions of opinions—far from

excluding each other, are instead deemed complementary for better regulation and decision-making.

Australia has also devoted a big effort towards grounding participatory exercises in a vision of political philosophy, with National Action Plans "jointly developed by Government and Civil Society to help make Governments more transparent, accountable and publicly engaged" [68]. In this vision the concept of "public" has been reframed as "the citizens" "whose agency matters"; and "concepts such 'co-creation' and 'co-production' have been introduced to describe this systematic pursuit of sustained collaboration" between institutions, communities, and individual citizens, towards "a citizen-centric public service" [69].

Responsible Collaboration and Commitment: Merging Individual and Public Health After COVID-19

Xenotransplantation can be properly defined as a re-emerging technology since it has appeared and reappeared through time with increasingly adequate answers to problems of both feasibility and reduction of risks. In the 2010s successful developments with xenocell therapies seemed to allow overcoming several obstacles, with more harmonized regulatory approaches, and more manageable and acceptable risks [70, 71]. However, some disruptive factors in the recent times seem to have wiped out this reassuring landscape. COVID-19 unveiled a general lack of preparedness (even though the outbreak of a pandemic has been long expected); and the xenotransplantation scientific community was again confronted with assessing known and novel risks, while coping with supposedly skeptical public reactions [72, 73]. Then, toward the end of 2021 and the beginning of 2022, some partially unexpected experimental procedures with xeno-organs have revamped interest in xenotransplantation.

Three procedures were performed on brain dead subjects (two at NYU Langone Transplant Institute and one at the University of Alabama at Birmingham) [74, 75], and one on a living patient with end stage heart failure (at the University of Maryland School of Medicine) [76]. While the cases showed substantial progress in dealing with hyperacute rejection and added knowledge about the proper functioning of xeno-organs [77], they also renewed questions and concerns. But, while the ethical and social aspects of research on brain dead subjects have been already discussed in recent years and consensus has been reached about the ethical conditions that should be met in order to proceed [78], the xeno-heart transplant in a living patient, although authorized, was received in bewilderment. Commentators have harshly criticized the acceptability of informed consent, the absence of ethical approval due to the emergency situation, the authorization justified as compassionate use, and the complete absence of public awareness (not to mention public discussion) [79].

How has the role and meaning of the public dimension changed under the current circumstances? Reflection on, and practice of, the relations among institutions, researchers, and citizens have evolved greatly in the past few years. The overall perspective resulting from this evolution has led to making the most of both research

on public opinions and the dialogues with citizens. Currently, from the perspective of better innovation policy, both strategies can concur in gaining knowledge and building trust, and have become synergic factors towards improving the quality of decision making. On the one hand, research on public attitudes has the potential to add relevant knowledge on social acceptance of xenotransplantation by exploring the new issues raised by the recent experimental procedures. People, for example, could be asked: (a) if they were surprised or not by these forms of experimentation; (b) if they think that xenotransplantation is still a big challenge; (c) under which circumstances it could become a standardized treatment. On the other hand, it has been observed that the recent cases of experimental procedures reveal the relevance of public involvement for xenotransplantation to proceed as a widely accepted technology. "Increased public awareness and full transparency during clinical trial planning and execution will be needed to generate support for organ xenotransplantation trials" [77]. Surveying the public and creating awareness through an open dialogue represent converging strategies in legitimizing innovation.

Moreover, as uncertainties are concerned, the COVID-19 experience has provided relevant insights and practical evidence. What democratic societies have been experiencing is a collective learning process—involving regulators, experts, and citizens—in adequately absorbing knowledge and implementing it in daily behavior [80].

The crisis has shown that citizens' accurate understanding and implementation of scientific knowledge in everyday life have been at the core of infections containment strategies. Since the beginning of the pandemic citizens have been asked to acquire a lot of information about behaving safely in every aspect of their daily life: from washing hands to properly wear, and dispose of, masks; from keeping adequate distance to properly manage safety protocol at home or at work; from interpreting their symptoms to implementing procedures of self-isolation and quarantine.

All these new knowledge and practices require reciprocally trusted relations from both institutions and citizens. Institutions can offer clear and reliable information and have to rely on lay people's ability to adopt and properly use it with a crucial impact on keeping social life safe. But institutions are also learning from their collaborations with citizens. Several activities of so-called "citizen science" have been launched, for example, by the US National Institutes of Health (NIH), asking patients to collect evidence on long-haul COVID-19 for further studying the disease [81]. Collaborative research has become common in several fields [82, 83] and, increasingly, lay individuals are expected to properly manage sophisticated knowledge and technology. As some scholars in science policy commented, "the whole world becomes an extended peer community", because the appropriate behavior and attitudes of populations become crucial for a successful response to the virus [84]. The experience of COVID-19 showed that risks already are a daily part of contemporary life and that living with uncertainties has been largely acquired rationally and even emotionally. This is more than just expressing a hypothetical opinion or participating in a consultation exercise on new technologies. This is about how people live with risks.

Collaborative knowledge and exchange of knowledge make risks constantly redefined, clearer, and more manageable. This collaboration concerns also xenotransplantation that is no longer unique and can be performed in highly controlled environments. For instance, patients and their contacts can manage knowledge, perform complex tasks, and can be early "sensors" and "interpreters" of conditions and symptoms in relation to potential adverse events; the public can be supportive of collective forms of experimental procedures in a climate of full legitimacy, clarity, and transparency.

Some Provisional Conclusions for a Work in Progress

This chapter summarized the meaning and evolution of the roles of the public in xenotransplantation, and its broader connection to transplantation. These roles have been associated with public support of new technologies, acceptance of potential and potentially unknown risks, better regulation, harmonizing individual and public health, more transparent and legitimate public decisions. These multiple roles have been assessed through a variety of methodological tools, from measuring public attitudes to launching public dialogues.

However, the seemingly big divide among these different approaches in making sense of how people should get involved in xenotransplantation is becoming, at least practically, blurred as these approaches increasingly appear complementary in the actual governance of risks.

A wide convergence exists in thinking that conditions of scientific uncertainty need to be opened up and shared to achieve better "preparedness" in protecting individual and public health as a matter of safety and solidarity as civic commitments.

In highlighting the role of public education on transplants, it has been observed that "(t)he decision of an organ donor is one of the most important and significant behavior of a current world citizen" [8]. From this perspective—even though other medical technology may emerge and result as more viable—transplantation and xenotransplantation similarly show the connection between individual and public health as a civic commitment toward safety and solidarity.

The COVID-19 experience has strengthened this perspective. Current democratic societies can be defined as "democracies of experience". The active search for an improved quality of public decision making has thus moved from theoretical exercises to involve citizens toward the actual experience of deeper meanings of citizenship, requiring collaboration, responsibility, and commitment from and among all parts of the society [85].

References

1. Jasanoff S. Science and democracy. In: Felt U, Fouché R, Miller CA, Smith-Doerr L, editors. The handbook of science and technology studies. 4th ed. Cambridge: MIT Press; 2017. p. 259–88.
2. Lock M, Young A, Cambrosio A, editors. Living and working with the new medical technologies: intersections of inquiry. Cambridge: Cambridge University Press; 2000. (Cambridge Studies in Medical Anthropology).

3. Matesanz R, Dominguez-Gil B, Coll E, de la Rosa G, Marazuela R. Spanish experience as a leading country: what kind of measures were taken? Transpl Int. 2011;24:333–43.
4. Matesanz R, Marazuela R, Coll E, Mahillo B, Dominguez-Gil B. About the opt-out system, live transplantation, and information to the public on organ donation in Spain… Y ole! Letter to the editor. Am J Transplant. 2017;17:1695–6.
5. Chatterjee P, Venkataramani AS, Vijayan A, et al. The effect of state policies on organ donation and transplantation in the United States. JAMA Intern Med. 2015;175(8):1323–9.
6. Vanholder R, Domínguez-Gil B, Busic M, et al. Organ donation and transplantation: a multi-stakeholder call to action. Nat Rev Nephrol. 2021;17:554–68.
7. EP (European Parliament). Organ donation and transplantation facts, figures and European Union action. European Union, 2020. https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649363/EPRS_BRI(2020)649363_EN.pdf.
8. Cantarovich F. The society, the barriers to organ donation and alternatives for a change. In: Tsoulfas G, editor. Organ donation and transplantation-current status and future challenges. London: IntechOpen; 2018. https://www.intechopen.com/chapters/59201.
9. Stevens S. Xenotransplantation. In: Tsoulfas G, editor. Organ donation and transplantation-current status and future challenges. London: IntechOpen; 2018. https://www.intechopen.com/chapters/60883.
10. Weindling P. The origins of informed consent: the International Scientific Commission on medical war crimes, and the Nuremberg Code. Bull Hist Med. 2001;75(1):37–71.
11. Kaiser M. Xenotransplantation–ethical considerations based on human and societal perspectives. Acta Vet Scand. 2004;45:S65. https://doi.org/10.1186/1751-0147-45-S1-S65.
12. Selgelid MJ. Ethics and infectious disease. Bioethics. 2005;19(3):272–89.
13. Francis LP, et al. How infectious diseases got left out – and what this omission might have meant for bioethics. Bioethics. 2005;19(4):307–22.
14. Selgelid MJ, McLean A, Arinaminpathy N, Savulescu J. Infectious disease ethics: limiting liberty in contexts of contagion. Cham: Springer; 2011.
15. Selgelid MJ. Pandethics. Public Health. Special Issue. 2009;123(3):255–9.
16. Fishman JA. SARS, xenotransplantation and bioterrorism: preventing the next epidemic. Am J Transplant. 2003;3:909–12.
17. De Marchi B, Funtowicz S, Ravetz J. Seveso, a paradoxical classic disaster. In: Mitchell JK, editor. The long road to recovery: community responses to industrial disaster. Tokyo-New York-Paris: United Nations University Press; 1996. p. 86–120.
18. Coates JF. Why public participation is essential in technology assessment. Public Adm Rev. 1975;35(1):67–9.
19. Asilomar FDS, Recombinant DNA. The end of the beginning. In: Institute of Medicine Committee to study decision making (Hanna KE, editor). Biomedical politics. Washington: National Academies Press; 1991.
20. EC (European Commission), Communication from the Commission on the precautionary principle, 2000, February 2. Brussels COM (2000)1.
21. United Nations Conference on Environment and Development. Rio Declaration on environment and development. Rio de Janeiro, June 3–14, 1992.
22. FDA (Food and Drug Administration), DHHS (Department of Health and Human Services), PHS (Public Health Services). Draft Public Health Service guidelines for xenotransplantation. Fed Regist. 1996;61(185):49919–32.
23. Nuffield Council on Bioethics. Animal-to-human transplants: the ethics of xenotransplantation. London: Nuffield Council on Bioethics; 1996.
24. Patience C, Takeuchi Y, Weiss RA. Infection of human cells by an endogenous retrovirus of pigs. Nat Med. 1997;3:282–6.
25. Bach FH, Fishman JA, Daniels N, Proimos J, Anderson B, Carpenter CB, et al. Uncertainty in XT: individual benefit versus collective risk. Nat Med. 1998;4:141–4.
26. Bach FH, Fineberg HV. Call for moratorium on xenotransplants. Nature. 1998;391:326.
27. Ivinson AJ, Bach F. The xenotransplantation question: public consultation is an important part of the answer. Can Med Assoc J. 2002;167:42–3.

28. COE (Council of Europe). Recommendation 1399 (1999) on xenotransplantation. Text adopted by the Council of Europe Assembly on 29 January 1999.
29. EEA (European Environment Agency). Late lessons from early warnings: the precautionary principle 1896–2000. Environmental issue report No 22, 2001. https://www.eea.europa.eu/publications/environmental_issue_report_2001_22.
30. PHS (Public Health Service). Guideline on infectious disease issues in xenotransplantation. 2001. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/phs-guideline-infectious-disease-issues-xenotransplantation.
31. Tallacchini M. Risks and rights in xenotransplantation. In: Jasanoff S, editor. Reframing rights. Bioconstitutionalism in the genetic age. Cambridge: MIT Press; 2011. p. 169–92.
32. FDA-CBER (Center for Biologics Evaluation and Research). Source animal, product, preclinical, and clinical issues concerning the use of xenotransplantation products in humans. Guidance for Industry. 2003, updated December 2016. https://www.fda.gov/media/102126/download.
33. COE (Council of Europe). Recommendation (2003)10 of the Committee of Ministers to Member States on xenotransplantation. Adopted by the Committee of Ministers on 19 June 2003.
34. EC (European Commission). Scientific Committee on medicinal products and medical devices. Health & Consumer Protection Directorate General. Opinion on the state- of- the- art concerning xenotransplantation. Doc.SANCO/SCMPMD/2001/0002 Final, 2001. http://ec.europa.eu/health/ph_risk/committees/scmp/documents/out38_en.pdf.
35. CPHA (Canadian Public Health Association). Animal- to- human transplantation: Should Canada proceed? A public consultation on xenotransplantation. 2001.
36. Wynne B. Misunderstood misunderstanding: social identities and public uptake of science. Public Underst Sci. 1992;1(3):281–304.
37. NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. Animal- to- human transplantation research: How should Australia proceed? Response to the 2002 public consultation on draft guidelines and discussion paper on XT. Commonwealth of Australia 2003.
38. NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. Animal- to- human transplantation research: A guide for the community. Public consultation on XT. 2003/04, Commonwealth of Australia 2003.
39. NHMRC (National Health and Medical Research Council). Communiqué from the NHMRC's 154th session 2004.
40. EC (European Communities) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
41. NHMRC (National Health and Medical Research Council). NHMRC statement on xenotransplantation. 2009.
42. Toi te Taiao, The Bioethics Council. The cultural, ethical and spiritual aspects of animal-to-human transplantation. A report on xenotransplantation by Toi te Taiao: The Bioethics Council, New Zealand. Ministry of the Environment 2005.
43. Living Cells Technology Announcement, 'First Patient In Living Cell Technologies' New Zealand DIABECELL® trial drops insulin dose without ill effects. http://www.asx.com.au/asxpdf/20120926/pdf/428z0ty9pjdq55.pdf.
44. Beehive.govt.nz. The official website of the New Zealand government. Living cell technologies trial approved, 2008. October 21. https://www.beehive.govt.nz/release/living-cell-technologies-trial-appoved/.
45. ScienceMedia. Xenotransplantation and the LCT trials in New Zealand, 2009. July 17. https://www.sciencemediacentre.co.nz/2009/07/17/xenotransplantation-and-the-lct-trials-in-new-zealand/.
46. WHO (World Health Organization). Xenotransplantation: guidance on infectious disease prevention and management. WHO/EMC/ZOO/98.1, 1998. http://apps.who.int/iris/bitstream/

handle/10665/65511/WHO_EMC_ZOO_98.1.pdf;jsessionid=952F9963F743E1326D82DD045BF17253?sequence=1.
47. Jones KE, et al. Global trends in emerging infectious diseases. Nature. 2008;451:990–3.
48. Cook P, Kendall G, Michael M, Brown N. Xenotourism and xenotravel: some notes on global regulation. In: Bailey C, Barnett K, editors. Social change in the 21st century conference proceedings. Queensland: Queensland University of Technology; 2005. p. 1–11. https://eprints.qut.edu.au/3449/1/3449.pdf.
49. WHO (World Health Organization). Fifty-seventh World Health Assembly, Agenda Item 12.14, 2004. Resolution 57.18. http://www.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf.
50. WHO (World Health Organization). First WHO global consultation on regulatory requirements for xenotransplantation clinical trials. Changsha, 2008. The Changsha Communiqué. http://www.who.int/transplantation/xeno/ChangshaCommunique.pdf.
51. WHO (World Health Organization). Second WHO global consultation on regulatory requirements for xenotransplantation clinical trials. 2011. http://www.who.int/transplantation/xeno/report2nd_global_consultation_xtx.pdf.
52. Hawthorne WJ, Cowan PJ, Bühler LH, Yi S, Bottino R, Pierson RN, et al. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China December 12–14, 2018. The 2018 Changsha Communiqué. The 10-Year anniversary of the international consultation on xenotransplantation. Xenotransplantation. 2019;26(2):e12513.
53. Nowotny H, Scott PB, Gibbons MT. Re-thinking science: knowledge and the public in an age of uncertainty. London: Wiley; 2001.
54. Funtowicz SO, Ravetz JR. Science for the post-normal age (1993). Common Places. 2020, May 5 (republished with a new foreword). https://commonplace.knowledgefutures.org/pub/6qqfgms5/release/1.
55. Gallup Organization, Inc. The American public's attitudes toward organ donation and transplantation, conducted for the partnership for organ donation. Midlothian: Virginia's Organ Procurement Agency, 1993.
56. Mohacsi PJ, Blumer CE, Quine S, et al. Aversion to xenotransplantation. Nature. 1995;378:434.
57. Mohacsi PJ, Thompson JF, Nicholson JK, et al. Patients' attitudes to xenotransplantation. Lancet. 1997;349:1031.
58. Mohacsi PJ, Thompson JF, Quine S. Attitudes to xenotransplantation: scientific enthusiasm, assumptions and evidence. Ann Transplant. 1998;3:38–45.
59. Cooper DKC. Organ transplants. Nature. 1996;379:578.
60. Ward E. Attitudes to xenotransplantation. Lancet. 1997;349:1775.
61. Michaels M. Publics performing publics: of pigs, pips and politics. Public Underst Sci. 2009;18:617–31.
62. Casabona CR, Jorqui Azofra M, Cozzi E, editors. Scientific, ethical, social and legal aspects of xenotransplantation. Padova: Zampieron; 2012.
63. Sobbrio P, Jorqui M. An overview of the role of society and risk in xenotransplantation. Xenotransplantation. 2014;21(6):523–32.
64. Padilla LA, Hurst DJ, Jang K, Rosales JR, Sorabella RA, Cleveland DC, Dabal RJ, Cooper DK, Carlo WC, Paris W. Racial differences in attitudes to clinical pig organ. Xenotransplantation. 2021;8(2):e12656.
65. Hurst DJ, Padilla L, Cooper D, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684.
66. Burgess J, Stirling A, Clark J, Davies G, Eames M, Staley K, Williamson S. Deliberative mapping: a novel analytic-deliberative methodology to support contested science-policy decisions. Public Underst Sci. 2007;16:299–322.
67. HC & PHAC (Health Canada and the Public Health Agency of Canada). Guidelines on public engagement, Ministry of Health, 2019. https://www.canada.ca/en/health-canada/services/publications/health-system-services/health-canada-public-health-agency-canada-guidelines-public-engagement.html.

68. OGPA (Open Government Partnership Australia), National Action Plan 2020–22 (NAP3), 2020. https://www.opengovpartnership.org/wp-content/uploads/2020/03/OGPs-Implementation-Plan-2020-2022-FINAL.pdf.
69. Holmes B. Citizens' engagement in policymaking and the design of public services, Parliament of Australia, Research Paper 1, 2011–2012, 2011, Canberra: Parliamentary Library. https://www.aph.gov.au/about_parliament/parliamentary_departments/parliamentary_library/pubs/rp/rp1112/12rp01#_Toc299099864.
70. Cowan PJ, Tector AJ. The resurgence of xenotransplantation. Am J Transplant. 2017;17(10):2531–6.
71. Tallacchini M. Medical technologies and EU law: the evolution of regulatory approaches and governance. In: Cremona M, editor. New technologies and EU law. Oxford: Oxford University Press; 2017. p. 9–37.
72. Knoll MF, Cooper DKC, Bottino R. How the COVID-19 pandemic may impact public support for clinical xenotransplantation in the United States? Xenotransplantation. 2020;27(5):e12623. https://doi.org/10.1111/xen.12623.
73. Opriessnig T, Huang Y-W. Coronavirus disease 2019 COVID-19 outbreak: could pigs be vectors for human infections? Xenotransplantation. 2020;27(2):e12591. 2020 03.
74. Montgomery RA. Results of two cases of pig-to-human kidney xenotransplantation. N Engl J Med. 2022;386:1889–98.
75. Porrett PM, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;00:1–17.
76. Jee C. A gene-edited pig's heart has been transplanted into a human for the first time. MIT Technology Review. 2022. https://www.technologyreview.com/2022/01/11/1043374/gene-edited-pigs-heart-transplant.
77. Pierson RN III. Progress toward pig-to-human xenotransplantation. N Engl J Med. 2022;386:1871–3.
78. Parent B, Gelb B, Latham S, Lewis A, Kimberly LL, Caplan AL, (NYU Medical Ethics Working Group on research on the recently deceased). The ethics of testing and research of manufactured organs on brain-dead/recently deceased subjects. J Med Ethics. 2020;46(3):199–204.
79. Caplan A, Kimberly L, Parent B and Schiff T. Here are some questions about the pig heart transplant that people actually should be asking, The Washington Post. 2022. January 14. https://www.washingtonpost.com/opinions/2022/01/14/questions-about-the-pig-heart-transplant.
80. Tallacchini M. Through the lenses of the pandemic: three short reflections on science policy and citizens' rights. Epidemiol Prev. 2020;44(2):341–2.
81. Collins F. Citizen scientists take on the challenge of long-haul COVID-19, NIH Director's blog. 2020. https://directorsblog.nih.gov/2020/09/03/citizen-scientists-take-on-the-challenge-of-long-haul-covid-19.
82. Holdren JP. Memorandun to the Heads of Executive Departments and Agencies, Executive Office of the President Office of Science and Technology Policy, Washington, D.C., 2015.
83. Boucher P, Nascimento S, Tallacchini M. Special issue on: Emerging ICT for citizens' veillance: theoretical and practical insights. Sci Eng Ethics. 2018;24(3):821–1021.
84. Waltner Toews D, Biggeri A, De Marchi B, et al. Post-normal pandemics: why COVID-19 requires a new approach to science. STEPS Center. 2020. https://steps-centre.org/blog/postnormal-pandemicswhy-covid-19-requires-a-new-approach-to-science.
85. Funtowicz S and Ravetz JR, Peer review and quality control. In: Wright J, editor-in-chief. International Encyclopedia of the Social & Behavioral Sciences, 2nd ed, Amsterdam: Elsevier; 2015. p. 680–684.

Xenotransplantation and Clinical Ethics

4

Jordan Potter and Lexi White

Introduction

The practice of xenotransplantation engenders numerous ethical issues that have long been thoroughly covered in the literature. These issues range from xenozoonotic risk and public health ethics [1], to animal rights and the appropriate use of animals for the benefit of humankind [2], all the way to issues surrounding natural law [3] and religious arguments both for and against the practice of xenotransplantation [4]. Most of these ethical issues will be covered elsewhere in this book. However, given the unique nature of xenotransplantation and the fact that it is still a future-oriented concept that is only now seriously gaining prominence as a realistic and practical possibility [5], little has been written regarding clinical ethics issues in xenotransplantation. This chapter will outline some of the major anticipated clinical ethics issues in xenotransplantation as this practice progresses from the purely theoretical, pre-clinical stages to a practical and available clinical therapy.

Background of Clinical Ethics in Xenotransplantation

Clinical ethics (also commonly referred to as medical ethics or healthcare ethics) is a sub-field of the larger field of bioethics that takes a "structured approach to ethical questions in medicine" [6]. The goal of clinical ethics is to "improve the quality of patient care by identifying, analyzing, and attempting to resolve the ethical problems that arise in [clinical and healthcare] practice" [7]. Clinical ethics is then a

J. Potter (✉)
Ethics Program, Community Health Network, Indianapolis, USA
e-mail: jpotter3@ecommunity.com

L. White
Wellstar Health System, Atlanta, USA
e-mail: lexi.white@wellstar.org

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_4

broad field that addresses countless different dilemmas in clinical and healthcare practice, and it is situated at the intersection of many different more specialized areas of applied ethics, such as end of life ethics, organ donation and transplantation ethics, religious bioethics, reproductive ethics, etc. Some common clinical ethics issues include the following: the accuracy of substituted judgment in surrogate medical decision-making; the creation and implementation of advance directives; patient rights to withhold and withdraw life-sustaining treatment; fair and equitable distribution of scarce medical resources; obligations surrounding offering non-beneficial or potentially inappropriate medical treatments; acquiring adequate informed consent to medical treatments; among numerous other issues.

Though there are various methods and approaches to addressing clinical ethics issues, principle-based approaches to clinical ethics are most widely used today, with Beauchamp and Childress' four-principle approach being the most dominant model [8]. A full explanation of this model is outside the scope of this chapter, but briefly this model posits four key ethical principles that serve as an analytic framework for addressing ethical issues within the healthcare environment: the principles of respect for autonomy, beneficence, non-maleficence, and justice. These four principles then serve as a general guide to our moral duties and obligations in healthcare and the clinical environment, with each principle able to be broken down into more specific rules and norms for the clinical environment (e.g., the rule of requiring informed consent for medical treatments from competent patients being derived from the principle of respect for autonomy) [8, pp. 120–121]. The model further suggests that each of the four principles hold equal weight and impose *prima facie* duties, and when these principles and duties conflict, we must pursue a deliberative "process of 'weighing and balancing' competing moral considerations" to determine the most ethically appropriate course of action [9].

While all four of these ethical principles are relevant in one way or another to clinical ethics issues in xenotransplantation, generally clinical ethics issues in xenotransplantation will revolve around the principles of respect for autonomy and justice. This includes some of the more specific derived rules, norms, and practices from these principles, such as informed consent and the equitable allocation of scarce medical resources within healthcare. In the following sections, we will outline some of the main ethical dilemmas revolving around the principles of respect for autonomy and justice that are likely to arise in healthcare and the clinical environment once the practice of xenotransplantation reaches large-scale clinical research trials and eventual clinical practice.

Before delving into these issues, though, we must first note that since we are exclusively focusing on clinical ethics issues in solid organ xenotransplantation, most of this content will be future-oriented and anticipatory, as this practice is still in its infancy and continues to be in the research stage with many unknowns. And when combining this future-oriented context with the broad and encompassing nature of the field of clinical ethics more generally, clinical ethics issues in xenotransplantation are then situated at a strange crossroads between several differing areas of applied ethics (Fig. 4.1). Thus, there is likely to be some overlap between the clinical ethics issues identified below and the remaining chapters of the book that examine these differing areas of applied ethics more closely in the context of xenotransplantation. Finally, note that the

Fig. 4.1 Clinical ethics issues in xenotransplantation and areas of applied ethics

following list is not exhaustive. There are other clinical ethics issues within this space that we do not address here for reasons of space and prioritization, and surely further clinical ethics issues will arise in the future once xenotransplantation is put into actual practice.

Autonomy, Patient Rights, and Informed Consent

Autonomy is an essential ethical principle not only in clinical research, but clinical medical practice. While a complex concept with both positive and negative obligations, the principle of respect for autonomy basically obligates healthcare providers to "acknowledg [e] the value and decision-making rights of autonomous persons and enable[e] them to act autonomously" [8, pp. 101–107]. The notion that a capacitated, competent individual has a right to make decisions about their own body and treatment underpins all medical research and treatment, especially in the United States. To respect the autonomy of individuals, it is essential when providing treatment or enrolling in a research study that the individuals are aware of any aspects of the treatment or study that might affect their decision to participate. Voluntary and informed consent is viewed as essential to maintain the independence and autonomy of both research participants [10] and patients [11].

Right to Withdraw

Grounded in the principle of autonomy and self-determination is the ability to withdraw participation from research. The right to withdraw is a key principle of ethical research and is explicit in the Nuremberg Code [12], Belmont Report [13],

Declaration of Helsinki [14], and the U.S. Code of Federal Regulations [15]. Those participating in clinical research can withdraw at any time, for any reason.

The right to refuse medical treatment is similarly grounded in autonomy but emerged in the United States via litigation well before the Nuremberg Code [16]. Courts in the U.S. as early as 1905 have likened a refusal to honor a patient's autonomy and bodily integrity to assault and battery [17, 18]. Competent individuals have a negative right to refuse medical treatment, even if it will result in their death [19].

However, refusal of treatment is not absolute. While autonomy is a linchpin of American medical ethics, as described above the ethical principle of respect for autonomy must be "weighed and balanced" against other relevant ethical principles, including the principles of beneficence (benefit others) and non-maleficence (do not harm others) when there is a threat to the public beyond the individual. Protecting the public's health from contagious diseases means that in specific situations, individuals may not have complete autonomy over their medical decisions. The United States legal history shows the potential for forced isolation and quarantine or even treatment to protect the public's health in the face of infectious diseases [20, 21].

With xenotransplantation there is concern that animal pathogens, most concerningly viruses, will be transmitted to humans during transplants and will then adapt to human-to-human transmission [22]. These xenozoonoses or xenoses can then spread from xenotransplant recipients into a population. The recent history of extremely infectious and deadly zoonoses emerging from non-human primates, including Marburg virus infection [23], Ebola virus [24], and human immunodeficiency virus (HIV) [25], have raised significant concerns about dangerous xenozoonoses that could spread from a recipient to the community at large.

With xenotransplantation, the most likely animal candidates for regular clinical usage are pigs, due to their availability, fast reproduction, fast maturity, organ size, genetic engineerability, and existing domesticated relationship with humans [26]. Pathogen-free pigs who are selectively bred and reared in strict isolation can reduce the risk of known pathogens like rabies, toxoplasma Gondii, and parvovirus [22]. Despite the ability to control for known zoonotic infections, with pigs there remains a concern about porcine endogenous retroviruses (or PERVs). All vertebrates have endogenous retroviruses in their DNA that cannot be removed. Endogenous retroviruses, including PERVs, rarely cause active infection in the initial species host, but PERVs specifically have been shown to infect human cells in vitro [27]. The concerns for an epidemic infectious disease are particularly acute with retroviruses since HIV is a zoonotic retrovirus (simian immunodeficiency virus) that moved to humans [28], and while recent research has suggested promising results to address the PERVs risk via use of CRISPR/Cas9 [29], there are still many unknowns regarding the true risk of PERVs once xenotransplantation is put into practice.

Given the current unknown potential for PERVs to become a xenozoonoses, there is a strong public health interest in protecting the community from potentially dangerous infectious disease. With the specific risks still very unclear, xenotransplant recipients will likely need consistent, lifelong treatment and monitoring for xenozoonoses [30]. This required treatment and monitoring means that

xenotransplant recipients may lack the ability to withdraw from treatment or monitoring, whether in the context of clinical research study or as a clinical therapy.

With xenotransplantation there are two separate considerations in deciding when it is ethically permissible to override individual autonomy: right to withdraw from medical treatment adherence and the right to withdraw from post-transplant monitoring.

Right to Withdraw from Medical Treatment Adherence

With respect to the right to withdraw from medical treatment adherence, the same balance between individual autonomy and potential risk to the public of xenozoonoses applies. In considering whether medical teams can require xenotransplant recipients to continue to take immunosuppressants and continue to submit to procedures related to their xenotransplant, it is not clear how much, if at all, these measures would reduce risk to the public. Given the desire to preserve patient autonomy, care teams would want to use the least restrictive means necessary to protect those around the patient. In the case of forced treatment following xenotransplantation, the countervailing interest of the medical team and establishment may not be sufficient to outweigh the patient's interest in making their own decisions regarding care. Forced immunosuppressant medication or invasive testing procedures that have unclear benefit to those outside the patient are ethically questionable at best and may even be impermissible depending upon the known facts of the benefits versus burdens and harms.

While a xenotransplant recipient may not be required to take specific medications or submit to medical procedures, that does not mean there will be no restrictions on their behavior. Certain behaviors have the potential to affect public safety. Xenotransplantation patients will likely be unable to donate blood, blood products, sperm, ova, tissues, or even breast milk for the rest of their lives [31]. This prohibition may also extend to the intimate contacts of xenotransplantation recipients. Even further, given the risks healthcare workers who have been exposed to xenotransplant recipient body fluids in a percutaneous manner may also be required to avoid blood and tissue donation [32].

Vaccine mandates for xenotransplant recipients present another complex issue. Currently there remains some debate about whether to require vaccinations for either transplant recipients or transplant donors. Requiring vaccination prior to a transplant hinges largely on the data regarding whether it improves the success of a transplant, and thus maximizes the utility of the allocation of scarce organs [33, 34]. If requiring vaccination does maximize utility in this way, it has been argued by one of us that these kinds of vaccine mandates for transplant recipients are ethically justifiable [35]. A more difficult proposition is whether care teams can require xenotransplant recipients to receive new vaccines for new zoonotic diseases in the future. COVID-19 is a zoonotic virus and is likely not the first highly infectious zoonotic disease that will reach international concern in the next several decades [36]. With xenotransplantation, if there is theoretical potential for recombination of wild

zoonotic disease with xenozoonoses, there could be a risk to the public outside the xenotransplant recipient. While there currently is not research on this potential, if there is an indication that such zoonotic recombination is possible, it may be ethically permissible to require xenotransplant recipients to receive vaccination for zoonotic diseases.

Right to Withdraw from Post-Transplant Monitoring

When considering the right to withdraw from post-transplant monitoring, the balance is again between the autonomy of the patient and the risk to the public. Here, because monitoring is less invasive and provides clear benefit to the public, it seems to be more ethically permissible to require xenotransplant recipients to submit to life-long monitoring for xenozoonoses [37].

Unlike with requiring treatment, requirements for xenozoonoses monitoring offer a clear benefit to the public, along with seemingly fewer burdens and autonomy violations to the patient or research study participant. Continued monitoring of xenotransplant recipients will allow both the care team and the public to be expediently aware of any potential xenozoonoses that could become dangerous to individuals outside the transplant recipient. This need is so great, the U.S. Public Health Service Guidelines abrogate the right to withdraw from monitoring even in death [38]. The guidelines emphasize the need for an autopsy after the death of the recipient, even if the organs have been removed.

Ulysses Contracts

Ulysses contracts are a tool in psychiatry that allow a patient to create an advance directive for future treatment, even in the event of their refusal [39]. Ulysses contracts have been proposed in the context of general medicine in both the treatment of addictive behaviors (such as quitting smoking) or in painful, ongoing, but beneficial procedures such as physical therapy or burn treatment [39]. Spillman and Sade propose Ulysses contracts as a potential analog for future xenotransplantation informed consent documents [37]. They propose that xenotransplantation Ulysses contracts could explicitly create a surveillance schedule and even contain penalties.

There are, however, crucial differences between the use of Ulysses contracts in psychiatric and mental health treatment and the xenotransplantation context. Notably, in the traditional mental health context the Ulysses contract is predicated on the patient losing decision-making capacity. In the case of xenotransplantation there is no assumption that the patient lacks capacity—they are cogently choosing to withdraw cooperation. Even compared to the potential use of a Ulysses contract in the context of medical treatment such as physical therapy or burn treatment, the contract would provide some direct benefit to the patient, even if the results are not immediate. In the case of xenotransplantation, it is not clear there is any direct patient benefit from required monitoring [40].

Risks to Third Parties

Given the risks of xenozoonoses, xenotransplantation does pose a risk to third parties interacting with xenotransplant recipients in a way that allotransplantation does not. This additional xenozoonoses risk again shifts the balance of the autonomy interest of the xenotransplant recipient in privacy and the risk to third parties of novel infection [37].

In the United States, we already recognize an ethical and legal prerogative to require disclosure of HIV status. Twenty-four states legally require disclosure to sexual partners and 14 require disclosure to needle-sharing partners [41]. As of 2021, knowingly exposing another individual to HIV is even criminalized in 35 states [42]. Similarly, xenotransplantation presents a public health risk. Due to the increased risk of xenozoonoses, it may be ethically permissible—if not obligatory—to require xenotransplant recipients to inform their sexual partners and close contacts of the potential for xenozoonoses. There remain additional questions as to whether the risk of xenozoonoses so extends beyond the immediate patient that we should require not only notification, but consent and behavioral modification from household contacts of xenotransplant recipients.

It is already standard practice to consider psychosocial factors, including family support, in allotransplantation [43]. The clinical ethics consultation team at Loyola University Health System recently recommended COVID-19 vaccination be a requirement for the support person and eligible family members of an allotransplant recipient [44]. However, family compliance with considerations such as vaccination or lifestyle changes generally affects eligibility and priority for transplantation and is hardly enforceable after the transplant is complete. Given the unclear risks to the public, it might be ethically permissible to require long-term household members of xenotransplant recipients to submit to long-term monitoring for xenozoonoses.

Enforcement of Treatment and or Monitoring

Practically, enforcing these requirements is extremely difficult. Forcing a patient to continue to receive treatment or continue to take medication is practically impossible. Any enforcement would require significant autonomy violations that would likely cause substantial harm to the person. However, risks of potential xenozoonoses are unclear and the harm to the community may be substantial without such enforcement.

McConnell suggests that the law itself can be changed to authorize public health surveillance of xenotransplant recipients [43]. As Florencio and Ramathan point out, generally applicable public health law provisions are insufficient to allow for sufficient surveillance of xenotransplantation recipients [45]. Even the expanded Model State Emergency Health Powers Act, which at one point had provisions enacted in 35 states [46], require imminent threat of an infectious agent and thus would likely not be triggerable until there was a significant problem. Even further, in response to the most recent COVID-19 pandemic, 15 states have proposed, and 9

states have enacted bills or ballot measures that curb public health authority even in response to an imminent threat [47, 48]. Leaving surveillance on potentially dangerous xenozoonoses exclusively to public health authorities after the fact might prove unwise.

The Centers for Disease Control and Prevention recommends states enact laws that facilitate mandatory treatment and direct observed therapy for tuberculosis [49]. Tuberculosis, however, has known infectious capabilities and is treatable and curable, thus meaning any forced interventions are time limited. Similar legal support for requiring HIV/AIDS treatment has not received the same ethical or legal support [50]. Given that the current risks of xenozoonoses from xenotransplantation are largely theoretical and not actualized, it is unlikely that jurisdictions in the United States would actively force xenotransplant recipients to receive treatment or even enforce monitoring mandates.

Practical Considerations in Providing Informed Consent for Xenotransplantation

The actual provision of informed consent for xenotransplantation also has many ethical considerations. Myths and misconceptions associated with organ donation and brain death are already prevalent [50]. Many people outside of healthcare have a poor understanding of what constitutes brain death and organ donation from brain-dead, heart-beating donors [51]. Xenotransplantation, which involves complicated science, a very fraught intersection of religious ethics, animal rights, research ethics, and clinical ethics, and even some "fantastical" elements, is likely to exacerbate many of these myths and misconceptions and be even more confusing for patients.

Part of informed consent for xenotransplantation will require informing patients they have the potential to become a public health risk. This information extends beyond the clear communication that the patient, and perhaps their household members, will have to submit to life-long monitoring. Consenting physicians must also communicate regarding the emotional weight of potentially being a patient zero for an outbreak. Additionally, given the life-saving nature of the procedure it is difficult to ensure that patients are not pressured by circumstances to agree to any available option. When the choice for patients is between death and an alternative, it is not clear patients will be able to process the potential changes to their quality-of-life following xenotransplantation.

Pediatric Contexts

Given the above considerations, it is especially difficult to tease out whether it would be ethical to allow pediatric populations to receive xenotransplants [52]. While United States laws allow parents to consent to procedures for their minor children, the indefinite monitoring as well as disclosure requirements associated with xenotransplantation present significant ethical concerns. Committing a

pediatric patient to lifelong commitments related to xenotransplantation is questionable without the ability of the child to clearly assent. Parents do regularly make irreversible medical decisions for their children, and in this case the need for viable organs is even greater given the extremely limited supply of pediatric organs. Pediatric considerations will be discussed in more depth in a later chapter.

Justice, Equity, and the Allocation of Scarce Medical Resources

Though integral for clinical ethics, of the four principles the principle of justice is the most difficult to define and delineate. While Beauchamp and Childress posit a "formal" principle of justice—the Aristotelian "treat equals equally and unequals unequally"—they note that this principle is "formal" because "it identifies no particular respects in which equals ought to be treated equally and provides no criteria for determining whether two or more individuals are in fact equals" [8, pp. 249–251]. Justice, then, requires additional "material" principles to provide substance and content to the "formal" principle of justice, to which Beauchamp and Childress take a more pluralistic approach identifying six different, competing "material" principles to offer substantive accounts of justice in action [9].

A full account of Beauchamp and Childress' conception of justice is outside the scope of this chapter. What is relevant to our conversation is their focus on distributive justice as a central component of the principle of justice in bioethics, which they define as referring "to fair, equitable, and appropriate distribution of benefits and burdens determined by norms that structure the term of social cooperation" [8, p. 250]. In healthcare, especially organ transplantation [53], the concept of distributive justice is best represented by the strong focus on ensuring equitable access and allocation of scarce medical resources [8, pp. 279–292]. The practice of xenotransplantation is then likely to raise several ethical concerns regarding equitable access and allocation of scarce medical resources.

Allocation of Xenografts

The allocation of organs for allotransplantation in the U.S. is a complex process, and the process differs between transplants from living and deceased donors. For transplants from living organ donation, virtually the entire process is handled at individual transplant centers, dependent upon whether the living organ donation is directed, non-directed, or part of the paired kidney donation program [54]. Transplants from deceased organ donors are slightly more complicated. Individual transplant centers serve as the first line of access to the organ waiting list, as they evaluate and select prospective transplant recipients who are referred or apply to be on their program's transplant waiting list. These centers use both medical and non-medical criteria—e.g., life expectancy, potentially injurious behavior, adherence, social support, etc.—to determine whether the applicant is a good candidate to be on their center's transplant waiting list [55]. Those who are accepted into the

transplant center's waiting list are then entered into a system managed by the United Network for Organ Sharing (UNOS) and local Organ Procurement Organizations (OPOs), which uses an algorithm to match organs from deceased donors to those on transplant center waiting lists. These determinations for organ allocation are based on various set criteria that slightly differ for each organ, such as histocompatibility, medical urgency, survival benefit, geography and distance from hospital, etc. [56].

It is unclear how xenotransplantation access and allocation will be structured in the U.S. Likely it will be structured similarly to transplants from living organ donors where individual transplant centers will administrate most of the process, and it will probably be those transplant centers that have separate xenotransplantation programs that engage in this practice, at least initially. This leads to several ethical concerns. More generally, concerns have already been raised regarding bias in transplant referrals and transplant center evaluations [57, 58], manipulating waitlist priority [59, 60], and other access barriers to transplant center services [61]. More specifically to xenotransplantation, treating xenotransplantation allocation like transplants from living organ donors could lead to further equity and fairness issues around geographical disparities that are already rampant in our system [62]. Every transplant center is unlikely to be involved with xenotransplantation due to lack of resources or expertise, especially in its infancy. This will limit the areas of the country with access to xenotransplantation, leaving residents in those areas to rely solely on the current allotransplantation system that is burdened by supply and demand issues. Further, this might also unfairly benefit more affluent Americans who have the means and ability to pursue listing at distant transplant centers—or multiple centers—with xenotransplantation capabilities that average Americans do not have the means to pursue.

Determining who receives an allotransplant versus an xenotransplant is another complex ethical and practical issue in the allocation of xenografts. If xenotransplantation is administered by individual transplant centers, xenotransplants are likely to be allocated to recipients similarly to how non-directed living donors are, with the transplant center generally controlling the recipient selection process from those on their center's waiting list [63]. However, this raises concerns about what criteria these transplant centers might use to determine who receives an allotransplant versus an xenotransplant. It may be that transplant centers will have differing waiting lists or referral/application processes for xenotransplants and allotransplants where prospective recipients can pursue one type of transplant or the other—or potentially apply for both types to increase their chances. But this still raises the question about what criteria transplant centers will use to determine access to xenotransplantation itself. This is especially true given the likely significant differences between xenotransplants and allotransplants in graft failure, rejection, and success, let alone the significantly higher burdens and risks that xenotransplants may hold for the recipient and their close contacts as described in the previous section. And if these criteria are left to individual transplant centers to develop, this could lead to substantial differences in these evaluation criteria across transplant centers, which may create inequity in access and evaluation processes.

In an alternative model, xenotransplantation could be treated similarly to allotransplantation from deceased organ donors where transplant centers, UNOS, and the local OPO are all involved in the allocation process. Similar to when an organ becomes available from a brain-dead donor and UNOS and the local OPO determine an appropriate match from the waiting list at local or regional transplant centers, when xenografts become available it may be that the local OPO makes the offer to the next match on the waiting list. Beyond the obvious issues for informed consent that this model would entail for those on the waiting list given the differing benefits, burdens, and risks between xenotransplantation and allotransplantation, this raises the question of whether waiting list recipients and transplant centers would retain the right to refuse an xenotransplant offer (or vice versa) for the reasons of preferring an allotransplant.

Currently, individuals on the waiting list and even transplant teams themselves retain the right to refuse an organ offer per the ethical principle of respect for persons (autonomy), which generally occurs when there are concerns about quality of the organ or infectious disease transmission [59, 64]. Yet given the potential differences in benefits, burdens, and risks between xenotransplantation and allotransplantation, it may be that one type of transplantation is greatly preferred by patients on waiting lists or even transplant teams, which could lead to unequal distribution and continued supply and demand issues if left unchecked. Further, there are likely to be religious and philosophical objections (e.g., those practicing veganism or vegetarianism [65]) to xenotransplantation that will prompt xenograft offer refusals under such a model. Clearly, then, there are multiple practical, logistical, and ethical issues in the allocation of xenografts that will need to be addressed prior to putting xenotransplantation into widespread practice.

Xenotransplant Failure, Relisting, and Retransplantation

Another ethical issue in xenotransplantation allocation arises when a xenotransplant fails and the patient or participant seeks retransplantation, i.e., a second organ transplant whether from an allograft or xenograft. Already a controversial and complex issue in its own right [66, 67], retransplantation in cases of xenotransplant failure engenders additional questions and complexity. These additional questions arise in both the clinical and therapeutic contexts.

For both participants in xenotransplantation clinical research trials and eventually those patients who receive a therapeutic xenotransplant, there are questions regarding these individuals' status for retransplantation upon xenotransplant failure. Are these participants and patients required to continue down the path of re-xenotransplantation, or are they eligible to be considered for retransplantation with an allograft after xenotransplant failure? Further, how does the fact that they are seeking retransplantation affect their priority on the waiting list? Currently, the presence of a previous transplant is generally not an explicit factor or contraindication in consideration for transplant candidacy and organ allocation, though other related medical and non-medical factors—such as likely survival and mortality outcomes after retransplantation and

patient adherence to post-transplant protocols after the first transplant—are utilized as factors for consideration of candidacy and allocation [68]. Obviously, no data are yet known about retransplantation outcomes after xenotransplant failure, so more deliberation and data are needed to effectively address these questions.

An additional ethical question for xenotransplantation clinical research trial participants involves the experimental nature of their xenotransplant and any afforded protections for these participants in the event of failure. It may be argued that these xenotransplantation research trial participants should have the opportunity to remain on their respective organ transplant waiting list in case of xenotransplant failure. This could be ethically justified as additional protection of research participants given their sacrifices to benefit medical research and society more generally. However, as stated above no data currently exist to suggest possible outcomes or likely benefits of retransplantation after xenotransplant failure, which should ultimately be the primary deciding factor in these deliberations.

Expanded Access

The most significant benefit to pursuing xenotransplantation is the dramatic increase in viable organs for transplantation that this practice would entail, meaning more patients would receive the life-saving organs that they need. However, because currently the demand for organs for transplantation drastically outweighs the available supply, there are strict criteria—both medical and non-medical—that are used for transplant evaluations and access to the waiting list to maximize the probability of benefit and success of the transplant [59, 62]. This means that many people who seek access to transplants each year are denied due to not being considered good candidates, and this problem is also complicated by federal transplant standards aimed at increasing surgical and mortality outcomes post-transplant that can lead to organ waste and more waiting list deaths [69]. Further, some classes of patients, such as the developmentally disabled, have been historically excluded from organ transplant activities due to concerns about adherence to post-transplant treatment, questions about quality of life, and perceived lack of benefit, among other issues, though this is now starting to change across the country [70, 71].

When xenotransplantation is then put into regular practice and the overall supply of organs begins to better meet the demand, the complex ethical question of how to expand access to transplant services will arise given the likely relaxing of transplant recipient selection criteria [72]. Ideally, the practice of xenotransplantation—in conjunction with other advances in organ donation and transplantation—would be able to immediately meet the needs of the transplant community with enough viable organs for transplantation for everyone in need. Realistically, though, the introduction of xenotransplantation is likely (and appropriately) going to be slow and methodical, meaning any expanding of access to transplant services will also be slow. This will raise complex ethical questions for transplant centers looking to expand access to their transplant services, as there are many types of individuals and social groups that could potentially benefit from expanded access.

The most obvious individuals that could benefit from expanded access to xenotransplantation are the current marginal transplant candidates, who would benefit from a transplant but are not considered a good candidate due to other medical reasons, such as having other major comorbidities. There are also the marginal transplant candidates who would benefit from a transplant but are not good candidates due to non-medical reasons, such as limited social or financial support, psychiatric or developmental delays, questionable adherence to medical recommendations, or other psychosocial barriers to transplant. Another group are those who would benefit from an early transplant but have other means of maintaining their organ failure until they reach a certain clinical deterioration status or time on the waiting list. In particular, those with End Stage Renal Disease (ESRD) show much better transplant outcomes with early, preemptive kidney transplantation before spending time on dialysis [73], but it is unclear how to weigh this group versus groups like the marginal transplant candidates. Finally, some transplant centers may look to expand access to historically marginalized groups like racial and ethnic minorities or those with lower socioeconomic status where structural injustice may have contributed to their need for organ transplant. How to weigh and analyze expanding transplant access to these groups is a complex ethical dilemma that requires further deliberation.

Fair and Equitable Access to Xenotransplantation

One final ethical issue to highlight is the concern surrounding fair and equitable access to xenotransplantation, especially given the fact that the act of undergoing a transplant is an expensive process for both the insured and uninsured alike [74]. As discussed above, because transplantable organs are a vitally important scarce healthcare resource and allotransplantation requires specific resources both pre- and post-transplant, non-medical criteria such as financial and social support are critical factors that are considered during transplant candidacy evaluations. This leads to serious ethical concerns regarding equitable access to transplant services [75, 76]. Several studies have already found that access to transplant waiting lists is associated with socioeconomic status, specifically finding that those with public insurance and an annual household income of less than $25,000 were more likely to be excluded from the transplant waiting list [77]. Other studies have found similar results with those transplant evaluation candidates holding private insurance having more access to transplant services and likelihood of being admitted to the transplant waiting list [78].

This current ethical concern is even more pressing when considering the practice of xenotransplantation, which is likely to be more expensive than standard allotransplantation given the added component of the creation and development of the xenograft. This could exacerbate issues with fair and equitable access to transplant services, particularly for minority patients who are more likely to have a lower socioeconomic status and already deal with other health disparities related to their racial and ethnic identities [79]. This long history of health disparities in these

populations—both minorities and those of lower socioeconomic status—have led some authors to question the development of xenotransplantation, given concerns that xenotransplantation may just further exacerbate health disparities in these populations (https://bioethicstoday.org/blog/we-asked-for-racial-equity-and-they-gave-us-pig-hearts/#). And while this concern may be premature given the fact that xenotransplantation could substantially increase the supply of available organs for transplant—thereby likely increasing access to transplant services for all patients—the history and current status of inequitable access to transplant services makes this concern plausible.

Equity in healthcare is defined as "the absence of socially unjust or unfair health disparities" [80]. Currently, the practice of organ transplantation in the U.S. does not seem to fully meet the criteria to be labeled a just and equitable healthcare service given some of the unjust disparities in access to transplant services detailed above. The practice of xenotransplantation could potentially further exacerbate these access issues given its likely cost. If as a society we value the concept of justice and equity in healthcare, special care and attention will need to be paid to these current and future concerns about equity in access to xenotransplantation, making this one of the most pressing clinical ethics concerns associated with the future practice of xenotransplantation.

Conclusion

To conclude, there are numerous clinical ethics issues revolving around the practice of xenotransplantation that must be considered and addressed as this practice starts its eventual transition into clinical research trials and standard clinical practice. These issues are wide-ranging, spanning from questions surrounding autonomy, informed consent, and risk to third parties to concerns involving the concepts of allocation and just and equitable access to xenotransplantation. While the practice of xenotransplantation holds great promise for the future of organ transplantation, thoughtfully exploring and addressing these ethical questions will be paramount to ethically and effectively practicing xenotransplantation in the clinical environment.

Acknowledgement The authors would like to thank Erica Ronning for completing a literature review that was integral to the completion of this chapter.

References

1. Sparrow R. Xenotransplantation, consent and international justice. Dev World Bioeth. 2009;9(3):119–27.
2. Mani V, Ryan M. Xenotransplantation: animal rights and human wrongs. Ethics Med. 2003;19(1):55–61.
3. Reiss MJ. The ethics of xenotransplantation. J Appl Philos. 2000;17(3):253–62.
4. Paris W, Seidler RJ, FitzGerald K, Padela AI, Cozzi E, Cooper DK. Jewish, Christian and Muslim theological perspectives about xenotransplantation. Xenotransplantation. 2018;25(3):e12400.

5. Reardon S. First pig-to-human heart transplant: what can scientists learn? Nature. 2022;601(7893):305–6. https://www.nature.com/articles/d41586-022-00111-9
6. Jonsen AR, Siegler M, Winslade WJ. Clinical ethics: a practical approach to ethical decisions in clinical medicine. 8th ed. New York: McGraw-Hill Education; 2015. p. 1–2.
7. Singer PA, Pellegrino ED, Siegler M. Clinical ethics revisited. BMC Med Ethics. 2001;2(1):1–8.
8. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th ed. New York: Oxford University Press; 2013.
9. Moskop JC. Ethics and health care: an introduction. Cambridge University Press; 2016. p. 30–4.
10. Barker JH, Polcrack L. Scientific contribution: respect for persons, informed consent and the assessment of infectious disease risks in xenotransplantation. Med Health Care Philos. 2001;4(1):53–70.
11. Capron A. Informed consent in catastrophic disease research and treatment. Univ Pa Law Rev. 1974;123:340–438.
12. Annas GJ, Grodin MA. The Nazi doctors and the Nuremberg code. New York: Oxford University Press; 1992.
13. Department of Health Education and Welfare. The Belmont Report Office of the Secretary Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979.
14. World Medical Association. WMA declaration of Helsinki—ethical principles for medical research involving human subjects. 1964. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
15. General requirements for informed consent in human subjects research. U.S. Code of Federal Regulations. 45 CFR 46.116(a)(8).
16. Bazzano LA, Durant J, Brantley PR. A modern history of informed consent and the role of key information. Ochsner J. 2021;21(1):81–5.
17. Mohr v Williams . (1905) 95 Minn 261, 104 NW 12.
18. Schloendorff v. Society of New York Hospital. (1914) 211 N.Y. 125, 129–30, 105 N.E. 92, 93.
19. Cruzan v. Director Missouri Dept of Health. (1990) 497 U.S. 261.
20. Gostin LO, editor. Public health law & ethics. 2nd ed. University of California Press; 2010. p. 50–75.
21. City of New York v. Antoinette R. (1995) 630 N.Y.S. 2d 1008.
22. Boneva RS, Folks TM. Xenotransplantation and risks of zoonotic infections. Ann Med. 2004;36(7):504–17.
23. Malherbe H, Stickland-Cholmley M. Human disease from monkeys (Marburg virus). Lancet. 1968;1(7557):1434.
24. Jacob ST, Crozier I, Fischer WA, Hewlett A, Kraft CS, de la Vega MA, Soka MJ, Wahl V, Griffiths A, Bollinger L, Kuhn JH. Ebola virus disease. Nat Rev Dis Primers. 2020;6(1):13. https://doi.org/10.1038/s41572-020-0147-3.
25. Hillis DM. Origins of HIV. Science. 2000;288:1757–9.
26. Daar A. Ethics of xenotransplantation: animal issues, consent, and likely transformation of transplant ethics. World J Surg. 1997;21(9):975–82.
27. Denner J, Scobie L, Schuurman HJ. Is it currently possible to evaluate the risk posed by PERVs for clinical xenotransplantation? Xenotransplantation. 2018;25(4):e12403.
28. Denner J, Tönjes RR. Infection barriers to successful xenotransplantation focusing on porcine endogenous retroviruses. Clin Microbiol Rev. 2012;25(2):318–43.
29. Niu D, Wei HJ, Lin L, George H, Wang T, Lee IH, Zhao HY, Wang Y, Kan Y, Shrock E, Lesha E. Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9. Science. 2017;357(6357):1303–7.
30. U.S. Department of Health and Human Services. PHS guideline on infectious disease issues in xenotransplantation. 2001.
31. U.S. Department of Health and Human Services, Food and Drug Administration, & Center for Biologics Evaluation and Research. Source animal, product, preclinical, and clinical issues

concerning the use of xenotransplantation products in humans; guidance for industry. 2016. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
32. U.S. Department of Health and Human Services, Food and Drug Administration, & Center for Biologics Evaluation and Research. Guidance for industry precautionary measures to reduce the possible risk of transmission of zoonoses by blood and blood products from xenotransplantation product recipients and their intimate contacts DRAFT GUIDANCE. 2002. http://www.fda.gov/cber/guidelines.htm
33. Hippen BE. Mandating COVID-19 vaccination prior to kidney transplantation in the United States: no solutions, only decisions. Am J Transplant. 2022;22(2):381–5.
34. Hippen BE, Axelrod DA, Maher K, Li R, Kumar D, Caliskan Y, Alhamad T, Schnitzler M, Lentine KL. Survey of current transplant center practices regarding COVID-19 vaccine mandates in the United States. Am J Transplant. 2022;00:1–9.
35. Hurst DJ, Potter J, Padilla LA. Organ transplant and covid-19 vaccination: considering the ethics of denying transplant to unvaccinated patients. Clin Transpl. 2022;36(5):e14589.
36. Centers for Disease Control and Prevention. Importance of one health for covid-19 and future pandemics. 2021. https://www.cdc.gov/media/releases/2021/s1103-one-health.html
37. Spillman MA, Sade RM. Clinical trials of xenotransplantation: waiver of the right to withdraw from a clinical trial should be required. J Law Med Ethics. 2007;35:265–71.
38. Center for Biologics Evaluation and Research, Food and Drug Administration, Health Resources and Services Administration, National Institutes of Health, National Center for Infectious Diseases, Centers for Disease Control and Prevention, & Assistant Secretary for Planning and Evaluation Office of the Secretary Department of Health and Human Services. U.S. public health service guideline on infectious disease issues in xenotransplantation. MMWR. 2001;50(RR15):1–46. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5015a1.htm
39. Spellecy R. Reviving Ulysses contracts. Kennedy Inst Ethics J. 2003;13(4):373–92.
40. McConnell T. The inalienable right to withdraw from research. J Law Med Ethics. 2010;38(4):840–6.
41. Lehman JS, Carr MH, Nichol AJ, Ruisanchez A, Knight DW, Langford AE, Gray SC, Mermin JH. Prevalence and public health implications of state laws that criminalize potential HIV exposure in the United States. AIDS Behav. 2014;18(6):997–1006.
42. Centers for Disease Control and Prevention. HIV and std criminalization laws. 2021. https://www.cdc.gov/hiv/policies/law/states/exposure.html
43. Maldonado JR. Why it is important to consider social support when assessing organ transplant candidates? Am J Bioeth. 2019;19(11):1–8.
44. Kuczewski M, Wasson K, Hutchison PJ, Dilling DF. Putting ethics and clinical decision making before politics: requiring COVID-19 immunization for Solid Organ Transplantation (SOT) candidates and their support team. J Heart Lung Transplant. 2022;41(1):17–9.
45. Florencio PS, Ramanathan ED. Legal enforcement of xenotransplantation public health safeguards. J Law Med Ethics. 2004;32:117–21.
46. Orenstein DG, White LC, Weidenaar K, Hodge JG. Emergency declaration authorities across all states and D.C. In: The network for public health law; 2015. https://www.networkforphl.org/wp-content/uploads/2020/01/Emergency-Declaration-Authorities.pdf.
47. The Network for Public Health Law, & National Association of County and City Health Officials. Proposed limits on public health authority: dangerous for public health. 2021; https://www.networkforphl.org/resources/proposed-limits-on-public-health-authority-dangerous-for-public-health-3/
48. Changes to state emergency power laws in response to the coronavirus (COVID-19) pandemic, 2020-2022. Ballotpedia. https://ballotpedia.org/Changes_to_state_emergency_power_laws_in_response_to_the_coronavirus_(COVID-19)_pandemic,_2020-2022. Accessed 23 Mar 2022.
49. Thombley ML, Stier DD. Menu of suggested provisions for state tuberculosis prevention and control laws. 2010. https://www.cdc.gov/tb/programs/laws/menu/tblawmenu.pdf

50. U.S. Department of Health and Human Services. National survey of organ donation attitudes and practices, 2019. Report of findings. Feb 2020. https://www.organdonor.gov/sites/default/files/organ-donor/professional/grants-research/nsodap-organ-donation-survey-2019.pdf
51. Shah SK, Kasper K, Miller FG. A narrative review of the empirical evidence on public attitudes on brain death and vital organ transplantation: the need for better data to inform policy. J Med Ethics. 2015;41(4):291–6.
52. Hurst DJ, Padilla LA, Walters W, Hunter JM, Cooper DKC, Eckhoff DM, Cleveland D, Paris W. Paediatric xenotransplantation clinical trials and the right to withdraw. J Med Ethics. 2020;36:311–5.
53. U.S. Department of Health and Human Services. Ethical principles in the allocation of human organs. Cited March 31, 2022. https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/#:~:text=Utility%2C%20justice%2C%20and%20respect%20for,of%20scarce%20organs%20for%20transplantation
54. UNOS. Living donation. Cited March 31, 2022. https://unos.org/transplant/living-donation/
55. U.S. Department of Health and Human Services. General considerations in assessment for transplant candidacy. Cited March 31, 2022. https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/general-considerations-in-assessment-for-transplant-candidacy/
56. UNOS. How we match organs. Cited March 31, 2022. https://unos.org/transplant/how-we-match-organs/
57. Roberts GV. Understanding my racial heritage—thanks, ancestry.com—could have gotten me a kidney transplant earlier. STAT News; 2021. https://www.statnews.com/2021/11/01/kidney-disease-ancestry-dot-com-transplant/
58. Lai JC, Pomfret EA, Verna EC. Implicit bias and the gender inequity in liver transplantation. Am J Transplant. 2022;00:1–4.
59. U.S. Department of Health and Human Services. Manipulation of the organ allocation system waitlist priority through the escalation of medical therapies. Cited March 31, 2022. https://optn.transplant.hrsa.gov/media/2500/ethics_whitepaper_201806.pdf
60. Khazanie P, Drazner MH. The blurred line between gaming and patient advocacy. Circulation. 2019;140(25):2048–50.
61. Bearl DW. Ethical issues in access, listing and regulation of pediatric heart transplantation. Transl Pediatr. 2019;8(4):278–83.
62. Salvalaggio PR. Geographic disparities in transplantation. Curr Opin Organ Transplant. 2021;26(5):547–53.
63. U.S. Department of Health and Human Services. Living non-directed organ donation. Cited March 31, 2022. https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/living-non-directed-organ-donation/
64. Husain SA, King KL, Pastan S, Patzer RE, Cohen DJ, Radhakrishnan J, Mohan S. Association between declined offers of deceased donor kidney allograft and outcomes in kidney transplant candidates. JAMA Netw Open. 2019;2(8):e1910312.
65. Fraux C, Sastre MT, Kpanake L, Sorum PC, Mullet E. French people's views regarding xenotransplantation. Transplant Proc. 2021;53(2):529–38.
66. Ubel PA, Arnold RM, Caplan AL. Rationing failure: the ethical lessons of the retransplantation of scarce vital organs. JAMA. 1993;270(20):2469–74.
67. Andrews TD. Restarting the clock… again: ethical considerations in retransplantation. Dimens Crit Care Nurs. 2009;28(5):209–13.
68. National Health and Medical Research Council. Ethical guidelines for organ transplantation from deceased donors. https://www.nhmrc.gov.au/sites/default/files/images/nhmrc-ethical-guidelines-organ-transplant.pdf. Accessed 5 Apr 2022.
69. Ross C. Hospitals are throwing out organs and denying transplants to meet federal standards. PBS; 2016. https://www.pbs.org/newshour/health/hospitals-throwing-organs-denying-transplants-meet-federal-standards
70. Reardon S. Push is on for states to ban organ transplant discrimination. NBC News; 2021. https://www.nbcnews.com/health/health-news/push-states-ban-organ-transplant-discrimination-n1259662

71. Ross LF. Ethics of organ transplantation in persons with intellectual disability. J Pediatr. 2021;235:6–9.
72. Sykes M, d'Apice A, Sandrin M. Position paper of the ethics committee of the international xenotransplantation association. Xenotransplantation. 2003;10(3):195.
73. Gourlay W. Preemptive kidney transplantation: what's the hold up? Transplantation. 2018;102(7):1035.
74. Jesse MT, Abouljoud M, Goldstein ED, Rebhan N, Ho CX, Macaulay T, Bebanic M, Shkokani L, Moonka D, Yoshida A. Racial disparities in patient selection for liver transplantation: an ongoing challenge. Clin Transpl. 2019;33(11):e13714.
75. Wadhwani SI, Lai JC, Gottlieb LM. Medical need, financial resources, and transplant accessibility. JAMA. 2022; https://jamanetwork.com/journals/jama/article-abstract/2790858
76. Laurentine KA, Bramstedt KA. Too poor for transplant: finance and insurance issues in transplant ethics. Prog Transplant. 2010;20(2):178–85.
77. Ng YH, Pankratz VS, Leyva Y, Ford CG, Pleis JR, Kendall K, Croswell E, Dew MA, Shapiro R, Switzer GE, Unruh ML. Does racial disparity in kidney transplant wait-listing persist after accounting for social determinants of health? Transplantation. 2020;104(7):1445.
78. Patzer RE, Perryman JP, Schrager JD, Pastan S, Amaral S, Gazmararian JA, Klein M, Kutner N, McClellan WM. The role of race and poverty on steps to kidney transplantation in the southeastern United States. Am J Transplant. 2012;12(2):358–68.
79. Williams DR, Priest N, Anderson NB. Understanding associations among race, socioeconomic status, and health: patterns and prospects. Health Psychol. 2016;35(4):407–11.
80. Braveman P, Gruskin S. Defining equity in health. J Epidemiol Community Health. 2003;57(4):254–8.

Xenotransplantation and Pediatric Ethics Issues

5

Luz Padilla, Kathryn Maxwell, and Daniel J. Hurst

Introduction

In 1984, an infant with hypoplastic left heart syndrome would become the first infant to receive a xenograft—a baboon heart. "Baby Fae," as the infant was known, would die 21 days after the transplant of heart failure from her body's immune system rejecting the xenograft. The Baby Fae event would prove to be a landmark in the field of xenotransplantation (XTx) and would spur a flurry of writings on the ethics of XTx, including pediatric XTx and experimental therapies in a pediatric population. To date, Baby Fae is the only known pediatric recipient of a cardiac xenograft.

XTx, which has since the time of Baby Fae moved to a pig model, has been proposed as a potential therapy in children to help alleviate the critical organ shortage that exists. Currently, nearly 2000 children in the United States (US) are on an organ transplant waiting list.[1] For children under the age of 1, the majority of patients on the waitlist are in need of a heart or liver. For children between 1 and 18, most are waiting for a kidney.

[1] https://www.donatelife.net/wp-content/uploads/2016/06/2021-NPTW-Donation-and-Transplantation-Statistics-FINAL-3.4.21.pdf.

L. Padilla
Department of Epidemiology and Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA

Department of Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: lpadilla@uabmc.edu

K. Maxwell
Department of Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: ksmaxwell@uabmc.edu

D. J. Hurst (✉)
Department of Family Medicine, Rowan-Virtua School of Osteopathic Medicine, Stratford, NJ, USA
e-mail: hurst@rowan.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_5

Some commentators have proposed that initial clinical trials of XTx will focus on adult kidney xenografts, with pediatric cardiac transplants for children with congenital heart disease (CHD) not too far behind [1]. Ethical concerns arise in the pediatric population in regard to XTx due to the potential of performing experimental therapeutic research in this population without having first conducted trials in an adult population, which is not recommended by governing bodies such as the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO). XTx may not be as needed for adults with heart failure as there are other clinical alternatives that currently hold longer survival than pig xenografts, however these clinical alternatives have poor outcomes in pediatric patients with CHD. Therefore, testing XTx in adults before children would seem infeasible and pose ethical issues. While this is an issue in any medical intervention involving children, XTx represents a special case. In XTx, it has been proposed that recipients of a xenograft should be monitored for the remainder of their life to ensure they have not acquired a xenozoonotic infection. This chapter will explore these challenges of advancing XTx—particularly heart xenografts—in the pediatric population as clinical trials are likely to begin soon after adult kidney xenograft clinical trials. We will attempt at providing some solutions to the issues we have identified.

Informed Consent

Informed consent (IC) is considered one of the most important elements of research. While IC is much more than a document, it does oftentimes, especially in the research context, result in a document that a research subject and/or their surrogate must agree to and then sign. The IC document is a tool meant to inform the potential subject of all the activities they would have to undergo in order to participate, as well as the risks and benefits associated with participation [2]. In the United States (US), IC documents are reviewed and approved by institutional review boards (IRBs) and can vary, but all must contain and address the minimum required elements established by the US Department of Health and Human Services (HHS) under Title 45 Code of Federal Regulations part 46 [3]. The basic elements from the HHS and the ethical challenges that kidney XTx would impose on these elements have previously been described elsewhere and would apply also to children [2]. In addition to the basic elements, section subpart D only applies to research in children [3, 4], including instructions surrounding assent, risk category determinations, children who are wards of the State or other agencies, and possible additional reviews and approvals beyond IRBs by HHS for certain risk determinations. Challenges for parental/guardian consent to this particular vulnerable population have not been discussed previously.

It is highly unlikely that XTx research in children will be classified as minimal risk, especially in the absence of cardiac clinical trials in adults. Thus, the clinical trials will likely fall into risk determination categories that involve greater than minimal risk to the child and vary based on whether or not the argument can be made that there is a direct benefit to the child, or if it is only to provide scientific

knowledge and possibly advance the field. Lastly, if the IRB does not classify the research into any of the aforementioned categories, it would require additional HHS approval beyond the institutional IRB level. This instance is applicable to research that is not otherwise approvable but is an opportunity to alleviate a serious problem affecting the health or welfare of children. Although there is the argument that children with CHD pose a unique opportunity for XTx due to their immature immune system that would decrease their chance of rejection [5], coupled with the worse outcomes they face over adults and other solid organ waitlists/mortalities, it is unknown which category IRBs will determine the research application. Before this can happen, there would need to be details of the study design and development of pre-clinical trials for cardiac XTx data that can be generalizable for children. It is also unknown if clinical trials will explore the use of cardiac XTx as a bridge to allotransplant to increase waitlist survival, or as an alternative to allotransplantation. If XTx is only used as a bridge, IRBs may differ on perceived benefits and risks for extending waitlist survival via XTx compared to other clinical alternatives; for example the comparison of using Berlin hearts or if they weigh the risk of exploring the use of XTx for children with CHD lower than their current risk and mortality faced by their disease or waitlist. It would also be interesting to see how HHS would weigh these risks if it were to become applicable [4].

Subpart D also provides additional provisions about age when a child can consent for themselves, assent for children, and parental permissions. These ages for consent and assent by the child vary by state, a child's maturity, and psychological state. For cardiac XTx for children with CHD it is most likely that children will be too young to consent or assent for research or clinical treatments. Most often, parents and/or legally authorized representatives (LAR) are the medical decision makers. Nevertheless, the discussion for when the child should be involved and allowed to consent/assent is required. At what point should the child choose whether they want to wait for a human organ or accept a genetically engineered pig organ? What if a child does not want to accept the organ but the parents do? The answer to age involvement may also be influenced if it is a life sparing organ (heart) vs. an organ that has other clinical organ replacement alternatives, like dialysis for kidneys. If the child was too young to provide an opinion to accept a xenograft, should they be re-consented at some point? If so, when? It has been discussed that a subject would potentially not lose their place on the waitlist if they accept a xenograft [2]. When can the child decide if they want to remove a theoretically functioning xenograft and undergo a second surgery to replace it with a human organ?

This leads to the challenge of the child's ability and right to withdraw from the XTx research. When can a child assess the implications of lifelong treatment and monitoring (to monitor for xenozoonotic risks)? [6] Non-adherence to needed medications to prevent transplant rejection in pediatrics are even faced in allotransplantation. A study by Oliva et al. reported that 9% of pediatric heart transplant recipients reported non-adherence and that this most commonly occurred during adolescence (15 years old) [7]. Non-adherence results in poor outcomes, rejection and death in some instances, and it is very likely that cardiac XTx will face non-adherence challenges by children as well. How will these be addressed? Could non-adherence be

higher since an adolescent may have more negative feelings about having a pig heart in their bodies compared to a human heart? Exploring the age of children involvement and what adolescents may think about cardiac and other organ XTx and the demands of participating in such clinical trials may be warranted.

Research on Pediatric Perspectives and Ethical Issues

To date there have been few studies that explore the viewpoints of either parents/guardians of having their child receive a xenograft, or a mature minor perspective (i.e., a minor who may be able to be treated as an adult for certain procedures). A recent meta-analysis on public perception toward XTx concluded that there is insufficient information known about patient attitudes in particular [8]. This can be extended to the pediatric population in which there is generally not much known regarding how parents/guardians or mature minors feel.

There are two studies that have attempted to assess the attitudes of various stakeholders for the use of cardiac XTx for children with CHD [9, 10]. Assuming XTx has similar outcomes to allotransplantation, acceptance among congenital heart surgeons and pediatric cardiologists is high (>80%). However, this high acceptance dropped if the outcomes were not comparable to allotransplantation even if the xenograft was only used as a bridge to an allograft. However, if the xenograft is effective then most participants would not remove it even if a human heart became available. When parents of children with CHD were surveyed in another study using a Likert scale survey, they too showed a high acceptance (70–80%) for XTx if results were similar to allotransplantation. Similar to other studies, acceptance dropped if the results were not comparable to allotransplantation.

In one focus group study with parents of children with CHD, there was near unanimous agreement that they would certainly accept a pig heart in order to save their child [11]. Further, parents also seemed comfortable in choosing XTx as a clinical option if their physician and/or healthcare team thought it was a good option. There seemed to be an opportunity that if educated on XTx their acceptance could possibly increase. The approval and advancement of kidney XTx may exceed that of CHD in adults but it would be interesting to see if kidney XTx reaches use in pediatric populations with end stage renal disease (ESRD) before cardiac XTx does for children with CHD. If this is the case, what would parent attitudes be of accepting a kidney xenograft for their child? Do parents feel the same way about kidney XTx as cardiac XTx given the renal replacement therapies available? This is something that has not been addressed in the literature and would be worthwhile to start exploring.

The studies on CHD attitudes among parents also showed two important factors that may influence acceptance: religion and psychosocial concerns. In one study, nearly 50% of surveyed parents of a child with CHD stated that religious beliefs were always or often influential in their decision-making [10]. Regression analysis indicated that those whose religious beliefs have a greater impact on their medical decision-making were less likely to accept a xenograft. While there has been at least

one significant publication from the Catholic Church on the permissibility of XTx [12], the theological literature from other faith groups on XTx is sparse and mostly has come from academic theologians. While an entire section of this volume is dedicated to exploring the religious viewpoints toward xenotransplantation, there is also a noticeable lack of commentary on organ transplantation from a religious perspective that differentiates between pediatric and adult recipients. This could be an area for major world religions to begin considering how their faith group might respond.

Parents seem to be concerned with the way that being a pig organ recipient would affect their child socially. Even patients who receive human organs face psychological challenges and body image challenges from receiving an allograft. One could assume that a child as they grow may also be faced with similar concerns. Similar to allotransplantation, the support of counseling and therapy would be advisable. Bullying is a common parental concern for any child these days, and the effects of a child being bullied for having a pig heart may be real as pigs hold a negative and dirty connotation in many societies. Pigs are dirty animals and the word 'pig' is often used as an insult. What exactly these parental concerns are and how best to address them while providing the best support for children if XTx would become an option for them is needed.

Experimental Therapeutic Research in Pediatrics

In the development of therapeutic options for the pediatric population, investigators must avoid two harms: (1) exploiting this vulnerable population in research, as a tarnished history of pediatric research shows, and (2) excluding children from research due to fear of harming a vulnerable population. The pediatric population has been called "therapeutic orphans" for this reason, because children have either been denied access to new medications or exposed to medications that have only been evaluated on the adult population [13]. Additionally, it can, understandingly, be difficult for parents to allow their children to participate in novel therapies from fear of individuals experimenting with their child. The paradigm is shifting from a perspective that protects children from research by exclusion to a "cautious advocacy" that values the participation of children in research with proper consideration to risks and benefits and scientific necessity [14].

Clinical trials in a pediatric population can be a challenging endeavor. Conducting trials in children is often more difficult than in adults due to the increased cost and liability along with decreased commercial interest, especially for the pharmaceutical industry. Yet, children need high-quality clinical trials too before a new therapy is used. Or, to paraphrase Klassen et al., children are not little adults [15], thus generalizability from adult trials sometimes is limited. They are a heterogeneous group ranging from preterm neonates to post-pubertal adolescents (or mature minors) and often experience different outcomes with the same drug [13, 15, 16]. Children can have physiological differences dependent on the age or developmental stage that can affect a clinical therapy or outcome. There are additional clinical goals in pediatric medicine of getting the patients to adolescence and adulthood

rather than simply maintaining or regaining previous quality of life [16]. Similarly, in clinical trials for adults, success is achieved by delaying the inevitable, whereas for children, the objective is to find a treatment that can offer as "normal" quality of life as possible. These differences suggest an ethical rationale for not relying solely on adult outcomes, which often lack generalizability for the pediatric population, but also the establishment of independent pediatric clinical research and rigorous clinical trials in pediatric patients [16].

The field of pediatric cardiology and congenital heart surgery has seen major advancements in the past 50 years, with many procedures that were experimental not long ago now part of common practice [17, 18]. Successful congenital cardiac repairs were rarely performed before the advent of the early heart-lung machine, which was in the early stages of development in the 1950s. Early attempts at open-heart surgery with a heart-lung machine at that time had a high mortality rate [17]. Over the next 20 years, practice changed to recognize the benefit of early surgical intervention in infants rather than delaying repairs for 5–7 years [17]. Arterial switch operations on infants with transposition of the great arteries and ventricular septal defects were being performed successfully by the late 1970s, thus marking a new era of early primary repair for complex congenital heart defects. The first successful infant heart allotransplant was in 1984, and post-transplant survival rates continue to improve every year [19, 20]. The year after Baby Fae died, the same surgeon transplanted a human heart to another HLHS newborn who is still alive today [19]. Although complex CHDs were uniformly fatal at the beginning of the twentieth century, the field has reached an era where skilled individuals and rapidly improving technology have substantially improved long-term survival for most CHDs [16, 18].

Recently, an adult man in Maryland received a porcine heart, provisionally allowed by the FDA through compassionate use [21]. The first approved pediatric cardiac XTx instances may also be through compassionate use allowances. Although the implication is that the child would be extremely sick, so were many of the first pediatric cardiac allotransplant recipients and pediatric patients who received the first CHD repairs. In 2021, a new organ preservation technology was used under compassionate use authorization in a 14-year-old patient to perform "donation after circulatory death" (DCD) heart transplant, just 2 years after it was first used under the same terms for an adult transplant [22]. Subsequently, the technology was tested in clinical trials and gained FDA approval for use in adults the same week the pediatric patient was transplanted.

In considering the prospect of cardiac XTx for the pediatric population, with the need for hearts for this population being greater than adults, how do we begin to conduct these clinical trials? What pediatric age group would be appropriate? Somehow we must reconcile the commitment to not treat children as little adults with the acknowledgement that if this is to become a clinical option, someone will have to go first. In some ways, the first heart transplants probably carried more risk than this era's first xenotransplants will—established immunosuppressant regiments, experienced multidisciplinary teams and pig-to-baboon animal studies all

suggest higher preparedness. However, the results of the Maryland patient show that so many factors are yet unknown [21].

To summarize, experimental therapeutic options for the pediatric population are tested for safety and efficacy first, and perhaps approved for use in the adult population before pediatric. Next, or perhaps concurrently, testing for cardiac XTx is done cautiously, as compassionate use in the absence of a suitable allograft and other life-sustaining measures are not thought to be adequate, and then in clinical trials to test that the therapeutic drug or technology is also tolerated and successful in the pediatric population. Testing the feasibility for cardiac XTx in adults knowing that their age group holds better clinical options and that results from adult cardiac XTx may have limited generalizability for children may be not be appropriate. It may also be important to consider that advancement should happen through formal clinical trials with clear inclusion/exclusion criteria and not with isolated experiments blanketed by compassionate use for desperate patients and dire clinical scenarios.

Conclusion

XTx is making scientific advancements to become a clinical reality. After approval for adult kidney XTx it is thought that cardiac XTx for children with CHD will follow shortly thereafter. Additionally if kidney xenografts are approved for adults with ESRD it would be unethical to deprive children in a similar transplant need to this clinical option. Therefore, we must acknowledge the unique challenges that potential pediatric recipients of a xenograft could face such as those during the consent process and the psychosocial implications. Lastly, the risk they will face if involved in testing a new technology or the non-benefit if left out of the initial clinical trials must be considered. Children with CHD, specifically those under the age of one who are in need of a heart, face the highest waitlist mortality. Children provide an opportunity over adults to decrease the years of potential life loss if saved. Studies and assessments that involve important stakeholders that can help best prepare for inclusion of children in XTx in order to best protect them while attempting to benefit them is crucial.

References

1. Hurst DJ, Padilla LA, Cooper DKC, Cleveland DC, Paris W. Clinical trials of pediatric cardiac xenotransplantation. Am J Transplant. 2021;21(1):433–4.
2. Padilla LA, Hurst D, Maxwell K, Gawlowicz K, Paris W, Cleveland D, Cooper DKC. Informed consent for potential recipients of pig kidney xenotransplantation in the United States. Transplantation. 2022;106(9):1754–62. https://doi.org/10.1097/TP.0000000000004144. Epub ahead of print.
3. US Department of Health & Human Services. Office for human research protections. General requirements for informed consent. hhs.gov. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/regulatory-text/index.html#46.116. Published July 14, 2019. Accessed 10 Sept 2021

4. US Department of Health & Human Services. Research with children FAQs. In: Office for human research protections. hhs.gov. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/children-research/index.html. Accessed 10 Sept 2021.
5. Li Q, Hara H, Banks CA, Yamamoto T, Ayares D, Mauchley DC, Dabal RJ, Padilla L, Carlo WF, Rhodes LA, Cooper DKC, Cleveland DC. Anti-pig antibody in infants: can a genetically engineered pig heart bridge to allotransplantation? Ann Thorac Surg. 2020;109(4):1268–73. https://doi.org/10.1016/j.athoracsur.2019.08.061. Epub 2019 Sep 30.
6. Hurst DJ, Padilla LA, Walters W, Hunter JM, Cooper DKC, Eckhoff DM, Cleveland DC, Paris W. Paediatric xenotransplantation clinical trials and the right to withdraw. J Med Ethics. 2019;46(5):311–5. https://doi.org/10.1136/medethics-2019-105668.
7. Oliva M, Singh TP, Gauvreau K, Vanderpluym CJ, Bastardi HJ, Almond CS. Impact of medication non-adherence on survival after pediatric heart transplantation in the U.S.A. J Heart Lung Transplant. 2013;32(9):881–8. https://doi.org/10.1016/j.healun.2013.03.008.
8. Mitchell C, Lipps A, Padilla L, Werkheiser Z, Cooper DKC, Paris W. Meta-analysis of public perception toward xenotransplantation. Xenotransplantation. 2020;27(4):e12583.
9. Padilla L, Sorabella R, Carlo W, et al. Attitudes to cardiac xenotransplantation by pediatric heart surgeons and physicians. World J Pediatr Congenit Heart Surg. 2020;11(4):426–30.
10. Padilla LA, Rhodes L, Sorabella RA, et al. Attitudes toward xenotransplantation: a survey of parents and pediatric cardiac providers. Pediatr Transplant. 2021;25(2):e13851.
11. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684.
12. Pontifical Academy for Life. Prospects for xenotransplantation: scientific and ethical considerations. Vatican. http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html. Accessed 26 May 2020.
13. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357–69. https://doi.org/10.1111/bcp.12305.
14. Roth-Cline M, Gerson J, Bright P, Lee CS, Nelson RM. Ethical considerations in conducting Pediatric research. In: Seyberth H, Rane A, Schwab M, editors. Pediatric clinical pharmacology. Handbook of experimental pharmacology, vol. 205. Berlin, Heidelberg: Springer; 2011. https://doi.org/10.1007/978-3-642-20195-0_11.
15. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med. 2008;5(8):e172. https://doi.org/10.1371/journal.pmed.0050172.
16. Gidding SS. The importance of randomized controlled trials in pediatric cardiology. JAMA. 2007;298(10):1214–6. https://doi.org/10.1001/jama.298.10.1214.
17. Castañeda A. Congenital heart disease: a surgical-historical perspective. Ann Thorac Surg. 2005;79(6):S2217–20. https://doi.org/10.1016/j.athoracsur.2005.03.031.
18. Mayo Clinic. Congenital heart disease: the first 50 years … the next 50 years. Mayo clinic cardiovascular diseases and cardiac surgery. 2019. https://www.mayoclinic.org/medical-professionals/cardiovascular-diseases/news/congenital-heart-disease-the-first-50-years-the-next-50-years/mac-20453657
19. Chinnock RE, Bailey LL. Heart transplantation for congenital heart disease in the first year of life. Curr Cardiol Rev. 2011;7(2):72–84. https://doi.org/10.2174/157340311797484231.
20. Dipchand AI. Current state of pediatric cardiac transplantation. Ann Cardiothorac Surg. 2018;7(1):31–55. https://doi.org/10.21037/acs.2018.01.07.
21. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, Lorber M, Grazioli A, Saharia KK, Hong SN, Joseph SM, Ayares D, Mohiuddin MM. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med. 2022;387(1):35–44. https://doi.org/10.1056/NEJMoa2201422. Epub 2022 Jun 22.
22. Duke Health. Duke performs first U.S. pediatric heart transplant using new method. Duke health news & media. 2021. https://corporate.dukehealth.org/news/duke-performs-first-us-pediatric-heart-transplant-using-new-method

Xenotransplantation and Informed Consent

6

Daniel J. Hurst

Introduction

At the time of this writing in early 2022, a pig heart was just transplanted at the University of Maryland Medical Center into a living adult male who did not meet criteria for an allograft [1–3]. While this incident of xenotransplantation (XTx) was not a clinical trial but implanted under an emergency use authorization by the Food and Drug Administration (FDA) in the United States (US) regulatory sense of the term,[1] other medical centers have plans to conduct XTx clinical trials, which are likely on the near horizon. However, before clinical trials may commence, regulatory and ethical issues surrounding the trials must be adequately considered. To date, there is little in regard to systematic considerations regarding informed consent for XTx clinical trials. Padilla et al. recently approached this subject offering the most comprehensive and updated account of factors that will need to be addressed, such as a research participant's ability to withdraw from the clinical trial, restrictions on participants' reproductive rights, and the possibility that a participant may need to quarantine for some length of time if there is a perceived risk of xenozoonosis [4]. Additional commentary has been provided on regulatory issues that Institutional Review Boards (IRBs) should be made aware of before an approval is granted [5], but the literature on practical consent issues is scant.

[1] Researchers at The University of Maryland had applied to the FDA to begin a clinical trial of pig-to-human cardiac transplants but were not approved due to lack of non-human primate studies. The FDA granted an emergency authorization for this particular procedure.

D. J. Hurst (✉)
Department of Family Medicine, Rowan-Virtua School of Osteopathic Medicine, Stratford, NJ, USA
e-mail: hurst@rowan.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_6

Informed consent straddles both regulatory and ethical realms; it is an ethical obligation that is codified into law. Hence, with the uptick of research in XTx, combined with the approaching trials that are planned, the dearth of recent literature on the subject of informed consent is surprising considering the notable differences that exist for informed consent in XTx clinical trials compared to other trials. This chapter provides an overview of the topic of informed consent within XTx clinical trials. Rather than focusing on regulatory matters that may differ between nations, this chapter focuses on philosophical and practical matters that will affect XTx programs regardless of locale and that are deserving of further consideration. The first section will provide a brief history of informed consent as a concept within medical research, then informed consent within the context of XTx is examined. The notion of community consent, distinguishing it from the individual consent of the research participant, is presented. Finally, the research participant's right to withdraw from a XTx clinical trial is explored.

Early History of Informed Consent

The history of modern informed consent is not lengthy. Distinctions can be made between consent for medical procedures in normal practice and consent provided by research participants in the context of a clinical trial. A modern understanding of informed consent is not found in classic medical texts, such as the Hippocratic Oath (ca. fourth century BC) or Thomas Percival's *Medical Ethics* (1803) [6]. The term "informed consent" would not be used extensively until the 1950s and many early decisions about the usefulness of informed consent—what physicians needed to disclose, what a patient had a right to know—played out in the courts [6, 7].

In the context of medical research, which is the focus of this chapter, informed consent took center stage in the aftermath of World War II. The medical research atrocities committed by Axis forces on their captives are well known [8]. After the Allied forces secured victory they established the Nuremberg tribunals (1946–1947), which brought forth charges and resulted in convictions for many of those involved in the Nazi medical experimentation [9]. Additionally, the Nuremberg tribunals are noteworthy due to the landmark establishment of what would be known as the Nuremberg Code—a set of ten research ethics guidelines regarding human clinical trials. The very first principle of the Nuremberg Code points to the importance of the principle in the minds of those who wrote it:

> The voluntary consent of the human subject is absolutely essential.This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter

> element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity [10].

The Nuremberg Code was designed to protect the rights and welfare of those who participate in human research. Other ethics guidelines for human research would follow, such as the Declaration of Helsinki (1964) and the Belmont Report (1979), each reiterating the need for the true informed consent of the research participant prior to research activities commencing.

Informed Consent and Xenotransplantation

This discussion begins in the 1960s with the pioneering surgeon James Hardy. In 1963, Hardy would perform the world's first lung allotransplant at the University of Mississippi, receiving much public acclaim. Hardy was also determined to carry out the first clinical heart transplantation and in 1964 decided to acquire some chimpanzees as potential "donors" in case he could not identify a deceased human donor. Hardy found a patient who, reportedly, was already in a state of dying and was a less than ideal candidate for transplantation [11]. Furthermore, the commentaries that exist on this event are not entirely clear if adequate consent was gained by the patient and/or surrogate decision-maker for the transplant. Regardless, Hardy transplanted a chimpanzee heart into his patient. Hence, from this event we have at least two serious ethical issues at hand: (a) the ethics of performing a xenotransplant—a very risky experimental surgery—on a patient who was unlikely to benefit due to their already declining state, and (b) the question of whether adequate consent was obtained. Granted, the concept of informed consent during the 1960s was not as developed as in today's medicine, yet the standard that a patient or their surrogate must agree to the procedure did exist [12, 13].

The reception by the public toward Hardy's xenotransplant was not welcoming. David Cooper has described that the ill public and medical professional response toward the heart XTx dissuaded Hardy from further attempts [11]. Unfortunately, it is not entirely clear in the existing literature what specifically the public and medical community found objectionable.

Box 6.1: Summary of 45 CFR 46.116(a)
The regulations require that the following information must be conveyed to each subject:

(a) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
(b) a description of any reasonably foreseeable risks or discomforts to the subject;
(c) a description of any benefits to the subject or to others which may reasonably be expected from the research;
(d) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
(e) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
(f) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
(g) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
(h) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

In US regulations governed by the Department of Health and Human Services, specific requirements exist as to the content of informed consent, which can be found in 45 CFR 46.116(a). These requirements are summarized in Box 6.1 [14].

From the requirements listed in Box 6.1, issues are immediately encountered in point (a) within XTx. As will be discussed further in a section below, the expected duration of a research participant's involvement in XTx is for their lifetime, which may even be mandated for the participant and possibly other close contacts. This conflicts with (h) as the participant would have no recourse to fully discontinue their participation. Furthermore, describing foreseeable risks and discomforts as required in (b) proves difficult because of the novelty of the therapy and the risk of xenozoonotic infection. There are known risks in XTx, such as possible graft failure. There are known unknown risks, such as the level of risk posed to the participant from xenozoonosis. However, there are also unknown unknowns—those unknown risks that are not likely to be known until XTx clinical trials proceed.

Patient selection for initial clinical trials of XTx has been discussed. Cooper et al. posit that elderly patients who may not survive on a waitlist long enough to receive a suitable deceased human donor organ could be considered for initial clinical trials as long as they are otherwise in stable health [15, 16]. A concern may arise within XTx that, for those patients who are either not candidates for a deceased human donor organ or will more than likely not survive on the waitlist long enough for transplant, a patient may believe they have limited options and accept the xenograft because of this (i.e., the alternative is death or continued dialysis with poor and/or declining quality of life). That is, the paucity of options may exert pressure upon the individual to consent to the xenograft. This is not a completely unique experience. We can make analogies to oncology clinical trials in which new therapies are being tested on patients who may have exhausted existing clinical therapies. The informed consent process must clearly explain the risks and potential benefits of the procedure but will have to do so in a way that does not seek to unduly influence the decision.

Community Consent

The unique risks of XTx clinical trials—primarily the unknown risk of xenozoonotic infection spread from the pig organ to the human recipient—has spurred some commentators to argue that the individual consent of the trial participant is inadequate. What is needed in addition, it is argued, is the consent of the community and perhaps the globe. While the risk of xenozoonotic infection in the human xenograft recipient is now thought to be low (compared to earlier research), the risk is not null and may not be able to be fully understood in the absence of clinical trials [17–19].

Abdallah Daar has written on the vexing issues with consent in XTx clinical trials. Daar was perhaps the first person to question whether, because of the unique risks that a community may bear from XTx trials (mainly risks in the form of possible xenozoonotic disease transmission in the xenograft recipient and then to other persons in the community), some form of community consent for clinical trials should be obtained [20]. Daar was quick to point out that a methodology for this is unclear as no model existed for it. These short lines, appearing in a special section of a 1999 *Bulletin of the World Health Organization* dedicated to topics of animal-to-human transplants, seem to be little more than a thought in Daar's writing. Nonetheless, others would more fully develop this idea in response articles. Fritz Bach makes the case that community consent may be possible via a public referendum that would allow a country's citizens to have a voice. If not a referendum, Bach states that a national committee composed of a heterogeneous assortment of persons could try to reach consensus that would represent the viewpoints of the public [21].

National referendums may be a fine option for gathering viewpoints on a country-level issue that will have minimal or no effect outside a nation's borders. However, let us remember that what is forcing this question is the issue of possible xenozoonotic disease transmission within the community. Infectious diseases are no respecter of borders and can become uncontainable in short order. Hence, a national

referendum does not seem to achieve the result that advocates for community consent are looking for. Regarding Bach's second point of a national committee, the same hesitations could be said for this solution. That is, having one nation's committee decide on an issue that may impact the globe is not sound.

Robert Sparrow has written one of the most thorough analyses on the concept of community consent for XTx clinical trials [22]. Sparrow notes that the relevant community that must be considered is global in scope due to the potential for spread of infectious diseases. With this in mind, he notes that no institution exists to establish such consent. The United Nations or one of its institutions, such as the World Health Organization (WHO) or United Nations Educational, Scientific and Cultural Organization (UNESCO) come to mind. Both institutions have been effective in gathering viewpoints from Member States on particular issues. For instance, the WHO has the World Health Assembly as its decision-making body which includes delegates from all Member States. Similarly, UNESCO in 2005 published a set of ethics guidelines, the Universal Declaration on Bioethics and Human Rights, that were approved by its Member States. A democratic process through these channels could be possible, but it still does not get to the core of what advocates of community consent seem to want, which is true consent by all those who may be affected (harmed) by the research.

In Sparrow's view, the major concern seems to be based on the distribution of risks and benefits that exists from XTx globally. High-income countries will be the sites of the clinical trials, will see XTx as a clinical option first, and will be better prepared than a low- or middle-income country to mitigate any infectious disease that is propagated by the procedure. Low- or middle-income countries, on the other hand, will continue to suffer from an organ shortage and will be less prepared to handle an infectious disease that may spread as the result of XTx. Hence, per Sparrow, the vast majority of the global population have very little to gain from XTx (at least in the immediate near-term) and a lot to lose.

Solutions out of this impasse have been offered. Martine Rothblatt has recommended that global surveillance programs for new xenozoonotic infections be established [23]. This may be relatively simple in countries with robust national health systems. For those countries without such infrastructure, Rothblatt states it will be necessary to establish networks of medical stations and surveillance systems to monitor for new pathogens. This would also include basic healthcare for the approximately one billion persons globally who currently do not have access to basic healthcare. To pay for such a schema, high-income countries would need to tax themselves—likely a tax on each xenotransplant that is performed—which would also create global buy-in for XTx, Rothblatt posits. Access to basic healthcare remains scarce in many places globally. The United Nations' 2015 Sustainable Development Goals set a target to achieve universal health coverage for all by 2030 (Goal 3.8)—a target that will not be met even in places of resource abundance who play major roles in the United Nations agenda (e.g., the United States) [24]. The political willpower here seems to be lacking.

In addition, Sparrow worries that tying the offer of access to basic healthcare in low- or middle-income countries to their willingness to consent to XTx calls into

question how free such a consent decision is and if this could constitute exploitation [22]. Sparrow thinks it does constitute exploitation, as the vulnerability of the low- or middle income country is being used to secure consent. The only way out of this quandary, per Sparrow, is to eliminate the inequalities in access to healthcare that endure globally.

While approaches to community consent for XTx exist, what is clear is that community consent in the sense of global consent is a minority opinion. The topic is not one that seems to be supported by a majority of researchers, likely because of its pragmatic difficulty. Nonetheless, the WHO has recommended that regulatory systems for XTx should involve public input [25]. The recommendation is nebulous, and some researchers have interpreted this as seeking the input of the local community in which clinical trials are likely to occur [26]. Nonetheless, the public's attitudes towards XTx is certainly an area in which further research is needed [27], and it seems unlikely that a true global community consensus is possible at this point.

The Right to Withdraw

The right to withdraw has been a persistent topic within XTx. As with community consent, the issue of a research participant's right to withdraw arises from the unknown xenozoonotic risk that is present. Since the Nuremberg Code was published, an established tenet in medical research is that persons participating in research should have the ability to withdraw from a clinical trial at any time and for any reason. In modern informed consent forms there is standard language that communicates this, and it should also be part of the conversation that a research team has with potential participants prior to the person agreeing to participate in the trial.

As noted above, the risk of xenozoonotic disease brings about the ethical dilemma here. If there is some unknown risk of xenoozoonosis post-transplant, then regular monitoring should—perhaps must—accompany follow-up care for the remainder of the patient's life. This would include if the xenograft is excised. Because novel pathogens could spread to close contacts, such as close family and intimate partners, these persons could also be subject to some form of monitoring. Many guidelines agree with this. The US Department of Health and Human Services, in its 2001 guidelines on XTx, stated that informed consent discussions should address the importance of the xenograft recipient complying with long-term or life-long monitoring, which could include items such as blood and other tissue samples and imaging [28]. Similarly, the WHO in the Changsha Communiqué (2008) noted that XTx would require the life-long follow-up of xenograft recipients and possibly their close contacts.

It would seem that not allowing a research participant to wholly withdraw from all aspects of a clinical trial (i.e., the infectious disease monitoring portion) counters the principles of research ethics that dictate a participant should be able to do so. The ethical implications of this have been written on in both adult and pediatric populations with still no resolution [29, 30]. In the US, regulations on these issues are woefully behind. Standards need to be implemented for the monitoring of

xenograft recipients, and perhaps their close contacts, prior to the conduct of clinical trials and, ideally, before more emergency procedures are conducted. Mechanisms for monitoring xenograft recipients, including courses of action that will be taken when a patient does not meet their scheduled monitoring appointment, should be clear in consent documents and conversations with potential recipients. With the unknown risk of disease spread, consent to the XTx should also imply consent to subsequent follow-up monitoring which the patient must comply with for the safety of the public. Mechanisms for doing this need development without further delay.

Conclusion

Informed consent is a vital part of the clinical trial process. In highly novel, experimental medicine such as XTx, there are many aspects of consent that have not been fully explored and are deserving of more attention. Additional stakeholder consultation on a number of these items seems appropriate, as well as more regulatory guidance to direct those research centers who are actively preparing for XTx clinical trials.

References

1. Kotz D. UM medicine performs historic xenotransplantation 2022 [updated January 11, 2022]. https://www.umaryland.edu/news/archived-news/january-2022/um-medicine-performs-historic-xenotransplantation.php
2. Reardon S. First pig-to-human heart transplant: what can scientists learn? Nature. 2022;601(7893):305–6. https://doi.org/10.1038/d41586-022-00111-9.
3. Maschke KJ, Gordon EJ, Gusmano MK. Opinion: after the pig-to-human heart transplant, the FDA, clinicians and insurers have some catching up to do: the Washington post; 2022 [updated January 13, 2022]. https://www.washingtonpost.com/opinions/2022/01/13/what-comes-after-pig-to-human-transplant-breakthrough/
4. Padilla LA, Hurst D, Maxwell K, Gawlowicz K, Paris W, Cleveland D, et al. Informed consent for potential recipients of pig kidney xenotransplantation in the United States. Transplantation. 2022;106(9):1754–62. https://doi.org/10.1097/TP.0000000000004144.
5. Hurst DJ, Padilla LA, Trani C, McClintock A, Cooper DKC, Walters W, et al. Recommendations to the IRB review process in preparation of xenotransplantation clinical trials. Xenotransplantation. 2020;27(2):e12587.
6. Beauchamp TL. Informed consent: its history, meaning, and present challenges. Camb Q Healthc Ethics. 2011;20(4):515–23.
7. Bazzano LA, Durant J, Brantley PR. A modern history of informed consent and the role of key information. Ochsner J. 2021;21(1):81–5.
8. Weindling P. The Nazi medical experiments. In: Emanuel EJ, Grady CA, Crouch RA, Lie RK, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics. Oxford: Oxford University Press; 2008. p. 18–30.
9. Annas GJ, Grodin MA. The Nuremberg code. In: Emanuel EJ, Grady CA, Crouch RA, Lie RK, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics. Oxford: Oxford University Press; 2008. p. 136–40.
10. The Nuremberg Code National Institutes of Health. https://history.nih.gov/display/history/Nuremberg+Code

11. Cooper DKC, Ekser B, Tector AJ. A brief history of clinical xenotransplantation. Int J Surg. 2015;23(Pt B):205–10.
12. Childress JF, Childress MD. What does the evolution from informed consent to shared decision making teach us about Authority in Health Care? AMA J Ethics. 2020;22(5):E423–9.
13. Capron AM. Informed consent in catastrophic disease research and treatment. Univ Pa Law Rev. 1974;123(2):340–438.
14. U.S. Department of Health and Human Services. Informed consent FAQs. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html
15. Cooper DKC, Wijkstrom M, Hariharan S, Chan JL, Singh A, Horvath K, et al. Selection of patients for initial linical trials of solid organ xenotransplantation. Transplantation. 2017;101(7):1551–8.
16. Jagdale A, Kumar V, Anderson DJ, Locke JE, Hanaway MJ, Eckhoff DE, et al. Suggested patient selection criteria for initial clinical trials of pig kidney xenotransplantation in the United States. Transplantation. 2021;105(9):1904–8.
17. Nellore A. Infections after xenotransplantation. Curr Opin Organ Transplant. 2018;23(6):628–32.
18. Fishman JA. Infectious disease risks in xenotransplantation. Am J Transplant. 2018;18(8):1857–64.
19. Pierson RN, Fishman JA, Lewis GD, D'Alessandro DA, Connolly MR, Burdorf L, et al. Progress toward cardiac xenotransplantation. Circulation. 2020;142(14):1389–98.
20. Daar AS. Animal-to-human organ transplants--a solution or a new problem? Bull World Health Organ. 1999;77(1):54–61.
21. Bach FH. Putting the public at risk. Bull World Health Organ. 1999;77(1):65–7.
22. Sparrow R. Xenotransplantation, consent and international justice. Dev World Bioeth. 2009;9(3):119–27.
23. Rothblatt M. Your life or mine: how geoethics can resolve the conflict between public and private interests in xenotransplantation. London: Routledge; 2004. p. 142–62.
24. United Nations. Sustainable Development Goals. 2015. https://sdgs.un.org/goals/goal3
25. Hawthorne WJ, Cowan PJ, Buhler LH, Yi S, Bottino R, Pierson RN 3rd, et al. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China December 12-14, 2018: "the 2018 Changsha communique" the 10-year anniversary of the international consultation on xenotransplantation. Xenotransplantation. 2019;26(2):e12513.
26. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684.
27. Mitchell C, Lipps A, Padilla L, Werkheiser Z, Cooper DKC, Paris W. Meta-analysis of public perception toward xenotransplantation. Xenotransplantation. 2020;27(4):e12583. https://doi.org/10.1111/xen.12684.
28. US Department of Health and Human Services. PHS guideline on infectious disease issues in xenotransplantation. 2001.
29. Hurst DJ, Padilla LA, Walters W, Hunter JM, Cooper DKC, Eckhoff DM, et al. Paediatric xenotransplantation clinical trials and the right to withdraw. J Med Ethics. 2020;46(5):311–5.
30. Spillman MA, Sade RM. Clinical trials of xenotransplantation: waiver of the right to withdraw from a clinical trial should be required. J Law Med Ethics. 2007;35(2):265–72.

Geoethics and Xenotransplantation

7

Martine Rothblatt

Introduction

Geoethics is an extension of bioethics and medical ethics to a domain that extends over a greater geographic area than that of the subject of a medical or biotechnological intervention [1]. Bioethics and medical ethics are necessarily concerned with the immediate subjects of therapeutic or scientific interventions upon people [2]. The limitation is inherent in the basic principles of bioethics and medical ethics. These principles revolve around the autonomy of the patient or scientific subject, which is ascertained by obtaining from such person or persons their informed consent. In addition, the principles of medical ethics require a determination that the intervention is being accomplished for the benefit of the patient. When doubt exists, there must be equipoise, meaning uncertainty as to whether the intervention is as good as any alternative [3]. Furthermore, bioethical principles of justice require efforts to ensure that all patients able to participate in therapeutic modalities are being treated equitably. None of these principles can reasonably be satisfied when persons who may be affected by the therapeutic intervention are unknown and geographically distant. Geoethics is a broad moral philosophy that incorporates medical ethics and bioethics but applies across geography and in contexts when the persons who may be affected by a technological intervention are unknown.

Xenotransplantation is now the transplantation of organs or tissues from a genetically modified pig into people [4]. While organs from animals other than pigs could in theory be used, as in theory could genetically unmodified organs with novel pharmacologic tolerance-inducing protocols, in practice the term "xenotransplantation" has come to mean organs from pigs who have been genetically modified with the intent that their organs and tissues are tolerable in human transplant recipients. The exclusive reliance on pigs for xenotransplantation arises from the combination of

M. Rothblatt (✉)
United Therapeutics Corporation, Public Benefit Company, Silver Spring, MD, USA
e-mail: mar@Unither.com

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_7

their phylogenetic distance from humans by nearly 100 million years, their anatomical homology with human vital organs and their relatively large litter sizes.

Xenotransplantation has the potential to impact persons across a greater geographic area than the hospitals in which patients are receiving xenografts. This is because there is a theoretical possibility that pathogens or pathogenic viral sequences could inadvertently be transferred to patients along with a xenograft, and that such patients could inadvertently further transmit an infectious disease across broad geographic domains. Geoethics provides an appropriate analytical framework in which to assess the impact of xenotransplantation beyond the hospitals in which it occurs [5].

The key principles of geoethical analysis are diversity, unity and viability. Diversity in the context of xenotransplantation means that technologists should be granted the latitude to provide xenografts in accordance with medical direction. The geoethical principle of unity requires a determination that providing a new technology, such as xenotransplantation, does not put geographically distant individuals at materially greater risk than that to which they have agreed. The geoethical principle of viability requires third-party assurance of technologists' compliance with any agreements made with geographically distant populations.

Bioethics and medical ethics are subsets of geoethics in the context of an immediate doctor-patient relationship. Respect for the physician's right to offer a therapeutic intervention to a patient is an extrapolation of the geoethical principle of diversity. Limiting the physician's rights to such instances in which a patient consents to the therapy, if there is a risk of adverse effect on the patient, is a micro-implementation of the geoethical principle of unity. Finally, should the patient agree to a medical intervention, the existence of institutional review boards and medical practice certification committees to ensure compliance with informed consent practices, are examples of the geoethical principle of viability.

Geoethical Diversity as Practiced by Xenotransplantation Technologists

Xenotransplantation cannot be offered to patients without the approval of medical and healthcare authorities in a sovereign jurisdiction. Geoethical diversity requires that xenotransplantation technologists be unencumbered in developing safe and effective organ replacements. In order to determine whether a xenograft is therapeutically appropriate it will be necessary for it to tested in people [6].

There is no animal model that can replicate human biochemistry in all its immunological mystery, and, unfortunately, the field of computational biology is yet too immature to accurately replicate human physiology in all its relevant biomolecular complexity. Accordingly, geoethical diversity requires that promising xenografts be offered to appropriate patients for whom they promise a plausible chance of health improvement.

In January 2022, doctors at University of Maryland Medical Center offered an end-stage heart disease patient, Mr. David Bennett Sr., a xenoheart of a type that had previously worked for over 6 months in baboons, including showing no sign of

rejection when used heterotopically with a native baboon heart for over 3 years [7]. While Mr. Bennett lived for only two further months with the xenoheart, there was a plausible basis to expect longer life and the 2 months was longer than he was expected to live without the xenotransplant.

The geoethical diversity principle is consistent with the environmental concept of precaution because the founding documents for the precautionary principle note that it can be satisfied without certainty. In other words, it is not necessary, for serious threats, to prove that a technology is certainly harmful before it can be mitigated. Reciprocally, though, for immaterial threats, it would not be necessary to prove that a technology is absolutely safe before it can be permitted. Were it otherwise, nothing could traverse from one country to another because in an interconnected biosphere there is nothing that is absolutely safe to everyone. As noted in the *Rio Convention*, "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." [8] There is a grey zone between the so-called precautionary and proactionary principles, with the latter requiring less a priori proof of safety than the former, but neither constituting a block on the diversity rights of technologists to develop therapeutics. The gist of the precautionary-proactionary continuum is that, even for serious threats, "full scientific certainty" is an irrational and hence inapplicable benchmark, and hence must be all the more inapplicable when a threat is minimal.

The geoethical question in every case is whether there are, in the words of the *Rio Convention*, "threats of serious or irreversible damage…." Where such threats do not exist, geoethics is permissive of the rights of biotechnologists to implement human trials of xenografts. Sovereign regulatory agencies such as the US Food and Drug Administration (FDA) do not permit anything to be offered as a therapeutic, outside of the gastro-intestinal tract, if it contains pathogens or is considered at all likely to cause infectious disease. Accordingly, in recent xenokidney-to-human cadaveric transplant cases xenografts were free of concerning pathogens because they came from pigs raised in a clinically appropriate facility (also known as specific pathogen free housing), and because the pigs were genetically unable to produce retroviruses of possible concern to humans [9]. Hence, there being "no threats of serious or irreversible damage", the geoethically right thing is supporting the diversity rights of the xenotransplantation team.

Geoethical Unity as Experienced by Xenotransplantation Participants

The geoethical principle of unity requires the assent of affected populations to any technological activity that places them at risk of material harm. When reduced to the microscopic geography of a hospital, this principle would require informed consent from the patient accepting a xenograft. As the circle of non-improbable harm widens, the number of people who must agree to a xenotransplant also widens. For example, for xenotransplantation, it might be sensible to include within the scope of

geoethical unity any persons who might exchange bodily fluids with a xenograft recipient, or who might be in prolonged close contact with such a patient should they evidence a fever or cough. However, if there is no evidence of a meaningful risk of harm from xenotransplantation, then such prophylactics need not go further.

At one time it was thought that disease-causing porcine endogenous retroviruses (PERVs) could leap from pigs to people via xenotransplants [10]. However, it was later shown that just one type of PERV—called PERV-C—was essential to enabling an infection of human cells, albeit without causing any evidence of disease, and biotechnologists soon learned how to breed just PERV-C negative pigs as xenograft sources [11]. Consequently, geoethics would not require agreements to xenotransplantation procedures from third parties, either distant or nearby, so long as just PERV-C negative and otherwise clinically-appropriate pigs were used.

In the January 2022 xenoheart case described above, it is likely that the patient agreed as part of the informed consent procedures to not exchange bodily fluids with other persons, to report regularly to the hospital for biopsies and health monitoring and to consent to in-hospital quarantine should any infectious disease manifest. These requirements may have been adopted in part to protect the hospital from legal liability, in part to maintain the rigor of the scientific research into xenotransplantation and in part to further reduce the already very small risk of a pathogen spreading geographically. Since these additional requirements would not otherwise impede the development of xenotransplantation, their satisfaction in the interests of geoethical unity would not undermine geoethical diversity.

Geoethical Viability in the Context of Xenotransplantation

The geoethical principle of viability requires ongoing third-party compliance monitoring for any agreements reached between those at a risk of meaningful harm and the technologists who created the risk. Indeed, geoethics requires the actual control of any problematic technology be automatically transferred to the monitoring organization, either directly or via legal authority, in the event of deviation from the terms of geoethical agreement.

As discussed above, xenotransplantation activities as are likely to be carried out do not put persons other than the patient at a risk of harm. However, to demonstrate the applicability of the geoethical principle of viability, let it be supposed that a kind of xenotransplantation was proposed in which there was a material risk of zoonotic virus transmission. In such a case, geoethics would require a priori agreement to the activity by representatives of those who would be placed at risk of harm. Since ‘viruses need no passports’, the population of people placed at risk would be global, and the only representatives of worldwide populations are international organizations supported by national authorities representing their populations. Examples of sources of geoethical unity for such pandemic-prone xenotransplantation activities are the World Health Organization (WHO) or a new international organization arising from a xenotransplantation-specific treaty amongst the world’s nations.

An international organization that was challenged with pandemic-prone xenotransplantation activities would likely condition its agreement with requirements that patients sign "Ulysses contracts" in which they agree to a prolonged period of post-transplant quarantine, ongoing biosurveillance and re-hospitalization with quarantine upon any sign of infectious disease. Ulysses contracts are non-cancellable agreements, and thus cannot be withdrawn as is generally the case for informed consents. In addition, such a global representative of the world's peoples at risk of a pandemic-prone form of xenotransplantation might reasonably also require the technologists to fund a global pathogen surveillance network to look for incipient signs of a pandemic. Finally, it would be sensible pursuant to the geoethical unity principle to also require that a fair allocation of xenotransplants be allocated to a random selection of appropriate patients from countries other than where the surgeries are occurring, so that there might be benefits to counterbalance the risks.

Under the geoethical viability principle, third-party experts would be required to monitor and enforce any agreements reached between an international organization representing at-risk populations and xenotransplantation technologists. The viability principle requires these third-party experts to be funded in advance by the technologists and to be provided with legal authority to shut off the flow of problematic xenografts if the terms of agreement are not being followed. Examples of third-party experts would be international law firms or consulting companies that would retain subject-matter expertise in xenotransplantation and public health. New companies may classify themselves as geoethical audit organizations, or GAOs.

Practical Consequences of Geoethics for Xenotransplantation

The towering obligations imposed by geoethics for xenotransplantation makes it highly probable that only non-risky xenografts will be used. It is vastly easier to ensure that xenografts are from PERV-C negative pigs raised in designated pathogen-free conditions than it is to establish a new international treaty, or to fund a new global biosurveillance system. It is vastly easier to ensure that one's xenografts do not create meaningful risks of harm to geographically distant populations than it is to manage the creation of such risks.

Consequently, it can be expected that the geoethical principles of unity and viability will not need to be deployed for xenotransplantation as it is likely to be practiced. Instead, the geoethical principle of diversity will prevail (freedom of technological innovation), implemented in the patient-focused micro-domain with the traditional bioethical principles of beneficence, non-malfeasance, autonomy and justice. In essence, the potential obligations of geoethical unity and viability create a "safe harbor" within which the field of xenotransplantation is free to develop xenografts that are safe both for the patient and for the greater geographic community.

Conclusion

Twenty-First century xenotransplantation looks nothing like historic examples of body part or fluid exchanges between sundry animals and humans. Xenografts are being tried, and with growing success, only from herds that pose no meaningful risk of infectious disease to the patient or to others, and that are phylogenetically distant, generally accepted food sources that coincidentally have some therapeutically relevant aspect of physiological or biochemical homology with humans. This situation prevails because the collective human consciousness that underlies geoethics raises extremely high barriers to any other form of xenotransplantation, while also being proactively encouraging of the safe types of xenografts now being tested.

Xenotransplantation provides an excellent example of how bioethics and medical ethics operate within a philosophical superset of geoethics. All require the consent of those affected by a therapeutic or scientific intervention, but geoethics extends the ambit of consent to geographically distant populations. All require that the intentions of the healthcare or scientific actor are beneficent, non-maleficent and just, but geoethics transfers those intentionality judgements to the representatives of geographically distant populations, like how an Institutional Review Board (IRB) operates within a hospital setting. Geoethics uniquely requires that the terms of consent between technologists and those facing material risks from the technology be independently monitored and enforced.

References

1. Rothblatt M. Your life or mine: how geoethics can resolve the conflict between public and private interests in xenotransplantation. Burlington: Ashgate; 2004.
2. Beauchamp T, Childress J. Principles of biomedical ethics. 8th ed. New York: Oxford University Press; 2018.
3. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987;317(3):141–5.
4. Cooper DKCC, Ekser B, Tector AJ. A brief history of clinical xenotransplantation. Int J Surg. 2015;23(B):205–10.
5. Rothblatt M. Key legal issues: determining the rise of geoethics as the optimum analytical paradigm. Graft. 2001;4(2):143.
6. Reichart B, Längin M, et al. Pathways to clinical cardiac xenotransplantation. Transplantation. 2021;105(9):1930–43.
7. Rabin R. In a first, man receives a heart from a genetically altered pig. New York Times. 2022;10:A1.
8. United Nations Conference on Environment and Development Rio de Janeiro, Brazil. 1993; Principle 15.
9. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;00:1–17. https://doi.org/10.1111/ajt.16930.
10. Weiss R. Circe, Cassandra, and the trojan pigs: xenotransplantation. Proc Am Philos Soc. 2004;148(3):281–95.
11. Denner J. Why was PERV not transmitted during preclinical and clinical xenotransplantation trials and after inoculation of animals? Retrovirology. 2018;15(1):28.

Animal Ethics and Zoonosis Risks

8

Tanja Opriessnig and Patrick G. Halbur

Introduction

Organ transplantation is commonly utilized in people who suffer from end-stage organ failure [1]. In the United States (U.S.), on average, 17 people die every day from the lack of available organs for transplant [2]. Almost 106,000 people are currently on the waiting list for an organ transplant [3]. Kidneys, livers, hearts and lungs, in that order, are the most commonly transplanted organs [4]. However, the supply of human donor organs for transplantation is limited. While the number of living donor kidney and liver transplants continues to increase, the vast majority of organ transplant procedures involve organs from deceased donors. The U.S. saw a 6% increase in deceased donors, from 11,870 in 2019 to 12,588 in 2020 [3]. Hence efforts have been made to use animal organs in human patients, in a process called "xenotransplantation".

Xenotransplantation is defined as any procedure that involves the transplantation, implantation or infusion of either (a) live cells, tissues or organs from a nonhuman animal source or (b) human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs into a human recipient [2, 5, 6]. Ideally, the donor organ size is similar to humans and this limits the selection of suitable donor species. Animal species most compatible with the size requirement for humans include pigs, cattle and non-human primates [7].

T. Opriessnig (✉)
Vaccines and Diagnostics Department, Moredun Research Institute, Penicuik, Edinburgh, UK

Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA, USA
e-mail: tanjaopr@iastate.edu; tanja.opriessnig@moredun.ac.uk

P. G. Halbur
Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA, USA
e-mail: pghalbur@iastate.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_8

Organs obtained from non-human primates are closest and most similar to human organs. Macaques, baboons, squirrel monkeys, owl monkeys, and marmosets are species most commonly used in research facilities [8]. Limitations often include time-to-maturation, the length of gestation and the number of offspring (Table 8.1).

In the past, a major problem with xenotransplantation was hyperacute xenograft rejection i.e. the body recognizes the organ as non-self and mounts an immune response. Advances in technologies such as somatic cell nuclear transfer, viral transduction of DNA and use of CRISPR/Cas (clustered regularly interspaced short palindromic repeats, CRISPR; CRISPR-associated proteins, Cas) has allowed for humanization of non-human xenograft tissues [9]. In fact, the first human heart xenograft was from a genetically modified pig and was successfully completed in January 2022 at the University of Maryland Medical Center [10].

Since the global coronavirus (COVID-19) pandemic, declared on March 11, 2020 [11], the number of xenotransplantation procedures dropped by 90.6% in France and 51.1% in the U.S. [12]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus was first identified on January 9th 2020 in a patient in Wuhan, China [13]. The origin of SARS-CoV-2 has been ascribed to wild animals that harbored the virus and subsequently transmitted it to humans [14] though this has not been definitively determined. Interestingly, since wide spread testing has been implemented, many species of animals have tested positive for the SARS-CoV-2 infection including felines, canines, and some animals such as mink and have become prime case studies for zoonosis and reverse zoonosis with SARS-CoV-2 [15]. This pandemic demonstrated that the potential dangers of transmitting known or unknown pathogens through xenotransplantation are substantial and as such exercising utmost caution is prudent. However, we are at present equipped with very powerful tools to enhance our understanding and assessing the risks of zoonotic infections during xenotransplantation.

Table 8.1 Comparison of factors related to offspring in animal species considered suitable for xenotransplantation

	Non-human primates					
	Macaque *Macaca fascicularis*	Baboon *Papio hamadryas*	Squirrel monkey *Saimiri sciureus*	Marmoset *Callithrix jacchus*	Cattle *Bos taurus*	Pig *Sus domesticus*
Female sexual maturity (years)	1238 days (3.4 years)	1514 days (4.1 years)	1003 days (2.7 years)	477 days (1.3 years)	548 days (1.5 years)	152–182 days (0.5 years)
Gestation period	165 days	171 days	161 days	144 days	277 days	115 days
Inter-litter interval (litters per year)	431 days (0.8 or every 1.2 years)	568 days (0.6 or every 1.5 years)	365 days (1)	169 days (2)	365 days (1)	156 days (2.3)
Average number of offspring/ pregnancies	1	1	1	2	1	10–15

Animal Ethics

General Consideration

Within xenotransplantation animal ethics is an increasingly important topic [16–19]. Concerns over animal usage for the purpose of xenotransplantation include animal welfare issues, usage of genetic engineering, biosafety, and the rights of the animals themselves. Furthermore, as an overall ethical issue, there is a widespread belief, primarily for religious reasons, that certain areas in genetic engineering such as manipulating animals for human usage should not be studied [20].

Animal Welfare

Today pigs are an important source of animal protein for people globally. They are raised in a variety of environments including modern confinement facilities with carefully monitored environmental conditions as well as alternative production practices such as pasture rearing. Welfare regulations are in place but may differ across pork production areas and systems. These regulations often include measurements such as number of pigs per m^2, defined areas of continuous solid floor in contrast to slatted floor, minimal and maximal temperatures which are achieved by ventilation, dry bedding areas for the pigs to move to, defined lighting and noise levels, and the ability to express natural behavior among others. Becoming a donor for xenotransplantation puts pigs under different welfare regulations. In general, biosafety protocols are often in place to isolate the donor pigs from acquiring common infections. In addition, these pigs may be subjected to individual and unnatural housing conditions (including no bedding material and often restraining the natural behavior of pigs), surgical procedures, artificial insemination, *in vitro* fertilization, embryo transfer, cesarean derivation and colostrum deprivation. In addition, the donor pigs are subjected to regular and frequent sampling procedures by non-invasive or invasive methods, necessitating manual or drug induced restraint. Thus, breeding of pigs and rearing to obtain tissues for xenotransplantation will likely impact their welfare and natural behaviors. Animals being kept under "research" conditions that fail to meet the needs dictated by the animals' biological and psychological nature is a significant concern for society today and may create additional concerns in the future.

Genetic Engineering of Animals for Xenotransplantation

If non-human tissues are transferred into a human there is a high risk of an immunological rejection of the organ as the human immune system recognizes the foreign organ as "not-self" and rejects it. In what is known as "hyper-acute rejection", the body begins to reject the organ as soon as it is implanted [21]. Transplantation of organs requires lifelong immunosuppression of the recipient,

which is associated with significant morbidity [22, 23]. This disparity has fueled intense interest focused on alternative organ sourcing and regenerative medicine. As a solution for this problem, interspecies chimeras have been created which aid in the generation of humanized organs. Several advancements in this area benefited from new technologies, including genome editing tools, such as zinc finger nucleases, transcription activator-like effector nucleases (TALEN), and CRISPR/Cas9 technologies [24]. Today the genome of pigs can be more easily manipulated resulting in multiple gene knockouts, human transgene insertions, and more recently, specific animal organ knock outs and replacement with a humanized organ [24]. For example, greater than 6-month survival of a life-supporting kidney co-transplanted with a vascularized thymic graft into non-human primates has been achieved [25]. This could indicate that a hybrid thymus in combination with immunosuppression may prolong pig xenograft lifespans [25]. Similarly, triple gene knockout pigs have been developed for renal transplants to reduce the reactivity of pre-existing anti-pig antibodies in pre-transplant patients [26]. Humanized pigs certainly can also have major disadvantages. Possible problematic pre-existing anti-pig antibodies and methods to stop these from becoming a problem have been reviewed [27]. A cytidine monophosphate-n-acetylneuraminic acid hydroxylase and glycoprotein, alpha1, 3-galactosyltransferase double knockout pig model has been produced to reduce immune reactions during xenotransplantation in the human recipient [28]. However, the so humanized pigs were found to suffer from clinical signs and pathologic lesions such as swollen liver and spleen, increased deposition of hemosiderin and severe bleeding due to the genetic engineering [28]. Concerns with genetic engineering include suffering of the created chimeric animals [20].

Animal Rights

Due to the need to have a defined health status, animals raised for xenotransplantation often live in confined research facilities with little or no interaction with other pigs [29] compromising its right to express natural behavior. In Europe, the law dictates five freedoms for farmed animal: (1) Freedom from hunger and thirst, (2) freedom from discomfort, (3) freedom from pain, injury and disease, (4) freedom to express normal behavior, and (5) freedom from fear and distress. As already discussed in the section “Animal Welfare,” many if not all of these freedoms and rights are not available to these animals raised in laboratories. Animal rights questions may also arise if an animal is eventually selected and sacrificed to provide a xenograft for a human organ recipient. In contrast, if the animal is not selected ore viable for xenotransplantation, for example due to incompatibilities or birth deformities, such animals may be destroyed which poses ethical questions. Due to food safety regulations, genetically engineered pigs currently cannot enter into a regular food supply chain and likely would be culled and incinerated. Hence their existence may be considered a waste.

Alternative Approaches to Usage of Animals

Human–animal chimeras produced through various techniques, including stem cell biotechnology, regenerative medicine, and blastocyst complementation may offer alternatives to usage of live pigs [30]. Typically, pig receptors are changed to human receptors in transgenic pigs. However, it has been shown that two of three human complement regulatory proteins are also receptors for human viral pathogens: CD46 is the cell-surface receptor for measles virus, and CD55 can serve as a binding receptor for Echo and Coxsackie B picornaviruses [31]. Coxsackie B virus causes myocarditis and might endanger the pig heart in an immunosuppressed recipient of a xenograft. It could also pose a risk to the pig directly if infected by staff working in the research facility [31]. Generation of organs by 3D printing technology and decellularized scaffolds *in vitro* is currently available but not quite ready for usage [30, 32]. A simple approach to 3D-printing, thick, vascularized, and perfusable cardiac patches, created by using the patient's own cells, that completely match the immunological, cellular, biochemical, and anatomical properties of the patient has been published in 2019 [33]. This may become an alternative to xenotransplantation in the future.

Xenotransplantation and Possible Impact of Pig Viruses

As bacteria and parasites are commonly controlled by antimicrobials or antiparasitic drugs, for the purpose of this review only viruses will be discussed (Table 8.2). Initial research on xenotransplantation was conducted with organs from non-human primates, which are the closest phylogenetic and evolutionary relatives to humans. Concerns of transmission of pathogens from non-human primate organs to humans, such as the transmission of Herpes B virus discovered in 1932 [41], Ebola virus, first recognized in 1976 [42], the Marburg virus discovery in 1967 [43] and human immunodeficiency virus [44, 45] are felt to be too great to continue to consider the use of non-human primate organs. The use of non-human primates for xenotransplantation was banned due to the perceived high risk of zoonotic infections by the U.S. Food and Drug Administration in 1999 [46]. The risk of transmission of infection from other donor species, such as pigs – currently the most popular source for xenografts to humans, is also a concern albeit at a lower level. However, pigs can harbor a wide variety of different viruses (Table 8.2) and extensive diagnostic workup may be needed to confirm absence of potential harmful viruses to humans.

Pig heart valves are already routinely used in humans [47]. For cell transplantations, pig pancreatic islets may benefit human recipients with diabetes [48–50]. The most commonly used U.S. organ transplants include kidney, liver, heart, lungs, pancreas and intestines, whereas commonly transplanted tissues are bones, tendons, ligaments, skin, heart valves, blood vessels and corneas [51, 52]. Currently pig kidneys and possibly hearts, due to the fact that heart disease has remained the leading cause of death at the global level for the last 20 years, are the most common organs

Table 8.2 Overview of selected viruses in pigs

Virus family	Structure	Genus	Viruses in pigs	Abbreviation	Disease manifestation	Site of replication in the pig with emphasis on xenotransplantation importance			Zoonotic potential
						Viremia	*Heart*	*Kidney*	*Replication in humans or in human cell lines*
Adenoviridae	dsDNA, linear	*Mastadenovirus*	Porcine adenovirus 1–5	PAdV-1-5	Enteric, respiratory, systemic	+			No evidence
Arteriviridae	ssRNA (+) linear env	*Betaarterivirus*	Betaarterivirus suid 1 and 2 (formerly porcine reproductive and respiratory syndrome virus)	PRRSV	Reproductive, systemic, respiratory	+	+	+	No evidence
Asfarviridae	dsDNA, linear, env	*Asfivirus*	African swine fever virus	ASFV	Systemic, skin, enteric	+	+	+	No evidence
Anelloviridae	ssDNA (−) circular	*Iotatorquevirus* *Kappatorquevirus*	Torque teno sus virus 1a, 1b, k2a, k2b	TTSuV1a, 1b, k2a, k2b	Subclinical	+			No evidence
Astroviridae	ssRNA (+) linear	*Mamastrovirus*	Porcine astrovirus 1–5	PAstV1-5	Enteric, CNS (PAstV3 only)	Unclear/rare			Unclear, suspected
Bunyavriridae	ssRNA (−or+) linear, env	*Orthobunyavirus*	Akabane virus		Subclinical	+			No evidence
		Not classified	Oya virus		Subclinical	+			No evidence
			Lumbo virus Tahyna virus		Subclinical	+			Zoonosis
		Herbevirus	Herbert virus	HEBV	Subclinical				Unknown
		Goukovirus	Gouleako goukovirus	GOLV	Subclinical				Unknown
Caliciviridae	ssRNA (+) linear	*Norovirus*	Porcine norovoris	PoNoV	Subclinical				No evidence
		Sapovirus	Porcine sapovirus	PoSaVs	Enteric	+			No evidence
		Unassigned	St-Valérien calicivirus	SVCV	Subclinical	+			No evidence
		Vesivirus	Vesicular exanthema of swine virus	VESV	Systemic, vesicular lesions				No evidence

Circoviridae	ssDNA (−) circular	*Circovirus*	Porcine circovirus 1, 2, 3, 4	PCV1, 2, 3, 4	Enteric, systemic, respiratory, reproductive	+	+	+	No evidence in humans, low level of PCV2 infectivity in cancerous and normal human cell lines[a]
Coronaviridae	ssRNA (+) linear, env	*Alphacoronavirus*	Swine acute diarrhea syndrome coronavirus also known as swine enteric alphacoronavirus	SADS or SeACoV	Enteric	+			No evidence in humans but several primary human lung cell types and primary human intestinal cells are susceptible [34]
			Transmissible gastroenteritis virus	TGEV	Enteric	+			No evidence
			Porcine respiratory coronavirus	PRCV	Respiratory	Unclear/rare (2 dpi)			No evidence
			Porcine epidemic diarrhea virus	PEDV	Enteric				No evidence
		Betacoronavirus	Porcine hemagglutinating encephalomyelitis virus	PHEV	Respiratory, CNS, systemic	+	+	+	No evidence
		Deltacoronavirus	Porcine deltacoronavirus	PDCoV	Enteric	+			No evidence in humans but human hepatoma (Huh7) cells and cells from other animal species are susceptible [35]
		Torovirus	Porcine torovirus	PToV	Subclinical				No evidence
Filoviridae	ssRNA (−) linear env	*Ebolavirus*	Reston ebolavirus	RESTV	Subclinical	+			Zoonosis
			Zaire ebolavirus	EBOV	Subclinical	+			Zoonosis

(continued)

Table 8.2 (continued)

Virus family	Structure	Genus	Viruses in pigs	Abbreviation	Disease manifestation	Site of replication in the pig with emphasis on xenotransplantation importance			Zoonotic potential
						Viremia	*Heart*	*Kidney*	*Replication in humans or in human cell lines*
Flaviviridae	ssRNA (+) linear env	*Flavivirus*	Japanese encephalitis virus	JEV	Subclinical, reproductive	+			Zoonosis
			Murray Valley encephalitis virus	MVEV	Subclinical	+			Zoonosis
			West Nile virus	WNV	Subclinical	+			Zoonosis
		Pestivirus	Atypical porcine pestivirus	APPV	Reproductive, CNS	+			No evidence
			Border disease virus	BCVV	Reproductive, respiratory				No evidence
			Bovine diarrhea virus	BVDV	Reproductive				No evidence
			Bungowannah virus		Reproductive	+			No evidence
			Classical swine fever virus	CSFV	Reproductive, skin, respiratory, systemic	+	+	+	No evidence
Hepeviridae	ssRNA (+)	*Orthohepevirus*	*Hepatitis E virus*	HEV	Subclinical	+			Zoonosis

Herpesviridae	dsDNA (+) linear env	*Macavirus*	*Ovine gammaherpesvirus 2* or Malignant catarrhal fever (Ovine herpesvirus 2)	OvHV-2	Ocular discharge, CNS, systemic				No evidence
			Suid gammaherpesvirus 3, 4 and 5 (Porcine lymphotrophic herpesvirus 1, 2 and 3)	PLHV 1–3	Subclinical	+			No evidence
		Roseolovirus	Suid betaherpesvirus 2 Porcine roseolovirus better known as porcine cytomegalovirus)	PRV or PCMV	Subclinical, respiratory	+			Zoonotic event during xenotransplantation
		Varicellovirus	Suid alphaherpesvirus 1 (Pseudorabies virus)	PRV	Respiratory, CNS	+		+	No evidence, humans are resistant
Orthomyxoviridae	ssRNA (−) linear env	*Influenza virus A*	Influenza A virus—swine	IAV-S	Respiratory				Zoonosis
		Influenza virus B	Influenza B virus	IBV	Respiratory				Zoonosis
		Influenza virus C	Influenza C virus	ICV	Respiratory				Zoonosis
		Influenza virus D	Influenza D virus	IDV	Respiratory				No evidence
Paramyxoviridae	ssRNA (−) linear env	*Rubulavirus*	Menangle virus		Reproductive				Zoonosis
			Blue eye paramyxovirus or La Piedad-Michoacan virus	BEPV or LPMV	CNS, corneal opacity, reproductive				No evidence
		Henipavirus	Nipha virus	NiV	Respiratory, CNS	+			Zoonosis
			Hendra virus		Respiratory				Zoonosis
		Respirovirus	Porcine parainfluenza virus 1	PPIV1	Respiratory				No evidence

(continued)

Table 8.2 (continued)

Virus family	Structure	Genus	Viruses in pigs	Abbreviation	Disease manifestation	Site of replication in the pig with emphasis on xenotransplantation importance			Zoonotic potential
						Viremia	*Heart*	*Kidney*	*Replication in humans or in human cell lines*
Parvoviridae	ssDNA (−) linear	*Parvoviruses*	Porcine parvovirus 1–7	PPV1–7	Reproductive, skin	+	+		No evidence in humans or in human cell lines [36]
Picornaviridae	ssRNA (+) linear	*Cardiovirus*	Encephalomyocarditis virus	EMCV	Sudden death		+		Zoonosis
		Aphthovirus	Foot and mouth disease virus	FMDV	Vesicular lesions, salivation, systemic	+	+	+	No evidence
		Enterovirus	Porcine enteroviruses	PEV	Skin				No evidence
		Kobuvirus	Porcine kubovirus	PKoV	Reproductive, enteric	+			No evidence
		Unassigned	Porcine picornavirus Japan	PPVJ	Subclinical				No evidence
		Sapelovirus	Porcine sapelovirus	PSV	Reproductive, enteric, CNS	+			No evidence
		Teschovirus	Porcine teschovirus	PTV	Subclinical, CNS	Unclear/rare			No evidence
		Senecavirus	Seneca Valley virus	SVV	Skin, fever, lameness	+			No evidence
		Pasivirus	Swine pasivirus A1-A3		Unknown, CNS?				Unknown
		Enterovirus	Swine vesicular disease virus	SVDV	Vesicular lesions, systemic				No evidence but likely
Poxviridae	dsDNA linear env	*Suipoxvirus*	Swinepox virus	SWPV	Skin				No evidence

Reoviridae	dsRNA segmented	*Rotavirus*	Rotavirus	RV A, B, C, E and H	Enteric	+			No evidence but RV A recombination with human RV has been observed [37] and human RAV can infect pigs [38]
		Orhoreovirus	Reovirus	ReoV	Enteric, respiratory, CNS				No evidence but human-bat transmission likely
Retroviridae	ssRNA (+) linear env	*Gammaretrovirus*	Porcine endogenous retrovirus A, B, C	PERVA-C	Subclinical	+			No evidence
Rhabdoviridae	ssRNA (−) linear env	*Lyssavirus*	Rabies virus	RV	CNS, salivation				Zoonosis
		Vesiculovirus	Vesicular stomatitis virus	VSV	Salivation, vesicular lesions	Unclear/rare			Susceptible
Togaviridae	ssRNA (+) linear env	*Alphavirus*	Eastern equine encephalitis virus	EEEV	CNS				Zoonosis
			Getha virus	GETV	CNS, enteric, reproductive, subclinical				No evidence
			Sagiyama virus	SAGV	Subclinical				No evidence

[a] Cancerous human cell lines (MCF-7, A549, HeLa, HepG2, U937, THP-1) and normal human cell lines (293T, WI-38, HUVEC, WISH, HSAS4, HEH2) [39, 40]

of interest to be transplanted into humans. Because of this, any virus that may replicate in kidneys or the heart is currently of most concern. In addition, many viral infections cause viremia i.e. presence of viruses in the blood and hence such viruses can be found at times in the kidneys, heart or any other organ.

In a landmark surgery, a porcine heart from a genetically modified pig was transplanted to a 57-year-old man with severe heart failure on January 7, 2022 at the University of Maryland School of Medicine [10]. The recipient's condition started suddenly deteriorating 40 days after the transplantation surgery and eventually the patient died on March 8, 2022. On April 20, 2022, during a webinar of the American Society of Transplantation, the surgeon who conducted the xenotransplantation announced the potential role of a porcine cytomegalovirus (PCMV) infection in the death of the recipient. An extremely low level of PCMV virus was detected in the recipient on the 20th day after the xenotransplantation and the virus levels became precipitous by the 40th day, potentially contributing to the recipient's deterioration. The PCMV is a herpes (DNA) virus in the genus *Roseolovirus* which can go into latency [53]. Though the highly genetically modified donor pig, supplied by a private company, was raised under stringent conditions to avoid infections and was screened for multiple pathogens, the latent infection with PCMV was not detected. Later analysis detected the PCMV in the donor pig's spleen tissue. This single event highlights the importance of zoonotic infections, including latent ones, in xenotransplantation.

A virus transmitted through xenotransplantation could evolve to be transmitted to other humans, potentially causing a wider outbreak and thus this event could pose an ethical quandary. Interestingly, concerns about xenotransplantation and a negative impact of PCMV were first raised in 2015 due to the observation that transplantation of PCMV contaminated pig organs into non-human primates was associated with a significant reduction of the survival time of the transplants [54]. PCMV is related to human cytomegalovirus and human herpesviruses 6 and 7 which can cause serious disease among immunocompromised human individuals, including transplant recipients [55]. The author suggested that the pathogenicity of PMCV may be due to disruption of the coagulation system and suppression and exhaustion of the immune system. Hence, PCMV should be eliminated from donor pigs despite the lack of knowledge on replication of the virus in human cells [55]. In a follow-up study, the distribution of PMCV in baboon organ recipients, who received PCMV contaminated hearts, was investigated [56]. Interestingly, PCMV antigen (as demonstrated by immunohistochemistry) was present in cells in all of the organs of two baboon recipients despite indications that herpes viruses are species-specific. In addition, the same research group also detected PCMV in several organs of the donor pigs that had not been detected in blood when tested at an earlier time point, indicating that testing blood is not an efficient way to detect PCMV in young pigs [56]. In another study, it was found that PCMV transmission in orthotopic pig heart xenotransplantation was associated with a reduced survival time of the transplant and increased levels of interleukin (IL) 6 and tumor necrosis factor (TNF)α were found in the baboon recipient [57]. Furthermore, high levels of tissue plasminogen activator (tPA)-plasminogen activator inhibitor type 1 (PAI-1) complexes were found, suggesting a complete loss of the pro-fibrinolytic properties of the

endothelial cells. These data show that PCMV has an important impact on transplant survival and emphasizes the importance for elimination of PCMV from donor pigs [57]. Based on these findings and the need to prevent PCMV transmission during xenotransplantation, new diagnostic nested and real-time PCR methods have been developed [58]. It has been suggested to use early testing of oral and rectal swabs by uniplex real-time PCR [59]. In addition to viral nucleic acid, a Western blot assay for detection of PCMV antibodies in donor pig candidates has also been described [60]. Early weaning at 24 hours after birth and removal of the dams from a newly established pig donor facility completely eliminated PCMV [61]. Alternatively, immunosuppression of the donor pigs to reactivate PCMV may also need to be considered in future.

Under experimental settings, porcine organs are transplanted into non-human primates for research purposes, and the personnel working on these projects are directly exposed to the experimental animals. This scenario leads to multiple risks of cross species infections involving all three species, which could potentially evolve and spill over to other animals and/or the general human population. Besides well-known pathogenic viruses there are numerous viruses that do not cause clinical signs. This group is divided into viruses that are recognized and may be monitored and viruses that are not recognized and hence are not monitored routinely. An example of a virus that falls into the first group is swine flu; the presence of asymptomatic viral swine infections potentially compatible with humans and not part of routine pig veterinary screening is a great concern for xenotransplantation. Pathogens that may fall into the latter group include porcine endogenous retrovirus (PERV), porcine astrovirus (PAstV), herpesviruses including PCMV and others. It has been shown previously that infectious complications are a major cause of morbidity and mortality after heart transplantation from human-to-human [62]. Among 113 patients included in the study, 92 (81%) patients developed at least one infection within 180 days after heart transplantation among which viral infections were diagnosed in 44 (34%) patients and involved mostly cytomegalovirus infection (n = 39, 34%) [62].

General Concepts on Pig Health Status and the Impact of Pig Derivation and Housing

Pig Health Status

As a general rule, a viral infection in a pig can result in a subclinical infection (no clinical signs, the pig appears healthy) or in clinical disease. Clinical disease can be further subdivided into different levels of severity (mild, moderate, severe) with different durations (acute, chronic, persistent). Clinical signs can vary considerably and can be suggestive of respiratory viruses (e.g. sneezing, nasal discharge, coughing), enteric viruses (e.g. diarrhea, lack of appetite, vomiting), systemic viruses (neurological signs, fever, lethargy) and others. The virus propagation at one point peaks and then declines. Once antibodies against the virus are produced, viremia/shedding becomes intermittent and eventually the virus is no longer detectable for most viruses.

Table 8.3 Definitions of pig types that can be procured and their expected virus status

Pig type	Housing		Caesarean section	Colostrum access after birth	Possible virus exposure	
	Dam	*Piglet*			*Vertical*	*Horizontal*
Conventional	Farm	Farm	No	Yes	Transplacental Birth canal passage	Litter mates Environment
CD[a]	Farm	Farm 1h→Exp.[b]	No	No	Transplacental Birth canal passage	Litter mates Environment
CDCD[c]	Farm/ Exp.	Exp.[b]	Yes	No	Transplacental	Littermates Environment
Gnotobiotic[d]	Farm/ Exp.	Exp.[b]	Yes	No	Transplacental	No

[a]Colostrum-deprived [63]
[b] Experimental unit or research facility
[c] Caesarean-derived-colostrum deprived pig
[d] Raised germ free

Pig Derivation and Housing Impacts Circulating Viruses

The overall number of pathogens and specifically the viruses or virus load in a pig ultimately depends on how the pig is derived, reared and housed. There are major differences in pig derivation (Table 8.3) and also in housing. In general, pigs used for research and transplants are often caesarean derived (birth by C-section) and may or may not be colostrum deprived. They are typically housed in biosecurity level 2 (BSL-2) or even BSL-3 units with direct contact to care staff or may be raised in gnotobiotic chambers. Gnotobiotic pigs are derived by C-section directly into a sterile chamber and reared with no direct contact to humans and fed sterilized food [64]. Often such high health pigs are housed in high efficiency particulate air (HEPA)-filtered, negative pressure facilities under biosecurity level 2 (BSL-2) or BSL-3.

Conventional High Health Pig Farm

Considerably different from gnotobiotic or caesarean-derived-colostrum deprived (CDCD) pigs, pigs can be sourced from a "high health herd". These pigs are typically raised in modern commercial confinement facilities and are documented to be free of certain pathogens. These herds are commonly monitored by surveillance testing and they may or may not utilize viral and bacterial vaccines. If a pig source is negative for certain pathogenic viruses it is often classified as having a high health status or specific pathogen free (SPF). However, high health or SPF status is not equivalent to being free of all pathogenic viruses or bacteria. Economically important pig viruses, based on geographic region and location, that are commonly tested for in pigs from high health farms include porcine reproductive and respiratory syndrome virus (PRRSV), influenza A virus (IAV), porcine circovirus type 2 (PCV2) and others.

Virus Transmission in Pigs to Assess the Potential of Introducing Viruses into Secure Research Facilities

Direct Pig-to-Pig Transmission or Vertical Transmission from the Dam to the Intrauterine Offspring

The direct transmission, also known as horizontal transmission, results from direct contact of infected and non-infected pigs on a farm and depends on virus shedding routes and the shedding duration. For example, PCV2, a ubiquitous pig virus, can be shed via various routes including nasal secretions, saliva, feces, urine, colostrum or semen [65] and the length of viremia has been determined to be up to 140 days [66]. On the other hand, vertical transmission is when the virus crosses the placental barrier and starts replicating in the endometrial and/or placental tissues. For some viruses including PRRSV [67, 68], PCV2 [69, 70], PPV [71, 72], vertical transmission is very important. Intrauterine virus infection of fetuses with any of these viruses often results in fetal death and abortion or mummification; however, pigs may also be born alive, often suffering from myocarditis [73], being more susceptible to other pathogens and may serve as virus source for other pigs.

Indirect Transmission

Different vectors such as insects and birds [74], contaminated fomites including shoes, clothing, feed [75] and others can also contribute to virus spread between pigs and farms. It has also been shown that airborne transmission of viruses [76, 77] is possible between different pens, barns, and even farms [78]. Some viruses can survive for extended time periods under favorable conditions such as organic material, high humidity, low UV light and low temperatures [79–81].

Viruses in Pigs

Virus Populations in a Pig

Table 8.2 includes a list of relevant pig viruses. However, it needs to be noted that at any given time, a pig harbors a number of organisms, including viruses, bacteria and parasites, which are important for normal day-to-day functions but can also result in disease. Virus infections in pigs can be divided into notifiable diseases, reportable diseases, economically important diseases and viruses of currently unknown importance. Next generation sequencing efforts have resulted in discovery of a large number of viruses in pigs [82] for which the importance in health and disease is largely unknown. Often no clinical signs have been associated with these viruses and further testing to understand their replication or prevalence are not commonly done.

Known Zoonotic Viruses

Per definition a zoonosis is an infectious disease that has jumped from a non-human animal to humans and includes viruses (further listed below), bacteria or parasites.

Lumbo Virus and Tahyna Virus

In pigs, members of the *Bunyaviridae* family including Lumbo virus and Tahyna virus are considered zoonotic but are not associated with clinical signs in pigs. Both viruses are widespread in some human populations with occasional clinical consequences. The role of pigs in the bunyavirus ecology is largely unknown [83, 84].

Reston Ebolavirus and Zaire Ebolavirus

Other well-known zoonotic viruses that can also infect pigs include Reston ebolavirus and Zaire ebolavirus both from the *Filoviridae* family. For the Reston ebolavirus, pig-to-human transmission has been confirmed [85]. Typically, pigs do not develop clinical signs [85].

Japanese Encephalitis Virus (JEV), Murray Valley Encephalitis Virus and West Nile Virus (WNV)

Within the *Flaviviridae* family several members are zoonotic including JEV [86, 87], which is distributed across most of Asia, the western Pacific and northern Australia. Clinical signs in pigs are often not evident despite increased numbers of stillborn and mummified fetuses. Murray Valley encephalitis virus [88, 89] is enzootic in the Kimberley region of Western Australia and in parts of the Northern Territory. The virus is epizootic in regions further south in Western Australia and the southern half of the Northern Territory. Finally, the WNV within the *Flaviviridae* is commonly found in Africa, Europe, the Middle East, North America and West Asia and also causes subclinical infection in pigs [90].

Hepatitis E Virus (HEV)

In pigs HEV was first detected in 1997 in the U.S. [91]. Today it is recognized that the virus is present in all major pork producing areas and infection of a pig is essentially always subclinical with most pig herds infected [92]. When pork products (particularly pork liver) are consumed raw, zoonotic transmission to humans can occur [93].

Influenza Viruses

It has been demonstrated that influenza A virus (IAV) can be transmitted from humans to pigs. A few pig-to-human transmissions of IAV are reported each year; however, evidence of onwards infection in humans is limited [94]. In contrast, influenza B virus (IBV) infections occur mainly in humans and are rare in pigs [95, 96]. A similar scenario is also true for influenza C virus (ICV) which is rare in pigs [97].

Influenza D virus (IDV) has been identified in pigs in 2011 [98] and this virus does not seem to occur frequently.

Menangle Virus, Nipha Virus and Porcine Parainfluenza Virus 1 (PPIV1)

In the family *Paramyxoviridae* there are several zoonotic viruses that can infect pigs including Menangle virus which has been reported in outbreaks in pigs in Australia, in Malaysia and Singapore. Pigs are considered amplifying hosts for Nipha virus which causes severe disease in humans [99]. Hendra virus is distributed in Africa and Australia. Experimental infection of pigs with Hendra virus resulted in mild respiratory symptoms [100]. Finally, PPIV1 has been demonstrated to replicate in experimentally infected pigs and induced mild respiratory signs [101]. There is no confirmed evidence of a zoonotic transmission of PPIV1 to humans; however, there is a high similarity with the human virus version.

Rabies Virus

Another well-known zoonotic disease in pigs is rabies virus which results in clinical disease in infected pigs [102]. Rabies is relatively rare in pigs and is characterized of a sudden onset of salivation, rapid chewing, muscle spasms, and aggression. Typically pigs die within 3 days.

Eastern Equine Encephalitis Virus

This virus from the family of *Togaviridae* causes clinical signs in pigs ranging from incoordination, depression, vomiting and mortality which is most evident in pigs less than 2 month of age. Occasionally there are outbreaks [103]. Virus distribution is in North, Central and South America.

Pig Viruses of Importance to Xenotransplantation

In addition to zoonotic viruses there are viruses circulating in pigs that are thought of as being pig specific but could pose a high risk to human transplant recipients.

Porcine Circoviruses (PCV)

Pigs are commonly infected with PCVs including PCV1, PCV2, PCV3 and PCV4 [104]. While there are disease manifestations associated with PCV2 and less frequently PCV3, pigs are commonly subclinically infected [105]. PCV2 is immunosuppressive [106] in pigs but it is currently unknown if a PCV infection could impair pig transplant functionality. In addition, vaccination against PCV2 is able to prevent PCV-associated disease in pigs; however, in most cases not transmission of the virus. Therefore, PCV2 has to be eliminated to obtain xenografts from uninfected healthy animals [106]. Even though circoviruses from pigs are

commonly found in human stool samples [107, 108], to this date, disease in people has not been observed even when PCV1 and PCV2 were transmitted by contaminated rotavirus vaccines to children as determined from vaccine trials containing data from more than 100,000 children [107, 109]. While a study showed that PCV1 DNA could be detected in feces of infants up to 36 days after vaccination, the authors concluded that the levels of PCV1 DNA detection were more supportive of virus passage in the gastrointestinal tract than replication [110]. Furthermore, there was no evidence of seroconversion to PCV1 in infants 1–2 months post administration of an oral rotavirus vaccine containing live PCV1 [111]. Although there is evidence that PCV2 does not infect at least immunocompetent-humans, donor animals should be screened using sensitive methods and ensure virus elimination by selection, caesarean delivery, vaccination, or embryo transfer [106].

Porcine Lymphotrophic Herpesvirus (PLHV) and Porcine Cytomegalovirus (PCMV)

Within the *Herpesviridae* family there are two genera with potential to infect humans via xenotransplantation. There is no evidence currently that PLHV can infect humans, although a recent review indicated that there is a great potential [112]. In contrast, for PCMV pig-to-primate [113] and pig-to-human transmissions [114] have been confirmed.

Encephalomyocarditis Virus (EMCV)

Within the *Picornaviridae* family, EMCV which as the name implies causes inflammation in the heart, is thought to have a low risk for being zoonotic; however, it may be of great importance for xenografts [115]. The virus is known to persist [116] and has been proven to transmit to mice during xenotransplantation of infected tissues from pigs [117]. Natural infection has been confirmed in *Macaca sylvanus* and *Hystrix cristata* from an Italian rescue center [118].

Swine Vesicular Disease Virus (SVDV)

The enterovirus SVDV is similar to human coxsackievirus B5 (CS-B5), in fact SVDV is a variant of CS-B5 [119] and both cause similar lesions. Host switching events have been reported [120].

Porcine Endogenous Retroviruses (PERV)

PERVs are yet another group of viruses which are causing concerns for xenotransplantation. Unlike regular viruses, which can be removed by rigorous strategies, PERVs are part of the cells of pigs. PERVs have been previously reviewed [121] and gamma and beta retroviruses have been found integrated into the genome of pigs [115]. Sequencing of the entire pig genome revealed 212 PERV insertions in the genome [115]. The gamma retroviruses include PERV-A and PERV-B, which are integrated into the genome of all pigs, and PERV-C, found in many (but not all) pigs. Ways to inactivate PERVs such as via CISPR-Cas9 [122, 123] are being investigated. In previous pig-to-small animal or pig-to-non-human primate

transplantation trials testing the impact of pharmaceutical immunosuppression, PERV replication was not upregulated [124, 125].

Cross Species Transmission Using the SARS-CoV-2 Example

General Concepts and Definitions

Most viruses normally have a narrow host range. Cross-species viral transmission describes a process by which a virus successfully infects (productive infection) a new host species and subsequently adapts to it. This process is also known as host jumping or spillover. Xenotransplantation recipients are often immunosuppressed and thus their immune system is not acting at full strength to fight pathogens. This opens a window of opportunity for a non-human pathogen to adapt to its new human host and spread to other humans.

The SARS-CoV-2 Pandemic: An Example for Virus Cross-Species Transmission

The ongoing COVID-19 pandemic associated with SARS-CoV-2, was initially observed with severe respiratory disease in a cluster of patients in Wuhan, Hubei Province, China during December 2019 [13]. The causative agent, a novel coronavirus (2019-nCoV), later re-named SARS-CoV-2, was identified and consequently reported to the World Health Organization [13] On 11-March-2020 the World Health Organization (WHO) upgraded SARS-CoV-2 infection to a global pandemic [11]. Overall the spread of SARS-CoV-2 in humans has been remarkable. A pool of 7.753 billion SARS-CoV-2 naïve people were present when the virus started infecting humans. Based on data from the U.S. and eight European countries it has been determined that the early epidemic grew exponentially at rates between 0.18 and 0.29 per day (epidemic doubling times between 2.4 days and 3.9 days) [126]. The virus spread with high speed through most countries and continents resulting in a high number of infected people that shed virus for extended periods of time. As people naturally have close relationships with pets, it was not surprising that cross-species transmission was reported on 28 March 2020 in a Belgian cat who belonged to a person confirmed infected with SARS-CoV-2 [127]. This was then followed by detection of the virus in other animals. SARS-CoV-2 was diagnosed. on two mink farms (designated NB1 and NB2) in the Netherlands on 23 and 25 April 2020, respectively [128]. A requirement for successful SARS-CoV-2 replication in humans but ultimately also of non-human species is having the correct angiotensin-converting enzyme 2 (ACE2) which serves as functional receptor for the spike protein of SARS-CoV-2. The ACE2 receptor is widely distributed in animals and has a protective role in the cardiovascular system and in alveolar epithelial cells [129]. Adaptive mutations in the viral genome can alter the virus's pathogenic potential. Even a single amino acid exchange can drastically affect the ability of a virus to

evade the immune system and complicate the vaccine development progress against the virus [130]. The receptor-binding domain (RBD) in the virus is therefore essential. Once the importance of ACE2 for human invasion of SARS-CoV-2 was realized, numerous studies have focused on identifying animal species that may have ACE2 receptors similar to humans and hence may be at higher risk to become a reservoir for the virus [131]. In silico structural homology modelling, protein–protein docking, and molecular dynamics simulation study of SARS-CoV-2 spike protein's ability to bind ACE2 from relevant species indicated the highest binding to human ACE2 with the next highest binding affinity to pangolin ACE2 whereas the affinity of monkey ACE2 was much lower [132]. Other ACE2 species in the upper half of the predicted affinity range (monkey, hamster, dog, ferret, cat) have been shown to be permissive to SARS-CoV-2 infection, supporting a correlation between binding affinity and infection susceptibility [132]. Similarly, other studies confirmed these results and predicted that the ACE2 receptor from animals such as dogs, tigers, camels, cats, dwarf hamsters, and sheep have a slightly increased affinity to SARS-CoV-2-RBD [133].

Cross-Species Transmission of SARS-CoV-2 from Humans to Animal Species

Shortly after SARS-CoV-2 entered and adapted to the human population, case reports started to be published indicating human-animal transmissions of virus. Initially this involved mainly indoor pets including cats [127] and dogs [134] living in close contact with COVID-19 affected owners. Later these findings were experimentally confirmed and SARS-CoV-2 infection was also found in other species [135].

Farmed Mink

Mink have a high susceptibility to SARS-CoV-2 infection. The first farm with SARS-CoV-2 infection in mink occurred in the Netherlands and was reported on 26-April-2020 [136]. During the outbreak investigation a few important things were found: (1) The mink were likely infected with SARS-CoV-2 through close contact with human care staff (Fig. 8.1), (2) the mink developed severe clinical respiratory disease and transmission within the farm happened fast, (3) an investigation in to the SARS-CoV-2 virus circulating in the mink revealed that while there was close relationship to the human SARS-CoV-2 strain, mutations had already occurred most likely as consequence of adjustment to the host, and (4) the adapted mink-SARS-CoV-2 strain was found in care takers indicating a true species jump from humans to mink and back into humans [137]. Shortly after finding the virus in Dutch mink, the virus was also found in farmed mink in Spain, Denmark, USA, Italy, Sweden, Greece, France, Poland and Lithuania. While further research indicated that the SARS-CoV-2 mutants in mink did not increase fitness in the human airway [138], the fast spread of the virus in mink and its adaption to its new host species resulted in large culling effort on mink farms [139].

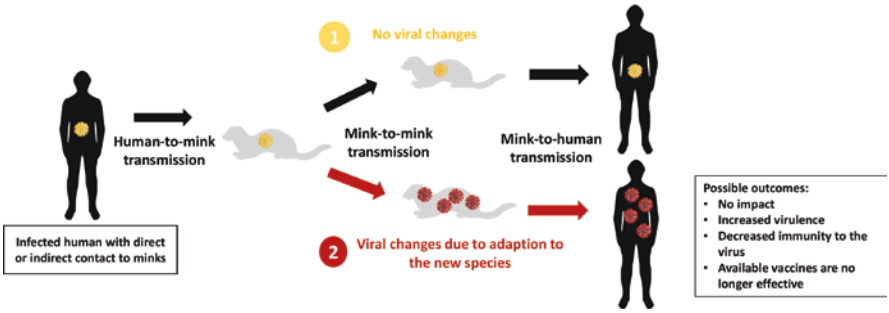

Fig. 8.1 Possible scenarios viruses undergo during cross species transmission with the example SARS-CoV-2 and human-to-mink transmission and subsequent mink-to-human transmission

Pigs

Several experimental studies on SARS-CoV-2 susceptibility were done using pigs [140–142]. The overall result indicated that pigs have a very low susceptibility to the virus. Initially, shortly after SARS-CoV-2 was discovered, a surveillance study conducted in China was not able to find any SARS-CoV-2 antibodies in 187 randomly selected pigs from commercial farms [143]. Several experimental challenge studies in pigs followed. Investigators used different challenge strains and different virus doses to infect the pigs; however, most studies could not confirm active virus replication, seroconversion or transmission [135, 144]. A Spanish study demonstrated seroconversion in experimentally infected pigs but the investigators were unable to find replicating virus in any of the pigs [141]. A U.S. study found no evidence of clinical signs, viral replication or SARS-CoV-2-specific antibody responses in nine 5-week-old pigs when infected through the oral, intranasal and intratracheal routes. However, the same study also found that porcine cell lines including a porcine kidney cell line and swine testicular (ST) cell line could be readily infected [142]. In contrast, a Canadian study using sixteen 8-week-old pigs inoculated with SARS-CoV-2 via an oronasal route found low susceptibility to infection in these pigs based on detection of viral RNA in nasal wash (2/16 pigs at 3 days post challenge) and pooled oral fluids (1/2 at 3 days post challenge), as well as the successful isolation of virus from a pig [145]. Furthermore, 2/16 pigs developed neutralizing antibody titers against SARS-CoV-2 between 11-days and 15-days post challenge [145]. Hence there appears to be a very low risk of pigs getting infected and developing an established active infection.

Summary and Conclusions

During xenotransplantation humans receiving donor organs or tissues are frequently immune suppressed for various time periods and therefore vulnerable to infectious diseases. Creating human-pig chimeras could be a major advantage as human organs are extremely limited. However, there could potentially be great risks as virus populations of two different host species would be mixing in a person with a suppressed immune system (Fig. 8.2).

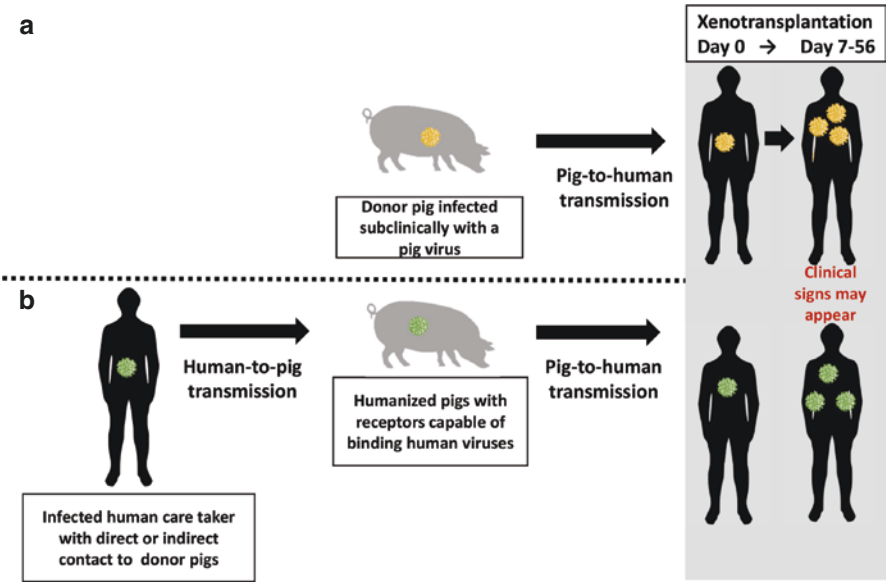

Fig. 8.2 Possible scenarios for cross species transmission of viruses during xenotransplantation using pigs (**a**) Presence of a pig pathogen in a pig organ donor and (**b**) presence of a human pathogen in a care staff, transmitted into the donor pig population due to presence of human cell receptors in the humanized pigs. In both cases, the virus will be transferred into the immunosuppressed human organ recipient with likely consequences to the donated organ and organ recipient but also possible onwards human-to-human spread

Scientists working in xenotransplantation need to work closely with scientists working with animals, particularly with pigs. A constant exchange of the latest knowledge on the ecology of donor pig viruses, a mutual understanding of the use of the best detection methods for these viruses and the limitations of these tests needs to occur to be as sure as possible that the donor pig is free of infectious agents. Essentially all of the latest molecular diagnostic techniques used in human medicine are also available today in veterinary diagnostic medicine and in many cases those techniques are used more routinely in modern pork production than in human health. For example, veterinary diagnostic laboratories such as the Iowa State University Veterinary Diagnostic Laboratory [146] routinely offer a menu of individual PCR assays and PCR panels for swine diseases, conduct next generation and whole genome sequencing and have a large number of serological assays available.

The SARS-CoV-2 observations in species other than humans has provided concern and insight into the ability of emerging viruses to jump species and spillover into the human population. The first pig-to-human heart transplant patient likely died of myocarditis due to a common pig pathogen (PMCV). Especially for the xenotransplantation application, methods to activate dormant/latent/quiescent viruses to replicate to detectable levels needs to be investigated. For instance, corticosteroids or immunomodulators or specific agents could be

utilized and if the method has been defined and is working, they may provide a way to activate silent or non-detectable viruses so that they replicate and are detected by screening tests.

Overall, the tremendous need for donor organs should drive advancement in science to effectively confirm that pigs are free of viruses that could potentially harm the human donor recipient. This is a great opportunity for collaboration between clinicians and researchers in animal and human health.

Acknowledgements Tanja Opriessnig received support provided by the Biotechnology and Biological Sciences Research Council (BBSRC) Institute Strategic Programme Grant awarded to the Roslin Institute (BB/J004324/1; BBS/E/D/20241864). The authors thank for Anbu K. Karuppannan and Lysan Eppink for valuable contributions to this chapter.

References

1. Pedersen PB, Henriksen DP, Brabrand M, Lassen AT. Prevalence of organ failure and mortality among patients in the emergency department: a population-based cohort study. BMJ Open. 2019;9(10):e032692. https://doi.org/10.1136/bmjopen-2019-032692.
2. Transplanation. World health organization web site. https://www.who.int/health-topics/transplantation#tab=tab_1. Accessed 14 Jun 2022.
3. Facts and myths about organ donation. American transplant foundation web site. https://www.americantransplantfoundation.org/about-transplant/facts-and-myths/. Accessed 14 Jun 2022.
4. Organ donation statistics. Health Resources & Serives Administration (HRSA) Web site. https://www.organdonor.gov/learn/organ-donation-statistics. Accessed 14 Jun 2022.
5. Kwisda K, Cantz T, Hoppe N. Regulatory and intellectual property conundrums surrounding xenotransplantation. Nat Biotechnol. 2021;39:796–8.
6. Xenotransplantation. 2022. U.S. Food & Drug Web site. https://www.fda.gov/vaccines-blood-biologics/xenotransplantation.
7. Denner J, Reichart B, Längin M. Does size matter? Xenotransplantation. 2018;25:e12383.
8. Tardif S, Carville A, Elmore D, Williams LE, Rice K. Reproduction and breeding of nonhuman primates. Nonhuman Primates Biomedical Res. 2012;2012:197–249.
9. Klymiuk N, Aigner B, Brem G, Wolf E. Genetic modification of pigs as organ donors for xenotransplantation. Mol Reprod Dev. 2010;77(3):209–21.
10. Reardon S. First pig-to-human heart transplant: what can scientists learn? Nature. 2022;601:305–6.
11. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157–60.
12. Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. Lancet. 2020;395:e95–6.
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
14. Lytras S, Xia W, Hughes J, Jiang X, Robertson DL. The animal origin of SARS-CoV-2. Science. 2021;373(6558):968–70.
15. Maurin M, Fenollar F, Mediannikov O, Davoust B, Devaux C, Raoult D. Current status of putative animal sources of SARS-CoV-2 infection in humans: wildlife, domestic animals and pets. Microorganisms. 2021;9(4):868.
16. Jasanoff S. Bodies in transition: ethics in xenotransplantation research. Hast Cent Rep. 2018;48(Suppl 4):S67–9.
17. Cengiz N, Wareham CS. Ethical considerations in xenotransplantation: a review. Curr Opin Organ Tran. 2020;25:483–8.

18. Daar AS. Ethics of xenotransplantation: animal issues, consent, and likely transformation of transplant ethics. World J Surg. 1997;21:975–82.
19. Rollin BE. Ethical and societal issues occasioned by xenotransplantation. Animals (Basel). 2020;10(9):1695.
20. Ormandy EH, Dale J, Griffin G. Genetic engineering of animals: ethical issues, including welfare concerns. Can Vet J. 2011;52:544–50.
21. Moreau A, Varey E, Anegon I, Cuturi M-C. Effector mechanisms of rejection. Cold Spring Harb Perspect Med. 2013;3:a015461.
22. Scherer MN, Banas B, Mantouvalou K, et al. Current concepts and perspectives of immunosuppression in organ transplantation. Langenbeck's Arch Surg. 2007;392(5):511–23.
23. Salam A, Peleva E, Wain EM. Management of skin cancer in recipients of solid organ transplants. Br J Hosp Med. 2019;80(6):331–6.
24. Meier RPH, Muller YD, Balaphas A, et al. Xenotransplantation: back to the future? Transpl Int. 2018;31(5):465–77.
25. Sekijima M, Sahara H, Shimizu A. Preparation of hybrid porcine thymus containing non-human primate thymic epithelial cells in miniature swine. Xenotransplantation. 2019;26(6):e12543.
26. Martens GR, Reyes LM, Butler JR, et al. Humoral reactivity of renal transplant-waitlisted patients to cells from GGTA1/CMAH/B4GalNT2, and SLA class I knockout pigs. Transplantation. 2017;101(4):e86–92.
27. Cowan PJ, Ierino FL. Reducing the threshold for clinical renal xenotransplantation. Transplantation. 2017;101(4):692–3.
28. Choe HM, Luo Z-B, Kang J-D, Oh MJ, An HJ, Yin X-J. Pathological features in 'humanized' neonatal pig. Anim Biotechnol. 2021;14:1–9. https://doi.org/10.1080/10495398.2021.1962896.
29. Mani V, Mathew R, Homer-Vanniasinkam S. Xenotransplantation: animal rights and human wrongs. Ethics Med. 2003;19(1):55–61.
30. Lu Y, Zhou Y, Ju R, Chen J. Human-animal chimeras for autologous organ transplantation: technological advances and future perspectives. Ann Transl Med. 2019;7(20):576.
31. Weiss RA. Transgenic pigs and virus adaptation. Nature. 1998;391(6665):327–8.
32. Wang P, Sun Y, Shi X, Shen H, Ning H, Liu H. 3D printing of tissue engineering scaffolds: a focus on vascular regeneration. Biodes Manuf. 2021;4(2):344–78.
33. Noor N, Shapira A, Edri R, Gal I, Wertheim L, Dvir T. 3D printing of personalized thick and perfusable cardiac patches and hearts. Adv Sci (Weinh). 2019;6(11):1900344.
34. Edwards CE, Yount BL, Graham RL, et al. Swine acute diarrhea syndrome coronavirus replication in primary human cells reveals potential susceptibility to infection. Proc Natl Acad Sci U S A. 2020;117:26915–25.
35. Li W, Hulswit RJG, Kenney SP, et al. Broad receptor engagement of an emerging global coronavirus may potentiate its diverse cross-species transmissibility. Proc Natl Acad Sci U S A. 2018;115(22):E5135–43.
36. Ferrari M, Gualandi GL. Cultivation of a pig parvovirus in various cell cultures. Microbiologica. 1987;10:301–9.
37. Jing Z, Zhang X, Shi H, et al. A G3P[13] porcine group a rotavirus emerging in China is a reassortant and a natural recombinant in the VP4 gene. Transbound Emerg Dis. 2018;65:e317–28.
38. Chandler-Bostock R, Hancox LR, Nawaz S, Watts O, Iturriza-Gomara M, Mellits KH. Genetic diversity of porcine group a rotavirus strains in the UK. Vet Microbiol. 2014;173:27–37.
39. Liu X, Ouyang T, Ouyang H, et al. Human cells are permissive for the productive infection of porcine circovirus type 2 in vitro. Sci Rep. 2019;9(1):5638.
40. Hattermann K, Roedner C, Schmitt C, Finsterbusch T, Steinfeldt T, Mankertz A. Infection studies on human cell lines with porcine circovirus type 1 and porcine circovirus type 2. Xenotransplantation. 2004;11:284–94.
41. Gay FP, Holden M. Isolation of a herpes virus from several cases of epidemic encephalitis. Proc Soc Exp Biol Med. 1933;30:1051–3.

42. Report of an International Commission. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ. 1978;56:271–93.
43. Siegert R, Shu HL, Slenczka W, Peters D, Müller G. On the etiology of an unknown human infection originating from monkeys. Dtsch Med Wochenschr. 1967;92(51):2341–3.
44. Centers for Disease Control (CDC). Pneumocystis pneumonia—Los Angeles. MMWR. 1981;30:250–2.
45. Centers for Disease Control (CDC). Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. MMWR. 1981;30:305–8.
46. Butler D. FDA warns on primate xenotransplants. Nature. 1999;398:549.
47. Manji RA, Lee W, Cooper DKC. Xenograft bioprosthetic heart valves: past present and future. Int J Surg. 2015;23:280–4. https://doi.org/10.1016/j.ijsu.2015.07.009.
48. Hammerman MR. Xenotransplantation of embryonic pig pancreas for treatment of diabetes mellitus in non-human primates. J Biomed Sci Eng. 2013;6(5A):6–11. https://doi.org/10.4236/jbise.2013.65A002.
49. Paget MB, Murray HE, Bailey CJ, Downing R. From insulin injections to islet transplantation: An overview of the journey. Diabetes Obes Metab. 2022;24(Suppl 1):5–16.
50. Kemter E, Denner J, Wolf E. Will genetic engineering carry xenotransplantation of pig islets to the clinic? Curr Diab Rep. 2018;18(11):103.
51. Zhu HT, Wang WL, Yu L, Wang B. Pig-islet xenotransplantation: recent progress and current perspectives. Front Surg. 2014;24(1):7.
52. Tranplant safety. Centers of disease control and prevention web site. https://www.cdc.gov/transplantsafety/overview/key-facts.html#:~:text=In%20the%20United%20States%2C%20the,providing%20on%20average%203.5%20organs. Accessed 14 Jun 2022.
53. Guedes MIMC, Risdahl JM, Wiseman B. Reactivation of porcine cytomegalovirus through allogeneic stimulation. J Clin Microbiol. 2004;42:1756–8.
54. Denner J. Xenotransplantation and porcine cytomegalovirus. Xenotransplantation. 2015;22(5):329–35.
55. Denner J. Reduction of the survival time of pig xenotransplants by porcine cytomegalovirus. Virol J. 2018;15:171.
56. Fiebig U, Abicht JM, Mayr T, et al. Distribution of porcine cytomegalovirus in infected donor pigs and in baboon recipients of pig heart transplantation. Viruses. 2018;10(2):66.
57. Denner J, Längin M, Reichart B, et al. Impact of porcine cytomegalovirus on long-term orthotopic cardiac xenotransplant survival. Sci Rep. 2020;10(1):17531.
58. Morozov VA, Morozov AV, Denner J. New PCR diagnostic systems for the detection and quantification of porcine cytomegalovirus (PCMV). Arch Virol. 2016;61(5):1159–68.
59. Morozov VA, Heinrichs G, Denner J. Effective detection of porcine cytomegalovirus using non-invasively taken samples from piglets. Viruses. 2017;9(1):9.
60. Plotzki E, Keller M, Ivanusic D, Denner J. A new Western blot assay for the detection of porcine cytomegalovirus (PCMV). J Immunol Methods. 2016;437:37–42.
61. Egerer S, Fiebig U, Kessler B, et al. Early weaning completely eliminates porcine cytomegalovirus from a newly established pig donor facility for xenotransplantation. Xenotransplantation. 2018;25(4):e12449.
62. Pons S, Sonneville R, Bouadma L, et al. Infectious complications following heart transplantation in the era of high-priority allocation and extracorporeal membrane oxygenation. Ann Intensive Care. 2019;9(1):17.
63. Opriessnig T, Gerber PF, Halbur PG. Refinement of a colostrum-deprived pig model for infectious disease research. MethodsX. 2018;5:403–13.
64. Yuan L, Jobst PM, Weiss M. Chapter 5 - gnotobiotic pigs: from establishing facility to modeling human infectious diseases. In: Schoeb TR, Eaton KA, editors. Gnotobiotics. Academic; 2017. p. 349–68.
65. Patterson AR, Opriessnig T. Epidemiology and horizontal transmission of porcine circovirus type 2 (PCV2). Anim Health Res Rev. 2010;11:217–34.

66. Opriessnig T, Prickett JR, Madson, et al. Porcine circovirus type 2 (PCV2)-infection and re-inoculation with homologous or heterologous strains: virological, serological, pathological and clinical effects in growing pigs. Vet Res. 2010;41(3):31.
67. Trevisan G, Johnson C, Benjamin N, Bradner L, Linhares DCL. Description of changes of key performance indicators and PRRSV shedding over time in a naïve breeding herd following a PRRS MLV exposure. Transbound Emerg Dis. 2021;68(6):3230–5.
68. Bøtner A, Nielsen J, Bille-Hansen V. Isolation of porcine reproductive and respiratory syndrome (PRRS) virus in a Danish swine herd and experimental infection of pregnant gilts with the virus. Vet Microbiol. 1994;40:351–60.
69. Madson DM, Opriessnig T. Effect of porcine circovirus type 2 (PCV2) infection on reproduction: disease, vertical transmission, diagnostics and vaccination. Anim Health Res Rev. 2011;12:47–65.
70. Madson DM, Patterson AR, Ramamoorthy S, Pal N, Meng XJ, Opriessnig T. Effect of porcine circovirus type 2 (PCV2) vaccination of the dam on PCV2 replication in utero. Clin Vaccine Immunol. 2009;16(6):830–4.
71. Serena MS, Dibárbora M, Olivera V, et al. Evidence of porcine circovirus type 2 and co-infection with ungulate protoparvovirus 1 (porcine parvovirus) in mummies and stillborn piglets in subclinically infected farm. Infect Genet Evol. 2021;89:104735.
72. Mengeling WL, Lager KM, Vorwald AC. The effect of porcine parvovirus and porcine reproductive and respiratory syndrome virus on porcine reproductive performance. Anim Reprod Sci. 2000;60-61:199–210.
73. West KH, Bystrom JM, Wojnarowicz C, et al. Myocarditis and abortion associated with intrauterine infection of sows with porcine circovirus 2. J Vet Diagn Investig. 1999;11(6):530–2.
74. Baldacchino F, Muenworn V, Desquesnes M, Desoli F, Charoenviriyaphap T, Duvallet G. Transmission of pathogens by Stomoxys flies (Diptera, Muscidae): a review. Parasite (Paris, France). 2013;20:26.
75. Pitkin A, Deen J, Dee S. Further assessment of fomites and personnel as vehicles for the mechanical transport and transmission of porcine reproductive and respiratory syndrome virus. Can J Vet Res. 2009;73(4):298–302.
76. Arruda AG, Tousignant S, Sanhueza J, et al. Aerosol detection and transmission of porcine reproductive and respiratory syndrome virus (PRRSV): what is the evidence, and what are the knowledge gaps? Viruses. 2019;11(8):712.
77. Kristensen CS, Bøtner A, Takai H, Nielsen JP, Jorsal SE. Experimental airborne transmission of PRRS virus. Vet Microbiol. 2004;99:197–202.
78. Bøtner A, Belsham GJ. Virus survival in slurry: analysis of the stability of foot-and-mouth disease, classical swine fever, bovine viral diarrhoea and swine influenza viruses. Vet Microbiol. 2012;157(1–2):41–9.
79. Edwards S. Survival and inactivation of classical swine fever virus. Vet Microbiol. 2000;73:175–81.
80. Gaudreault NN, Madden DW, Wilson WC, Trujillo JD, Richt JA. African swine fever virus: an emerging DNA arbovirus. Front Vet Sci. 2020;7:215.
81. Guan J, Chan M, Grenier C, et al. Degradation of foot-and-mouth disease virus during composting of infected pig carcasses. Can J Vet Res. 2010;74(1):40–4.
82. Cortey M, Díaz I, Vidal A, et al. High levels of unreported intraspecific diversity among RNA viruses in faeces of neonatal piglets with diarrhoea. BMC Vet Res. 2019;15:441.
83. Vapalahti O, Plyusnin A, Cheng Y, Manni T, Brummer-Korvenkontio M, Vaheri A. Inkoo and Tahyna, the European California serogroup bunyaviruses: sequence and phylogeny of the S RNA segment. J Gen Virol. 1996;77(Pt 8):1769–74.
84. Gould EA, Higgs S, Buckley A, Gritsun TS. Potential arbovirus emergence and implications for the United Kingdom. Emerg Infect Dis. 2006;12:549–55.
85. Marsh GA, Haining J, Robinson R, et al. Ebola Reston virus infection of pigs: clinical significance and transmission potential. J Infect Dis. 2011;204(Suppl 3):S804–9.

86. Henriksson E, Söderberg R, Ström Hallenberg G, et al. Japanese encephalitis in small-scale pig farming in rural Cambodia: pig seroprevalence and farmer awareness. Pathogens. 2021;10(5):578.
87. Ricklin ME, García-Nicolás O, Brechbühl D, et al. Vector-free transmission and persistence of Japanese encephalitis virus in pigs. Nat Commun. 2016;7:10832.
88. Kay BH, Young PL, Hall RA, Fanning ID. Experimental infection with Murray Valley encephalitis virus. Pigs, cattle, sheep, dogs, rabbits, macropods and chickens. Aust J Exp Biol Med Sci. 1985;63(Pt 1):109–26.
89. Gard GP, Giles JR, Dwyer-Grey RJ, Woodroofe GM. Serological evidence of inter-epidemic infection of feral pigs in New South Wales with Murray Valley encephalitis virus. Aust J Exp Biol Med Sci. 1976;54(3):297–302.
90. Teehee ML, Bunning ML, Stevens S, Bowen RA. Experimental infection of pigs with West Nile virus. Arch Virol. 2005;150:1249–56.
91. Meng XJ, Purcell RH, Halbur PG, et al. A novel virus in swine is closely related to the human hepatitis E virus. Proc Natl Acad Sci U S A. 1997;94(18):9860–5.
92. Meester M, Tobias TJ, Bouwknegt M, Kusters NE, Stegeman JA, van der Poel WHM. Infection dynamics and persistence of hepatitis E virus on pig farms – a review. Porcine Health Manag. 2021;7(1):16.
93. García N, Hernández M, Gutierrez-Boada M, et al. Occurrence of hepatitis E virus in pigs and pork cuts and organs at the time of slaughter, Spain, 2017. Front Microbiol. 2020;10:2990.
94. Kaplan BS, Kimble JB, Chang J, et al. Aerosol transmission from infected swine to terrets of an H3N2 virus collected from an agricultural fair and associated with human variant infections. J Virol. 2020;94:e01009–20.
95. Ran Z, Shen H, Lang Y, et al. Domestic pigs are susceptible to infection with influenza B viruses. J Virol. 2015;89(9):4818–26.
96. Tsai CP, Tsai HJ. Influenza B viruses in pigs, Taiwan. Influenza Other Respir Viruses. 2019;13(1):91–105.
97. Hause BM, Ducatez M, Collin EA, et al. Isolation of a novel swine influenza virus from Oklahoma in 2011 which is distantly related to human influenza C viruses. PLoS Pathog. 2013;9:e1003176.
98. Lee J, Wang L, Palinski R, et al. Comparison of pathogenicity and transmissibility of influenza B and D viruses in pigs. Viruses. 2019;11(10):905.
99. McLean RK, Graham SP. Vaccine development for Nipah virus infection in pigs. Front Vet Sci. 2019;6:16.
100. Atherstone C, Diederich S, Weingartl, et al. Evidence of exposure to henipaviruses in domestic pigs in Uganda. Transbound Emerg Dis. 2019;66:921–8.
101. Welch M, Park J, Harmon K, et al. Pathogenesis of a novel porcine parainfluenza virus type 1 isolate in conventional and colostrum deprived/caesarean derived pigs. Virology. 2021;563:88–97.
102. Luo Y, Zhang Y, Liu X, et al. Complete genome sequence of a highly virulent rabies virus isolated from a rabid pig in South China. J Virol. 2012;86:12454–5.
103. Elvinger F, Liggett AD, Tang KN, et al. Eastern equine encephalomyelitis virus infection in swine. J Am Vet Med. 1994;205:1014–6.
104. Opriessnig T, Karuppannan AK, Castro A, Xiao CT. Porcine circoviruses: current status, knowledge gaps and challenges. Virus Res. 2020;286:198044.
105. Oliver-Ferrando S, Segalés J, López-Soria S, et al. Exploratory field study on the effect of porcine circovirus 2 (PCV2) sow vaccination on serological, virological and reproductive parameters in a PCV2 subclinically infected sow herd. BMC Vet Res. 2018;14:130.
106. Denner J, Mankertz A. Porcine circoviruses and xenotransplantation. Viruses. 2017;9(4):83.
107. Esona MD, Mijatovic-Rustempasic S, Yen C, et al. Detection of PCV-2 DNA in stool samples from infants vaccinated with RotaTeq®. Hum Vaccin Immunother. 2014;10:25–32.
108. Li L, Kapoor A, Slikas B, et al. Multiple diverse circoviruses infect farm animals and are commonly found in human and chimpanzee feces. J Virol. 2010;84(4):1674–82.

109. Dubin G, Toussaint JF, Cassart JP, et al. Investigation of a regulatory agency enquiry into potential porcine circovirus type 1 contamination of the human rotavirus vaccine, Rotarix: approach and outcome. Hum Vaccin Immunother. 2013;9:2398–408.
110. Mijatovic-Rustempasic S, Immergluck LC, Parker TC, et al. Shedding of porcine circovirus type 1 DNA and rotavirus RNA by infants vaccinated with Rotarix®. Hum Vaccin Immunother. 2017;13(4):928–35.
111. Han HH, Karkada N, Jayadeva G, Dubin G. Serologic response to porcine circovirus type 1 (PCV1) in infants vaccinated with the human rotavirus vaccine, Rotarix™: a retrospective laboratory analysis. Hum Vaccin Immunother. 2017;13:237–44.
112. Denner J. Porcine lymphotropic herpesviruses (PLHVs) and Xenotranplantation. Viruses. 2021;13(6):1072.
113. Mueller NJ, Barth RN, Yamamoto S, et al. Activation of cytomegalovirus in pig-to-primate organ xenotransplantation. J Virol. 2002;76:4734–40.
114. Regalado A. The gene-edited pig heart given to a dying patient was infected with a pig virus. MIT technology review web site. https://www.technologyreview.com/2022/05/04/1051725/xenotransplant-patient-died-received-heart-infected-with-pig-virus/. Accessed 14 Jun 2022.
115. Denner J. The porcine virome and xenotransplantation. Virol J. 2017;14:171.
116. Brewer LA, Lwamba HC, Murtaugh MP, Palmenberg AC, Brown C, Njenga MK. Porcine encephalomyocarditis virus persists in pig myocardium and infects human myocardial cells. J Virol. 2001;75:11621–9.
117. Brewer L, Brown C, Murtaugh MP, Njenga MK. Transmission of porcine encephalomyocarditis virus (EMCV) to mice by transplanting EMCV-infected pig tissues. Xenotransplantation. 2003;10:569–76.
118. Cardeti G, Mariano V, Eleni C, et al. Encephalomyocarditis virus infection in *Macaca sylvanus* and Hystrix cristata from an Italian rescue centre for wild and exotic animals. Virol J. 2016;13:193.
119. Verdaguer N, Jimenez-Clavero MA, Fita I, Ley V. Structure of swine vesicular disease virus: mapping of changes occurring during adaptation of human coxsackie B5 virus to infect swine. J Virol. 2003;77(18):9780–9.
120. Huang HW, Chu PH, Pan CH, et al. Evolutionary histories of coxsackievirus B5 and swine vesicular disease virus reconstructed by phylodynamic and sequence variation analyses. Sci Rep. 2018;8(1):8821.
121. Denner J. Porcine endogenous retroviruses and xenotransplantation, 2021. Viruses. 2021;13(11):2156.
122. Niu D, Wei HJ, Lin L, et al. Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9. Science. 2017;357(6357):1303–7.
123. Yang L, Güell M, Niu D, et al. Genome-wide inactivation of porcine endogenous retroviruses (PERVs). Science. 2015;350(6264):1101–4.
124. Denner J. Recombinant porcine endogenous retroviruses (PERV-A/C): a new risk for xenotransplantation? Arch Virol. 2008;153:1421–6.
125. Specke V, Plesker R, Wood J, et al. No in vivo infection of triple immunosuppressed nonhuman primates after inoculation with high titers of porcine endogenous retroviruses. Xenotransplantation. 2009;16:34–44.
126. Ke R, Romero-Severson E, Sanche S, Hengartner N. Estimating the reproductive number R(0) of SARS-CoV-2 in the United States and eight European countries and implications for vaccination. J Theor Biol. 2021;517:110621.
127. Garigliany M, Van Laere AS, Clercx C, et al. SARS-CoV-2 natural transmission from human to cat, Belgium, March 2020. Emerg Infect Dis. 2020;26(12):3069–71.
128. Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, et al. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science. 2021;371(6525):172–7.
129. Samavati L, Uhal BD. ACE2, much more than just a receptor for SARS-COV-2. Front Cell Infect Microbiol. 2020;10:317.

130. Aleem A, Akbar Samad AB, Slenker AK. Emerging variants of SARS-CoV-2 and novel therapeutics against coronavirus (COVID-19)., *In:* StatPearls. StatPearls Publishing, Copyright ©. Treasure Island: StatPearls Publishing LLC; 2022.
131. Liu Y, Hu G, Wang Y, et al. Functional and genetic analysis of viral receptor ACE2 orthologs reveals a broad potential host range of SARS-CoV-2. Proc Natl Acad Sci U S A. 2021;118(12):e2025373118.
132. Piplani S, Singh PK, Winkler DA, Petrovsky N. In silico comparison of SARS-CoV-2 spike protein-ACE2 binding affinities across species and implications for virus origin. Sci Rep. 2021;11(1):13063. https://doi.org/10.1038/s41598-021-92388-5.
133. Bouricha EM, Hakmi M, Akachar J, Belyamani L, Ibrahimi A. In silico analysis of ACE2 orthologues to predict animal host range with high susceptibility to SARS-CoV-2. *3*. Biotech. 2020;10:483.
134. Sit THC, Brackman CJ, Ip SM, et al. Infection of dogs with SARS-CoV-2. Nature. 2020;586:776–8.
135. Shi J, Wen Z, Zhong G, et al. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science. 2020;368(6494):1016–20.
136. Oreshkova N, Molenaar RJ, Vreman S, et al. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Euro Surveill. 2020;25(23):2001005.
137. Hammer AS, Quaade ML, Rasmussen TB, et al. SARS-CoV-2 transmission between mink (Neovison vison) and humans, Denmark. Emerg Infect Dis. 2021;27:547–51.
138. Zhou J, Peacock TP, Brown JC, et al. Mutations that adapt SARS-CoV-2 to mink or ferret do not increase fitness in the human airway. Cell Rep. 2022;38(6):110344.
139. Fenollar F, Mediannikov O, Maurin M, et al. Mink, SARS-CoV-2, and the human-animal interface. Front Microbiol. 2021;12:663815.
140. Buckley A, Falkenberg S, Martins M, et al. Intravenous, intratracheal, and intranasal inoculation of swine with SARS-CoV-2. Viruses. 2021;13(8):1505.
141. Vergara-Alert J, Rodon J, Carrillo J, et al. Pigs are not susceptible to SARS-CoV-2 infection but are a model for viral immunogenicity studies. Transbound Emerg Dis. 2021;68(4):1721–5.
142. Meekins DA, Morozov I, Trujillo JD, et al. Susceptibility of swine cells and domestic pigs to SARS-CoV-2. Emerg Microbes Infect. 2020;9(1):2278–88.
143. Deng J, Jin Y, Liu Y, et al. Serological survey of SARS-CoV-2 for experimental, domestic, companion and wild animals excludes intermediate hosts of 35 different species of animals. Transbound Emerg Dis. 2020;67:1745–9.
144. Schlottau K, Rissmann M, Graaf A, et al. SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study. Lancet Microbe. 2020;1(5):e218–25.
145. Pickering BS, Smith G, Pinette MM, et al. Susceptibility of domestic swine to experimental infection with severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis. 2021;27(1):104–12.
146. Iowa State University, College of Veterinary Medicine, Veterinary Diagnostic Laboratory web site. https://vetmed.iastate.edu/vdl. Accessed 14 Jun 2022.

Part II

Regulatory Aspects

Regulatory Considerations and Oversight: A US Perspective

9

Judith A. Arcidiacono, Evgenij A. Evdokimov, and Harlan J. Howard

Introduction

Xenotransplantation has been proposed to alleviate the shortage of organs, tissues, and cells available for human transplantation since the 1990s. Early strategies focused on cellular products such as porcine-sourced pancreatic islets and liver assist devices seeded with porcine-sourced hepatocytes. Today, first-in-human (FIH) clinical trials are focused on whole organ xenotransplantation (heart, kidney, and lung). This is due to increased understanding of the mechanisms of xeno-rejection and molecular tools available for the intentional genomic alteration of source/donor animals to prevent rejection.

Despite the potential benefits of xenotransplantation, some challenges remain. Risks associated with the use of xenotransplantation products include the transmission of known and unknown pathogens to the patient, the patient's personal contacts, health care professionals, and the general population. Rejection of source/donor animal cells, tissues, or organs can cause adverse reactions in the patient. Patients receiving xenotransplantation products will likely need long-term immunosuppression, which entails risks that are currently unavoidable. Physiological and metabolic incompatibility between the source/donor animals and the recipient are additional risks associated with the use of xenotransplantation products.

J. A. Arcidiacono (✉)
OTP, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
e-mail: Judith.Arcidiacono@fda.hhs.gov

E. A. Evdokimov · H. J. Howard
DABCT, ONADE, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD, USA
e-mail: Evgenij.Evdokimov@fda.hhs.gov; Harlan.Howard@fda.hhs.gov

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_9

To overcome some of the immunological barriers to xenotransplantation, animals with intentional genomic alterations (IGAs) have been developed and the animals' organs have been used in preclinical studies [1]. The alterations include removal of pig antigens, addition of human genes that are naturally absent in the pig, or substitution of pig antigens with human counterparts. Potential adverse effects of IGAs in animals include altered organ function, metabolic changes, and other factors that may affect suitability of organs for xenotransplantation. Preclinical animal models for xenotransplantation may help evaluate these possibilities.

History of Xenotransplantation Regulation

In the early 1980s, virologists came to understand that the Human Immunodeficiency Virus (HIV) originated from a genetic shift in the Simian Immunodeficiency Virus (SIV) that allowed it to become zoonotic, transmissible from primates in Africa to humans [2]. This realization prompted immediate alarm over the risk of zoonoses arising from exposure to unknown or unidentified animal viruses as the result of a xenotransplantation. To address this concern, the US Secretary of the Department of Health and Human Services (DHHS), with experts from the Center for Disease Control and Prevention (CDC), FDA, the National Institutes of Health (NIH), and the US Public Health Service (US PHS) convened workshops and advisory committee meetings with infectious disease experts, veterinarians, transplant surgeons, and international regulators to develop US policy for xenotransplantation. These discussions resulted in the publication of guidance for the development and use of xenotransplantation products: *Public Health Issues Posed by the use of Non-Human Primate Xenografts in Humans* (1999);[1] *Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation* (2001) [3]; *Guidance for Industry: Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* (2003, revised 2016) [4]. Today, FDA continues to take part in the development of national and international policy on regulatory requirements for xenotransplantation products with the World Health Organization (WHO) and the International Xenotransplantation Association (IXA) [5].

FDA Definition of Xenotransplantation

FDA defines xenotransplantation as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source; or (b) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or

[1] Public Health Issues Posed by the use of Non-Human Primate Xenografts in Humans (1999), this document is no longer available. See Federal Register notice at https://www.federalregister.gov/documents/1999/04/06/99-8439/guidance-for-industry-public-health-issues-posed-by-the-use-of-nonhuman-primate-xenografts-in-humans.

organs" [4]. These products are regulated as biologics under section 351 of the Public Health Service (PHS) Act (21 U.S.C. 321 *et seq*.). Examples of xenotransplantation products include viable porcine hearts with the vasculature, porcine-derived pancreatic islets, and viable porcine skin.

Xenografts are defined by FDA as acellular (decellularized) products derived from animal tissues that are devoid of viable and non-viable cellular material regardless of the method used for decellularization [4]. Examples of these products include decellularized prosthetic heart valves derived from bovine or porcine tissues. Xenografts may be regulated as Class II or Class III medical devices by the FDA requiring premarket clearance (510(k) premarket notification) or premarket approval (PMA) [6].

Current Paradigm for Regulating Xenotransplantation Products in the United States

FDA has a well-established paradigm for the regulation of xenotransplantation products, including the regulation of IGAs in animals [7]. Tissues or organs from animals with IGA(s) may be intended for use as xenotransplantation products in humans. In this circumstance, there are two products, the IGA and the human xenotransplantation product, that two different FDA centers regulate: the Center for Veterinary Medicine (CVM) and the Center for Biologics Evaluation and Research (CBER).

CVM evaluates IGAs in animals that serve as sources of products for xenotransplantation, whereas CBER evaluates the xenotransplantation products derived from animals with IGAs that are used in human patients. CVM approval of IGAs in animals does not authorize the use of the xenotransplantation products derived from these animals in humans. Rather, the use of these products in human patients must go through a rigorous pre-clinical and clinical evaluation prior to CBER's approval of a biologics license application (BLA). Each Center's evaluation processes are complementary and can be carried out in parallel while sponsors are collecting safety and effectiveness data to support each Center's approval requirements. In the end, CVM's approval of the IGA necessarily precedes CBER's BLA approval(s).

During evaluation, the two Centers make independent regulatory and scientific determinations that follow each Center's existing policies and authorities. FDA reviewers from both Centers work together to ensure a comprehensive and non-redundant evaluation of xenotransplantation source animals and products [8]. CBER evaluates many aspects of manufacturing and product quality for xenotransplantation products prior to clinical trials and continues with more detailed assessments as product development proceeds as part of the investigational and approval process. These steps involve evaluation of animal husbandry, animal health, and manufacturing, clinical, preclinical, and statistical information supporting licensing of the proposed xenotransplantation product. CVM's evaluation focuses on the characterization, durability, and safety and effectiveness of the IGA(s) in animals that will be used as a source of organs and tissues for xenotransplantation.

The general principles that FDA considers as it reviews xenotransplantation products are described below. This is not an exhaustive list, but it provides a better understanding of how FDA regulates xenotransplantation products and ensures their safety and effectiveness.

CVM Oversight of Intentional Genomic Alteration(s) in Animals

CVM regulates IGAs in animals under the Federal Food Drug and Cosmetic Act (FD&C Act) (21 U.S.C 321 et seq.) and its implementing regulations (21 Code of Federal Regulations (CFR) Part 511 & 514). In 2009, CVM issued Guidance for Industry 187, which clarified how FDA's statutory and regulatory requirements apply to the regulation of IGAs in animals, including those intended for use in xenotransplantation. This guidance document explains the regulatory process for IGAs in animals, including approvals, provides recommendations to sponsors of IGAs in animals on how they can address FDA regulations, and aligns each step of the review process with these regulations. In 2017, CVM released a draft of the revised guidance that clarified that the scope of the guidance includes IGAs developed using genome editing technology [7]. Of note, some sponsors of IGAs in animals for use as sources of cells, tissues, or organs for xenotransplantation may choose to introduce single or multiple heritable IGAs into an animal lineage, i.e., disruption or knock-out of endogenous porcine genes and insertion of human gene sequences in the pigs' genome, with the aim of making biological materials from these pigs more immunologically compatible with the human immune system. CVM would generally consider a line of pigs with multiple IGAs to be subject to a single regulatory determination/approval in which all IGAs are considered as part of the safety and effectiveness assessment.

As applicable to CVM's oversight of IGAs in animals, to address the requirements related to safety and effectiveness of quality manufactured products, the risk-based review covers the following general areas: (1) product characterization (molecular characterization of the IGA and molecular characterization of the lineage), (2) phenotypic characterization of animals' IGAs (characterization of the phenotype and evaluation of the impact of the IGA on the health of the animals); (3) durability assessment and plan (demonstration that the IGA is durable (consistency of genotype/phenotype) over time/multiple generations and continued monitoring post-approval with corresponding reports submitted to CVM), (4) food safety (with recognition that source animals do not enter the human or animal food supply without prior authorization), (5) environmental impact, and (6) effectiveness. This review process constitutes a life-cycle regulatory approach where CVM evaluates data and information collected prior to approval and continues monitoring the safety and effectiveness of these products after approval until they are discontinued and/or removed from the market. The steps of the review process are described in the draft Guidance for Industry 187 [7] and summarized below.

Product Characterization

CVM's review process focuses on hazard identification and hazard characterization. Product Characterization, as described here, includes the Product Identification, Molecular Characterization of the IGA, and Molecular Characterization of the Lineage steps of the review process. Product Identification describes the IGA(s), the lineage of animals containing IGA(s), and the purpose of the IGA(s) (i.e., their intended use in the animals). Molecular characterization steps focus on assessing the design and ultimate incorporation of the IGA(s) in the animal's genome, incorporating concepts related to chemistry, manufacture, and controls in the early stages of development. Data collected during product characterization, in general, provide a foundation for future development of methods and assays that aim to ensure the safety and effectiveness of the IGA(s). Characterization should encompass a full description of the proposed IGA(s), the intended function, and how the IGA(s) was (were) achieved, supported by data that fully characterize the proposed IGA(s) in the animal's genome, including location and stability. Careful attention should be given to effects associated with the proposed IGA(s). Such effects can be intended or unintended, depending on the location of IGAs in the animals' genome and the function of the altered gene. The intended effects are associated with IGA(s) successfully targeting the intended locus in the genome. Unintended effects include off-target alterations or unexpected alterations at the target site (e.g., insertion of unintended sequences at the target site). These effects and risks associated with identified hazards are considered further under the Phenotypic Characterization, Food Safety, and Environmental Impact steps of the review process. CVM's conclusions about data and information reviewed under the Product Characterization step may also help to inform CBER's risk/safety assessment, which focuses on the use of products derived from animals with IGAs in human patients. Robust molecular characterization of the IGAs in the animals is necessary prior to proceeding with human trials.

Phenotypic Characterization

Demonstrating the health and well-being of animals with IGA(s) serving as sources of cells, tissues, or organs used in xenotransplantation is critically important for both CVM's and CBER's review processes. CVM's evaluation focuses primarily on overall herd health management and potential risks associated with the introduction of IGAs into the genome of the animals. CBER, while also considering many of these questions, has an additional consideration for health assessments on individual candidate animals used as sources of xenotransplantation materials.

Examples of the types of animal health and safety data evaluated in support of CVM's approval can be found in the Freedom of Information Summary for a December 2020 approval of an IGA in domestic pigs that may serve as sources of food or human therapeutics, including xenotransplantation.[2] CVM has also approved

[2] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/10168.

other "biopharm" products from animals with IGAs. Although these products are not intended for the production of cells, tissues, and organs for xenotransplantation, the data and information sponsors used to support animal safety could also apply to xenotransplantation products. Examples of these approvals include IGAs in chickens,[3] rabbits,[4] and goats.[5] For these approvals, sponsors included and CVM reviewed factors such as: (1) general management/husbandry procedures, including housing, nutrition, reproduction, health assessments (e.g., routine periodic and scheduled veterinary examinations), and procedures (e.g., vaccinations, other preventative health measures); (2) physical and biological containment/security, to assure the health of the animals as well as a full accounting of the animals and any biological materials collected from them; (3) other considerations based on the product's particular risk profile, such as growth of animals with IGAs and/or their organs, and (4) euthanasia of source animals according to guidelines of the American Veterinary Medical Association [9]. Sponsors may conduct studies to demonstrate animal safety as necessary to assess the risk profile of the IGA in the animal.

By reviewing data collected on the animals, CVM verifies that sponsors are implementing and following their documented procedures. Such review occurs on data formally submitted to CVM and/or during FDA inspections of sponsors' facilities.

Inspections may occur at any time during the lifecycle of product development, and generally occur prior to the approval of the application. Periodically after approval, FDA performs surveillance inspections to assure that the product remains consistent with the findings during pre-approval development.

The sponsor's scope of data collection is dependent on the level and nature of risks to the animal associated with the introduction of the IGAs into the animals. Like product characterization described above, CVM's evaluation of animal safety helps lay the groundwork, not only for hazard identification and risk assessment for other parts of CVM's review processes, but also for CBER's risk/safety assessments targeting the downstream xenotransplantation product. The complexity of functions of the cells, tissues, or organs that would occur in humans may influence the depth of evaluation sponsors may need to conduct to support development of the final human product.

Durability Assessment and Plan

One aspect of producing a quality product is ensuring the stability and consistency of IGA(s) in animals both pre- and post-approval. CVM's evaluation of stability and consistency of the IGA(s) in animals is supported by review of genotypic and phenotypic data demonstrating durability of the genetic modification(s) (known as the

[3] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/2558.

[4] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/6927.

[5] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/859.

durability assessment) as well as data to support continued durability, safety, and effectiveness post-approval (known as the durability plan).

The durability assessment entails an evaluation of the genotypic and phenotypic stability over time (e.g., over multiple generations or cohorts of the animals). This evaluation builds on data collected and evaluated during product characterization and additional molecular characterization, phenotypic characterization, and effectiveness data that sponsors may have collected during the development process. These data and information serve as a basis for the development of validated methods and assays for monitoring the stability of IGAs in animals' genomes and traits associated with these IGAs as part of the durability plan (e.g., sequence-based assay(s) demonstrating the intended genotype, and protein expression assay(s) confirming a gene knock in/out).

The durability plan is a commitment by sponsors of IGAs to assess their product (i.e., IGA(s) in animals with any associated traits) to demonstrate that the IGA(s) continue to be safe and effective post-approval. In addition to providing data to support durability of the IGA(s) post-approval, there are also requirements for post-approval reporting as described in 21 CFR 514.80. Post-approval reporting and monitoring support the continued health and well-being of the animals with IGA(s).

Although the focus of the plan is on the durability, safety, and effectiveness of the IGA(s), it closely aligns with the safety and quality assurance procedures considered by CBER for the xenotransplantation product. CVM and CBER's oversight are complementary and comprehensive for these products. For example, CVM monitors for diseases in animals with IGA(s) that may also be important considerations for CBER's evaluation of adventitious agents in tissues or organs for transplantation in pre-clinical and human clinical studies.

Food Safety

Although animals with IGAs intended for use in xenotransplantation are not likely to be used as sources of human or animal food, food safety is assessed if the source animals are from a recognized food animal species (e.g., swine). In the reviews of IGAs in animals of food-producing species that will be used for biomedical and not food use, CVM has focused on ensuring that there are adequate controls in place to prevent animals from inadvertently entering the food supply. CVM considers the level of concern for humans consuming edible products, and ensures that validated, suitable detection methods are in place that can distinguish the animals from those without IGA(s) in the unlikely event an animal with IGAs inadvertently entered the food supply.

If a sponsor intends to introduce their animals with IGA(s) into the food supply, CVM conducts a rigorous evaluation to determine whether edible tissues derived from the animal are safe for humans and animals consuming them [7].

Environmental Impact

In accordance with the National Environmental Policy Act (NEPA), the Agency evaluates the potential for significant environmental impacts from approving an application for an IGA in an animal, including the development and commercialization of animals with IGA(s). Under NEPA, FDA must determine if major Agency actions will have a significant impact on the environment. The approval of an application (21 CFR 514.1(b)(14)) is a major Agency action and evaluated by CVM as described in the draft revised Guidance for Industry 187 [7].

Effectiveness

CVM's evaluation of effectiveness focuses on the sponsor's claim(s) associated with IGA(s) in the animals. CVM focuses on the intended function of the IGA(s) in animals (such as the presence or absence of a protein introduced or knocked out by the introduction of the IGA(s)). CBER also considers the molecular aspects of IGA(s) and associated phenotypic traits in their review, however, they evaluate these aspects to determine whether the IGA(s) are appropriate for the successful function of xenotransplantation products in human patients in a clinical setting as part of CBER's effectiveness evaluation.

CBER Oversight of Human Biological Products

Xenotransplantation products are regulated as biological products under the authority of section 351 of the Public Health Service (PHS) Act (21 U.S.C. 321 *et seq*.) in CBER. If xenotransplantation products are to be used in a clinical investigation, an Investigational New Drug (IND) application must be in effect as specified by FDA regulations (21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR 312). Introduction of a xenotransplantation product into interstate commerce requires an approved Biologics License Application (BLA) (21 CFR 601). To receive an approval, the clinical trial data submitted to FDA must demonstrate safety and effectiveness for its intended use.

CBER's assessments for xenotransplantation products include five major components: (1) source herd, (2) source animals from which the xenotransplantation product is derived, (3) product processing and testing (chemistry, manufacturing, controls), (4) preclinical assessments, and (5) clinical requirements.

Source Herd

FDA's regulatory approach for source animals used in xenotransplantation is focused on building layers of safety that include a balanced risk assessment and the use of best practices and validated technologies. The use of appropriate

source herds is the first line of defense against the risk of zoonoses. Specific recommendations for source herds can be found in the FDA Guidance for Industry: *Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* [4]. Source herds should be bred from closed herds of known origin. These animals should breed two or more generations under specific-pathogen free (SPF) conditions prior to use for human transplantation products. Gamete donors should meet the same qualifications as donor animals. Sourcing of animal tissues or gametes from abattoirs is not acceptable.

Maintenance of animal herds used to derive xenotransplantation products should include screening and sentinel animal testing for infectious disease. The frequency, agents tested for, and the methods used for testing should be justified. Animal feed should be free of rendered animal material. Animal herds should be maintained in a well-controlled and monitored pathogen-free environment with appropriately trained staff. Plans for bio-secure transportation of the animal and/or the xenotransplantation product to the tissue harvest site and the clinical site should be in place.

Source Animals for Xenotransplantation Products

Source animals selected from a suitable herd from which the xenotransplantation product is derived should be placed in quarantine at least 3 weeks prior to harvest of the xenotransplantation product. The source animal should be assessed for general health and tested for infectious agents prior to entering quarantine and prior to harvesting of cells, tissues, or organs. Procedures should be in place to minimize infectious disease risks during harvesting and handling.

Animal Welfare

Source animal facilities and manufacturers of xenotransplantation products should have procedures in place for animal husbandry, tissue harvesting, and euthanasia of animals. Procedures should be approved by an appropriate Institutional Animal Care and Use Committee in accordance with the Animal Welfare Act (7 U.S.C. 2131, *et seq*.). In cases where funds are received from the PHS, procedures must also comply with the PHS Policy on Humane Care and Use of Laboratory Animals [10], according to Section 495 of the PHS Act (42 U.S.C. 289(d)), CBER recommends that source animal facilities be accredited by the AAALAC. Standards for accredited facilities when funds are received from the National Institutes of Health are provided in the National Research Council's Institute for Laboratory Animal Research, Guide for the Care and Use of Laboratory Animals [11]. Source animal facilities and production processes are subject to FDA inspection under Section 704 of the Act (21 U.S.C. 374) and Section 351(c) of the PHS Act (42 U.S.C. 262(c)) [4].

Chemistry, Manufacturing, and Controls (CMC): Product Processing and Testing

Manufacturers of xenotransplantation products are expected to follow current Good Manufacturing Practices (cGMP). The FDA uses a life-cycle approach for cGMP where manufacturers may implement manufacturing controls that are appropriate during Phase 1 of development and work towards full cGMP compliance as product knowledge and manufacturing experience advances (21 CFR 312.23(a)(7)). Given the public health risks of xenozoonoses, rigorous safety measures need to be in place at all stages of product development.

The regulatory requirements for biologics products outlined in 21 CFR 610 apply to xenotransplantation products. For example, 21 CFR 610.10 Potency, 21 CFR 610.12 Sterility, 21 CFR 610 13 purity, and 21 CFR 610.14 Identity require specific tests for each of these attributes on the final product or final container material, unless exempted from this requirement by the CBER Director. The strategies for meeting these standards depend on the type of product: cells, tissues, or organs. For example, sampling for testing of an organ used for xenotransplantation may include a whole organ biopsy. Surrogate samples from adjacent tissues may be used for identity, sterility, and viral testing. Tests for potency could be assays that measure the function of the organ prior to administration. For cells and tissues, testing can be done directly on the cells or tissues to be transplanted.

Preclinical Assessments

In general, preclinical evaluations provide rationale for a proposed therapy. Preclinical studies are designed to discern the mechanism(s) of action, identify safe starting dose levels and dose escalation schemes for a patient population, assess preliminary benefit/risk profiles, and identify parameters for clinical monitoring. Above all, these studies must provide sufficient information to evaluate whether “human subjects are or would be exposed to an unreasonable and significant risk of illness or injury” (21 CFR 312.42 (b)(1)(i)). Preclinical assessments of xenotransplantation products include appropriate consideration and/or analysis of risks from potential cross-species infections, immune reactions between source animal and recipient, and function of the xenotransplantation product. Proof of concept studies for xenotransplantation products should use animal models that resemble the disease being studied as closely as possible. In some situations, it may be advisable to use more than one species; in others, it may be possible to collect both safety and proof-of-concept data in a single study. Administration of the xenotransplantation product in a preclinical study should mimic the planned clinical transplantation procedure including the immunosuppression regimen, the use of an immune-isolation device, site and means of administration, and re-implantation of the product, if applicable. When animals with IGA(s) are planned for use, animals used for preclinical studies should have the same IGA(s) as the animal

intended to be used for human implantation. Such animals should be assessed by the CVM prior to the initiation of preclinical studies. FDA recommends that developers obtain feedback regarding design of preclinical studies via the INTERACT mechanism [12].

Clinical Requirements

Regulatory and scientific principles governing the conduct of clinical trials for xenotransplantation products, similar to those for other products, require the submission of an IND. Patient might qualify to access xenotransplantation products through FDA's expanded access/compassionate use pathway when no comparable or satisfactory alternative therapy options are available (21 CFR 312.300). Specific criteria must be met to qualify for expanded access [13]. Current Good Clinical Practice (GCP) guidelines are to be followed for all INDs.

A clinical trial may be initiated 30 days following receipt of an IND unless FDA imposes a Clinical Hold. The grounds for doing this are enumerated explicitly in regulation (21 CFR 312.42(b)). The most commonly cited are: "Human subjects are or would be exposed to unreasonable or significant risk of illness or injury" (21 CFR 312.42 (b)(1)(i)) and "The IND does not contain sufficient information required under 21 CFR 312.23 to evaluate the risks to subjects of the proposed trial" (21 CFR 312.42 (b)(1)(iv)). The factors to be weighed in deciding whether there is "unreasonable" risk include: the natural history of the indication selected for the investigation—with detailed description of inclusion/exclusion criteria—available alternative therapies, persuasiveness of the preclinical proof-of-concept data collected in studies using the same product as that to be investigated, the number and severity of safety signals observed during animal studies in the context of this indication, and the generalizable scientific data likely to be generated. Thus, a product intended to treat a serious or life-threatening condition (e.g., advanced invasive cancer, spinal cord injury) may have a different safety profile than would apply to a cosmetic indication.

As set forth in 21 CFR 312.22 (a), "although FDA's review of Phase 1 submissions will focus on the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the instigations will yield data capable of meeting statutory standards for marketing approval." For further details, see FDA Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products [14]. Common elements of early phase xenotransplantation clinical protocol, as for most products, include: a small number of subjects treated in a staggered pattern where the timing between treating the first and second subject and additional subjects will allow for a defined period of post-treatment monitoring for adverse events prior to treating the next subject, inclusion/exclusion criteria, a detailed safety monitoring plan that evaluates a range of clinical and pharmacodynamic endpoints to inform the design of later trials, monitoring for possible infections or signs of rejection, and informed consent, including risks to close contacts [5]. As for any human trial, sponsors of xenotransplantation clinical

trials are responsible for informing patients of new scientific information as soon as possible in the event that new information on risks benefits, or the need for additional treatment is needed [4]. Special considerations for xenotransplantation products include monitoring for potential zoonotic infections, adverse xenograft-related immune response(s), and physiological mismatch of the implanted/transplanted product in vivo.

Additional Considerations for Xenotransplantation Products

In addition to the points enumerated above, another special concern for xenotransplantation products is the potential for transmission of perhaps novel zoonotic diseases—particularly those that may have been difficult to detect by conventional culture methods—not only to subjects involved in trials but to the human population at large. Precautions to address this concern include logistics of donor material procurement, careful monitoring of subjects for immune phenomena that may be associated with rejection, appropriate salvage strategies should rejection occur, and collection of donor material and human subject material for detailed laboratory analyses.

It is crucial to coordinate procurement of the xenotransplantation source material, transportation from the animal facility to the harvesting/manufacturing site (if applicable), and then to the clinical site. The IND application should include a plan for biosecure transportation, which will be reviewed by CBER for acceptability.

To further evaluate risks of potential zoonoses, tissues and cells from source animals and human recipients should be collected and archived for future studies. The goals for establishing archives are to ensure the health and safety of recipients and their close contacts, and to provide a source of materials for "look back" in the case patient health issues or public health issues arise. Source animal samples should include portions of the harvested material (cells, tissues, or organ) and leukocytes from the source animal. These samples should be collected at the time of harvest, and at predetermined intervals. For human recipients, samples of blood, and plasma saliva, and leukocytes should be collected pre-transplant, post-transplant at pre-determined intervals, and post-mortem. Guidelines for sample archiving are outlined in the U.S. Public Health Service (PHS) Guideline on Xenotransplantation [3].

Concluding Remarks

When xenotransplantation was first introduced as a potential means to alleviate the shortage of human cells, tissues, and organs for transplantation, xenogeneic pancreatic islet and liver cells appeared to have the most potential. In the past several years however, the transplantation of xenogeneic organs has become closer to reality due to the availability of animals with intentional genomic alterations, pigs in particular.

Despite these advances, more studies are needed to ensure safe and effective xenotransplantation. FDA supports the responsible use of xenotransplantation products keeping in mind the welfare of animals and the health and safety human recipients and the community at large.

References

1. Cooper DKC, Hara H, Iwase H, Yamamoto T, Jagdale A, Kumar V, et al. Clinical pig kidney xenotransplantation: how close are we? J Am Soc Nephrol. 2020;31(1):12–21.
2. Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. Cold Spring Harb Perspect Med. 2011;1(1):a006841.
3. USFDA. Public health service guideline on infections disease issues in xenotransplantation. Rockville: USFDA; 2001.
4. USFDA. Guidance for industry: source animal, product, Preclinical, and Clinical issues concerning the use of xenotransplantation Products in humans. Rockville: USFDA; 2016.
5. Hawthorne WJ, Cowan PJ, Buhler LH, Yi S, Bottino R, Pierson RN, et al. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China December 12-14, 2018: "the 2018 Changsha communique" the 10-year anniversary of the international consultation on xenotransplantation. Xenotransplantation. 2019;26(2):e12513.
6. USFDA. Guidance for Industry and Food and Drug Administration staff medical devices containing materials derived from animal sources (Except for In Vitro Diagnostic Devices). Rockville: USFDA; 2019.
7. USFDA. Draft guidance for industry #187: regulation of intentionally altered genomic DNA in animals. Rockville: USFDA; 2017.
8. USFDA. FDA staff manual guide 4102 Intercenter coordination of regulatory activities for genetically engineered animals and their expression products. Rockville: USFDA; 2015.
9. AVMA. AVMA guidelines for the euthanasia of animals. 2020th ed. Schaumburg: American Veterinary Medical Association; 2020; 121p.
10. U.S. Department of Healthand Human Services. Public health service policy on human care and use of laboratory animals. Bethesda: USDHHS; 2015.
11. NRC. Guide for the care and use of laboratory animals. 8th ed. Washington: The National Academies Press; 2011. 246 p.
12. SOPP 8101.1: regulatory meetings with sponsors and applicants for drugs and biological product. USFDA.
13. Expanded Access: USFDA; https://www.fda.gov/news-events/public-health-focus/expanded-access
14. USFDA. Guidance for industry: considerations for the design of Early-Phase Clinical Trials of cellular and gene therapy products. USFDA, Rockville; 2015.

Regulatory Considerations and Oversight: A European Perspective

10

Hendrik Jan Schuurman

Abbreviations

ATMP	Advanced therapy medicinal product
CAT	Committee for Advanced Therapies
CBMP	Cell-based medicinal products
CHMP	Committee for Medicinal Products for Human Use
DPF	Designated pathogen-free
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IXA	International Xenotransplantation Association
PERV	Porcine endogenous retrovirus
SACX	Secretary's Advisory Committee on Xenotransplantation
UKXIRA	United Kingdom Xenotransplantation Interim Regulatory Authority
WHO	World Health Organization

Introduction

Xenotransplantation into humans is defined as any procedure that involves the direct transplantation, implantation, or infusion into a human recipient of live cells, tissues, or organs from a non-human animal source, or indirect exposure, where human body fluids, cells, tissues, or organs that have had ex vivo contact with live non-human animal cells, tissues, or organs before being administered. This definition was posted on the website of the World Health Organization (WHO) but is no longer

H. J. Schuurman (✉)
Schubiomed Consultancy BV, Utrecht, The Netherlands

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_10

a search item on the WHO website. This aside, this definition is nowadays used worldwide, including regulatory agencies like the Food and Drug Administration (FDA) in the USA [1]. The European Medicines Agency (EMA) was from the beginning in 2000 more focused on xenogeneic cell-based therapy [2]. In Europe, also the European Parliament became recently interested in xenogeneic transplantation [3]. This chapter focuses on the first category mentioned above. Viable products for use in humans are called xenotransplantation products, to be differentiated from non-viable products that are called xenografts: this differentiation was first mentioned in regulatory documents issued by the FDA [4].

Most xenotransplantation products are from porcine origin, despite the fact that the general definition is much broader, i.e., including any cross-species transplantation. Originally, organs (kidney, heart) received most attention. A second category includes cells [5], mainly pancreatic islets given either by infusion of naked cells in the portal vein with subsequent lodging in the liver, or positioned after encapsulation at various locations like the subcutaneous space or the peritoneum, or administered in devices at various body locations that were implanted there prior to the cells. Xenogeneic islet transplantation has also been a focus of attention by the scientific community organized in the International Xenotransplantation Association (IXA) [6]. Decellularized tissue represents a third category [7]. This is a heterogeneous group of products, representing matrix scaffolds in tissue repair like heart valves and corneas, or scaffolds used in reseeding of cells in regenerative medicine.

The fact that the rejection of a xenogeneic (porcine) graft is more stringent than that of an allogeneic (human) graft, together with the progress in genetic engineering, has initiated attempts to genetically modify donor pigs. The first achievement, now 25 years ago, was a swine carrying a transgene of a complement regulator, with the result that naturally occurring anti-pig antibodies did not induce so-called hyperacute rejection [8]. Since then, a large spectrum of transgenes has been introduced, mainly to diminish immune reactions, coagulation and inflammation at the surface of porcine cells. Genetic modification has also been introduced to delete xenogeneic antigens to which human immune reactions are directed, so-called knock-outs [9]. The efficacy of these genetic modifications has been shown in transplantation of pig organs in nonhuman primates, a large animal model that closely resembles the pig-to-human transplant condition. A Xenotransplantation Consortium in Germany has recently contributed to this success by showing 195 days survival in pig-to-baboon orthotopic life-supporting heart transplantation [10]. The efficacy results, especially data on long-term survival, enabled the perspective of initiating clinical explorations [11], which was the topic of a joint symposium organized by the FDA and IXA in 2017 [12]. A third target for genetic engineering is of more recent date, namely the knock-out of genes encoding elements of porcine endogenous retrovirus (PERV) [13].

Regulatory agencies became interested in xenotransplantation when, about 25 years ago, certain pharma and biotech companies started xenotransplantation programs, with the claim to introduce porcine organs at large scale in clinical medicine. Also, around that time it was shown that in an in vitro cell culture model

PERV could productively transmit from a pig to a human cell [14]. This raised concern about safety of a xenotransplantation product, i.e., the potential of transmission of infectious agents from the pig donor graft into the human recipient, subsequently causing disease, not only in the recipient but also in relatives or even the human population. This not only regarded exogenous pathogens but also endogenous agents like PERV. Advisory committees within the government were established in the UK (United Kingdom Xenotransplantation Interim Regulatory Authority, UKXIRA, in existence between 1997 and 2006) and USA (Secretary's Advisory Committee on Xenotransplantation, SACX, in existence between 1999 and 2005). In Europe, the establishment of UKXIRA was related with the focus of Imutran Ltd (a Novartis Pharma AG Company since 1996) to advance their research to clinical development. After Novartis left the field in 2000 [15], UKXIRA reduced its activities. Related to these activities, groups in the UK issued seminal evaluations of xenotransplantation ethics [16, 17]. Within the SACX a draft informed consent form was developed in 2004 which is nowadays available at the website of the IXA [18]. The first documents issued by regulatory agencies (Guidances by FDA or Guidelines by EMA), in particular from the FDA, addressed this safety aspect [4, 19]. Also, the WHO issued a Guidance at that time (2001) [20] and subsequently organized Global Consultation meetings, the third one in 2018 [21]. Already in 2004 the WHO expressed its concern in a resolution requesting proper control by regulatory agencies when using xenotransplantation products in clinical medicine [22].

In Europe, the EMA has issued a Guideline in 2009 focusing on the microbiological safety of cell therapy products [23]. In the following, the global regulatory approach in various topics of xenotransplantation oversight will be described focusing on the European Union, e.g., the approach by the EMA.

Regulation of Xenotransplantation

Medicinal Products in Europe

In Europe, xenotransplantation products for use in humans are considered a medicinal product. In line with Directive 2001/83/EC, the products fulfill one of the requirements for the substance: mico-organisms, whole animals, part of organs, animal secretions, toxins, extracts, blood products [24]. Following this consideration, xenotransplantation products are considered an advanced therapy medicinal product (ATMP), for which a Regulation was issued in 2007 [25]. ATMPs are medicines for human use that are based on genes, tissues or cells, and are classified in three main types [26, 27]:

- gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases,

- somatic cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics, or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases,
- tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue,
- combined ATMP, e.g., an ATMP covered in a medical device. Some ATMPs may contain one or more medical devices as an integral part of the medicinal product, which are referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold.

There are three main categories of xenotransplantation products: cell therapy products, organ transplants and decellularized products/scaffolds. These are described in more detail below.

Regulatory Oversight

Regarding medicinal products, globally, regulatory agencies are well equipped to address chemistry-based compounds and extraction-based biological compounds. The process in evaluation of new medical entities and its follow-ups is well established, e.g., by a large series of Guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that in part overlap with, or were followed by, documents issued by regulatory agencies [28]. This broad experience is less for product types that are of more recent date (i.e., last decades) in discovery and development, like ATMPs. For instance, the number of ATMPs that are nowadays on the market is quite limited: in 2018 there were 10 ATMPs approved for market authorization in Europe [29] which is discussed further below.

It is evident that the process and procedures used in evaluation of chemicals and biologicals do not apply for xenotransplantation products but require a different approach in oversight. From a philosophical view, such a regulatory approach is immensely difficult to establish: a simple (low molecular weight) chemical substance is very well characterized, while the product characterization is already causing problems for high molecular weight recombinant proteins with intrinsic variations, and almost impossible for cells that produce a huge variety of factors dependent on the environment in which they reside, and even can evolve becoming dangerous in the host (e.g., malignant transformation). Extending this to an organ, the question can be raised of how to control organ activities besides those intended to function properly in replacing the deficiency, i.e., organ activities that are either not known or not controllable. Essentially, presently used methodology in testing chemicals, or even recombinant proteins, cannot be applied, and results of clinical trials or long-term evaluation after market entry are awaited to learn more about these aspects. In part, the use of surrogate markers could contribute to solving these issues, being intrinsic to the nature of innovative products.

Regulation: Safety

Regarding xenotransplantation products, regulatory authorities have mainly addressed the safety aspects associated with transmission of infectious pathogens. The possibility of cross-species transmission of PERV mentioned in the section "Introduction" above resulted in a letter from the FDA in 1998 stating that clinical trials should be put on hold until adequate monitoring strategies are developed and implemented [30]. Subsequently, FDA issued a Guidance, which after some revisions in 2016 is still in place [4]. This Guidance applies to all xenotransplantation products, irrespective of the category mentioned in the section "Medicinal Products in Europe", and describes, amongst others, the way in which donor animals should be generated in high-hygiene conditions (designated pathogen-free, DPF). The Guidance does not present lists of pathogens that should excluded in the donor herd: such lists are published by the scientific community [31–34].

Regulation: Efficacy

Regulatory agencies have not issued detailed requirements regarding efficacy assessment. This is understandable because such requirements might be different for the different categories of products mentioned in the section "Medicinal Products in Europe", while safety aspects related to cross-species transmission of infectious pathogens is more universal. Also, efficacy features are indirectly associated with those of the human equivalent after replacing the deficient organ/tissue/cells by a porcine-derived product. There is one item that is not always considered, namely the physiological compatibility between the same organ/tissue/cell in a pig and a human. This was addressed already in the early days three decades before in exploratory comparisons for kidney and heart [35–37], and in more detail recently for islets [38]. This aside, regulatory agencies evidently require efficacy data in judgement of xenotransplantation products in the application of phase transition from nonclinical to clinical development, but do not define the respective specifications. It is realized that this requires a case-by-case approach, including a product-related appropriate animal model. This approach often requires discussion with the regulatory agencies about selecting the model and the study protocol. The preferred animal model differs between the various continents on earth: e.g., models in nonhuman primates seem still preferred in USA while this is not a preference in Europe. Also, for a first cornea xenotransplantation product in Korea nonclinical data in a nonhuman primate model were proposed [39]. The rationale for selecting nonhuman primates is the close similarity with humans in structure and function of the immune system including aspects of sensitivity to immune suppression (especially biologicals), and similarities in organ physiology. But, in Europe there is a strict Directive (i.e., not a Guideline) regarding research in nonhuman primate species [40]; unlike the situation in, e.g., the USA, there is no longer in Europe a widespread availability of centers where research in nonhuman primates is conducted. For some xenotransplantation products like cell therapy products, it has been proposed in

communications with regulatory experts to use animal models in rodents with properly designed studies addressing efficacy and safety (unpublished communications).

Regulation: Genetic Modification

Interestingly, changing from natural (wild-type) animals to genetically modified animals changes the picture on efficacy data. The best illustration comes from the FDA-IXA symposium mentioned above [12]: the genetic modification of an animal purposed to provide a xenotransplantation product requires not only data on normality in life of animals, e.g., during breeding and holding including animal welfare, but also the efficacy of the component inserted by transgenesis or the component deleted in a knock-out procedure. In other words, the product of genetic modification is considered a medicinal product. In practice, this might present a complication for complex modifications including multiple transgenes or knock-outs (in recent studies up to 10 [9]), when it is required to provide data separately for each individual component. First, just like in conventional approaches requiring multiple drugs (chemical compounds and/or biologicals), there is often synergy between the individual components and the assessment of each single component which requires multiple costly experiments in animal models. Second, even more important, the basic of a "drug" in genetic modification is nowadays a gene sequence combining multiple transgenes or knock-outs which cannot be separated from each other. Also, synergy assessments requiring different dose levels of individual components cannot be performed. There is not yet a solution reported for this potential complication by regulatory agencies, e.g., in proper Guidelines or Guidances, but the item is relevant if efficacy needs to be demonstrated for each individual component in a genetic modification.

Nowadays, there is detailed regulation of genetically modified organs in place, within Europe a specific Guideline [41]. Issues for consideration include the donors of xenotransplantation products, in which the focus is on the description of the genetic constructs, generation of genetically modified animals, husbandry and animal welfare, persistence of the synthesis and function of gene products in successive generations, special procedures in disposal of animal remains and materials (including but not limited to use of materials elsewhere like in clinical applications), assurance that there is no entrance of materials in the food chain, and respective record-keeping and reports.

Archiving and Storage of Materials

The focus of regulatory assessment on microbiological safety is considering not only a potential disease in the individual patient due to a pathogen acquired by a xenogeneic transplant, but also the subsequent spread among relatives and the population in general (i.e., safety is a public health issue). To this end regulatory

authorities demand that the recipient of a xenotransplantation product consents to a lifelong monitoring, donation of biological test samples, and finally a necropsy after death. Also, materials from the porcine donor and the human recipient should be stored for substantial periods (including storage of cells in liquid nitrogen), i.e., 50 years according to documents from US agencies [19] and 30 years in the EU ATMP Regulation [25]. This requirement asks for substantial financial investments by the sponsor of the trial and can only be resolved, especially regarding the logistics, in agreement between sponsor, the human recipient, and the respective governmental health institutions. There are no reports in literature whether and how a solution was achieved. This may be except for the situation in Switzerland, where clinical transplantation is overseen by law [42] and the government has issued an Ordinance on clinical xenotransplantation in which it is stated that the samples mentioned above should be made available to cantonal authorities [43].

Informed Consent

Clinical trials require an informed consent from the subject (or their surrogate) receiving the test material, and this is even more the case for a recipient of a xenotransplantation product [18]. Xenotransplantation-associated aspects include, as stated above, the consent of lifelong monitoring and agreement to an autopsy after death, which is in apparent contrast to the right of the patient to withdraw from a clinical trial without further consequences [44]. In a commentary on the first life-saving xenogeneic heart transplant in early 2022 a potential solution for this issue was proposed, namely the informed consent to be written as a Ulysses contract [45]. A Ulysses contract is a document by which one person binds himself by agreeing to be bound by others. In medicine such contracts have primarily been discussed as enabling to treat people with episodic mental illnesses, where the features of the illness are such that they now judge that they will refuse treatment at the time it is needed [46, 47].

Xenogeneic Cell Transplantation

Considering allogeneic islet transplantation, there was no regulatory oversight in place when the first transplants of human islets entered clinical medicine. Although logically being considered an ATMP, human islets received an exempt situation after the ATMP regulation was established [48]. As a consequence for xenogeneic cells, regulatory oversight cannot be just copied from the conditions for human islets [49].

Essentially, in Europe a substantial series of Regulations, Directives and Guidelines have been issued after the basic ATMP regulation 1394/2007 [25] that apply to the regulatory oversight of cell therapy products (called cell-based medicinal products, CBMP), being either autologous, syngeneic, allogeneic or xenogeneic (Table 10.1) [50]. In addition, the Guideline on genetically modified materials mentioned above has to be considered if applicable [41].

Table 10.1 Cell-therapy and tissue engineering: relevant EMA guidelines

Cell-therapy and tissue engineering	• The *overarching guideline* for human cell-based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) • Reflection paper on *stem cell-based medicinal products* (EMA/CAT/571134/2009) • Reflection paper on in vitro cultured *chondrocyte* containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009) • Guideline on *xenogeneic cell-based medicinal products* (EMEA/CHMP/CPWP/83508/2009) • Guideline on potency testing of *cell based immunotherapy medicinal* products for the treatment of cancer (CHMP/BWP/271475/06) • Reflection paper *on clinical aspects related to tissue engineered products* (EMA/CAT/573420/2009) • Guideline on *safety and efficacy follow-up and risk management* of advanced therapy medicinal products (EMEA/149995/2008)
Gene therapy	• Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019) • Quality, non-clinical and clinical aspects of medicinal products containing *genetically modified cells* (CHMP/GTWP/671639/2008)
Biologicals: drug product	• Guidance on the *use of bovine serum* in the manufacture of human biological medicinal products (CPMP/BWP/1793/02) • *Minimising the risk of transmitting animal apongiform encephalopathy agents* via human and veterinary medicinal products (EMA/410/01) • CHMP/CAT position statement on *Creutzfeldt-Jakob disease* and advanced therapy medicinal products (CHMP/CAT/BWP/353632/2010) • Position paper on re-establishment of *working seeds and working cell banks using TSE compliant materials* (EMEA/22314/02) • Guideline on the *use of porcine trypsin* used in the manufacture of human biological medicinal products (EMA/CHMP/BWP/814397/2011)
Biologicals: drug substance	• Note for guidance on *plasma derived medicinal products* (CPMP/BWP/269/95)
Quality: excipients	• Guideline on *excipients* in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006)
Quality: ICH	• ICH Q2 (R1) validation of *analytical procedures*: text and methodology (CPMP/ICH/381/95) • ICH Q5A (R1) viral safety evaluation of *biotechnology products derived from cell lines* of human or animal origin (CPMP/ICH/295/95) • ICH Q5C stability testing of *biotechnological/biological products* (CPMP/ICH/138/95) • ICH Q5D derivation and *characterisation of cell substrates* used for production of biotechnological/biological products (CPMP/ICH/294/95) • ICH Q5E comparability of *biotechnological/biological products* (CPMP/ICH/5721/03) • ICH Q7 good manufacturing practice for *active pharmaceutical ingredients* (CPMP/ICH/4106/00) • ICH Q8 (R2) *pharmaceutical development* (CHMP/ICH/167068/04) • ICH Q9 *quality risk management* (EMA/CHMP/ICH/24235/2006) • ICH Q10 *pharmaceutical quality system* (EMA/CHMP/ICH/214732/2007)

(continued)

Table 10.1 (continued)

Safety: ICH	For non-clinical specific guidance, see • ICH S6 (R1) preclinical safety evaluation of *biotechnology-derived pharmaceuticals* (CHMP/ICH/731268/1998)
Safety and efficacy: Biostatistics	• Guideline on *clinical trials in small populations* (CHMP/EWP/83561/2005) • Points to consider on applications with *1. Meta-analyses; 2. One pivotal study* (CPMP/EWP/2330/99)
Efficacy: ICH	• ICH E1 the extent of population *exposure to assess clinical safety* (CPMP/ICH/375/95) • ICH E3 structure and content of *clinical study reports* (CPMP/ICH/137/95) • ICH E4 dose response information to support *drug registration* (CPMP/ICH/378/95) • ICH E6 (R1) *good clinical practice* (CPMP/ICH/135/95) • ICH E7 *geriatrics* (CPMP/ICH/379/95) • ICH E8 general considerations for *clinical trials* (CPMP/ICH/291/95) • ICH E11 clinical investigation of *medicinal products in the paediatric population* (CPMP/ICH/2711/99)
Clinical safety and efficacy	*Existing clinical guidance* for the studied indication(s) should be consulted.
European Pharmacopoeia	The following monographs from the European pharmacopoeia (Ph. Eur) should be considered, where relevant: • Ph.Eur. monograph on *human haematopoietic stem cells* (Cellulae stirpes haematopoieticae humanae) version 7.2 • Ph.Eur. monograph on method of analysis (2.7.23.) *numeration of CD34/CD45+ cells in haematopoietic products*. Version 7.2 • Ph.Eur. monograph on method of analysis (2.7.28.) *Colony-forming cell assay for human haematopoietic progenitor cells*. Version 7.2 • Ph.Eur. monograph on *Nucleated Cell Count and viability* (2.7.29.) • Ph.Eur. monograph on *Nucleic Acid Amplification Techniques* (2.6.21.) • Ph.Eur. monograph on *flow cytometry* (2.7.24.) • Ph.Eur: (2.6.27) *microbiological control of cellular products* • Ph.Eur: (2.6.1.) *sterility* • Ph.Eur: (5.1.6) *alternative methods for control of microbiological quality* • Ph.Eur. monograph *Mycoplasmas* (2.6.7.) • Ph.Eur. monograph on *bacterial endotoxins* (2.6.14.) • General chapter 5.2.12 raw materials for the production of cell-based and gene therapy medicinal products

Data from reference [50]
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

A complex situation exists for the regulation of cells that are encapsulated. Since the optimal way of administration has not been established, and the need for protection from the local environment mediating destruction by immune and inflammatory reactivity was recognized, encapsulation has been introduced to facilitate ongoing function of the cells after transplantation. Two main tools have been introduced in research endeavors: (1) encapsulation in vitro using molecules, mainly alginate-based, that form hydrogel microspheres in an electrostatic network or covalent bonding, or (2) insertion in devices that are implanted at location and adapted to the local environment before administration of the cells. Generally, the encapsulated cells in the capsule are considered the product (the active pharmaceutical ingredient) and the encapsulated product is considered a combined ATMP, while in the second situation the naked islets are considered the xenotransplantation product independent of how the device is constructed and implanted. Evidently, this is because device-specific regulations are in place, which are not discussed here.

Xenogeneic Solid Organ Transplantation

It is not possible to translate regulatory oversight of a human solid organ to the situation of a xenogeneic solid organ transplantation product. This is because a human organ for transplantation, irrespective of the donor (e.g., a deceased individual or a living organ donor, a patient's relative), is not considered a medicinal product, because it fulfills the condition that the material is not substantially modified and/or exerts the same essential function in donor and recipient (i.e., homologous use). In Europe, human organ transplantation is defined as follows: "Human organ transplantation is the therapeutic use of human organs as a substitute for one that is nonfunctional. The organ may come from a deceased or a living donor" [51]. Human organ transplantation is overseen by regulatory agencies in each individual member state according to Directive 2010/45/EU [52], which is transposed into national legislation. A more detailed guideline concerning, for example, infectious risks, has been issued by the European Directorate for the Quality of Medicines & HealthCare [53].

Hence, although a solid organ was the apparent initiative for regulation of xenotransplantation products, there is no specific regulatory oversight established for a solid organ xenotransplantation product. This situation is even more complicated since solid organs are to be considered an ATMP, and many associated regulatory requirements in the network of Regulations and Directives do not easily apply to solid organs. This issue especially regards product quality for which requirements

associated with the ATMP status differ from those for a human transplant: noteworthy, human organs themselves used for transplantation are not subject to quality testing like is done in release of medicinal products.

In this discussion it should be realized that xenogeneic donors provide unique opportunities for product characterization and quality assessment that is not possible for their human equivalents. Such testing includes aspects of functional quality and consistency of parameters that are together with others normally part of quality assessment and release of medicinal products. In this view, a xenogeneic solid organ is fundamentally different from the organ of a human donor. Elsewhere this point is addressed in more detail [54] in relation to the flow chart of the process starting with the selection of an animal in the source facility and ending with the delivery of the solid organ product in the clinical transplant center (Fig. 10.1). Table 10.2 summarizes the main activities at the distinct locations in this flow chart as well as a proposal for the quality systems to be applied at each site for a solid organ from a (genetically modified) animal.

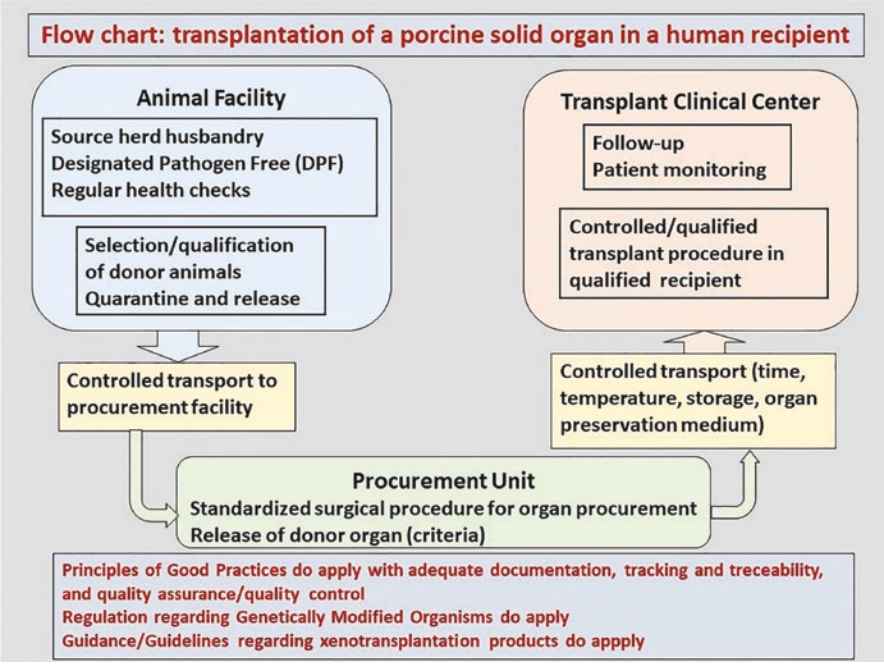

Fig. 10.1 Flow chart of the generation of an organ from a (genetically-modified) pig for transplantation in a human recipient. The three main locations are depicted, i.e., the animal facility, the procurement unit and the transplant clinical center, and the transport in between of the donor pig and the procured organ. Also the regulatory oversight of activities in this flow chart are summarized. Reproduced from reference [54], with permission

Table 10.2 Key activities in the process of a xenotransplantation clinical trial with an organ procured from a (genetically-modified) pig

Key activity[a]	Source animal	Organ procurement	Clinical application (transplantation)
Material acceptance (begin)	Herd health status and monitoring	Acceptance animal: macroscopic inspection according to GLP	Acceptance organ: macroscopic inspection
Quality management system	"Good husbandry practices"	"Good procurement practices"	Patient eligibility and selection: Informed consent Transplant functionality as part of routine follow-up according to GCP
Risk evaluation and management	Supply of animal	Supply of organ	Cross-species infection and physiologic incompatibilities
Quality control (end)	Release criteria: microbial safety (post release) Organ functionality according to GLP	Release criteria: microbial safety (post release) Organ inspection according to GMP	Monitoring for cross-species transmission post administration Archiving of tissue/cells Option for human transplant
Transport	Transport security	Shipment security according to GDP	N/A
Responsibility	Provider (husbandry)	Procurement organization	Principal investigator (responsible personal) at clinical center

Reproduced from reference [54], with permission
GCP Good clinical practices, *GDP* Good distribution practices, *GLP* Good laboratory practices, *GMP* Good manufacturing practices, *N/A* Not applicable
[a] Precludes regulatory oversight for distinct activities

Decellularized Products

Decellularized products include a scaffold in repair of tissue or scaffold in regenerative medicine for reseeding by autologous cells [55]. If the tissue is not containing viable cells, it is a xenograft and not a xenotransplantation product, and essentially a medical device as described in the section "Introduction". This situation is independent of the fact whether the donor animal is genetically modified or not. For any other condition, i.e., when the tissue contains viable cells, is reseeded with autologous cells, or is transplanted as fresh tissue after decellularization, the product is considered an ATMP. Considering the huge variability and in the absence of product-specific regulation, regulatory oversight evidently needs to be done on a case-by-case basis.

The Role of the European Medicines Agency

Within the European Union, each member state has its regulatory agency that oversees the development and use of medicinal products. For ATMPs a centralized process has been established in which the development, from advanced research to

market authorization, is overseen by EMA [56]. This central authorization of ATMPs via the EMA seems logical considering the huge variability in composition between products with its consequence for the CMC (Chemistry, Manufacturing and Control) part in product overview, and considering the low numbers of ATMPs proposed for clinical development requiring special expertise within the respective regulatory agency. There is flexibility in the routes toward market authorization, i.e., a first and subsequent contacts with regulators can be with a country-based agency. This includes scientific advice for items where the country-based agency has specific experience: an example is the Paul Ehrlich Institute in Germany, which is the competent authority for this group of medicines in Germany [57]. To illustrate this, staff of the institute conduct research in the field which includes xenotransplantation as illustrated by a reference [55].

Central in the oversight of ATMPs is the Committee for Advanced Therapies (CAT) [58]. The main responsibility of this committee is to prepare a draft opinion for each ATMP application submitted to EMA, before the Committee for Medicinal Products for Human Use (CHMP) prepares a final opinion on the marketing authorization. The activities of CAT span a wide range and include, amongst others, classification of a new product for the status as ATMP [27, 59], and scientific advice at various stages of the development process [60, 61]. CAT also organizes workshops on various topics related to development of ATMPs [62, 63]. All aspects in development, illustrated by the network of Regulations and Directives (Table 10.1) [50], are considered in the evaluation of ATMPs during development, in contacts between sponsor and CAT.

As stated in the section "Regulatory Oversight" the number of ATMPs that received market authorization in Europe is rather low, i.e., 10 in 2018, and this low number is at first view related to the high costs in production and/or small target patient populations. This low number prompted a survey among companies involved with development of ATMPs aiming to identify challenges experienced in ATMP development [29]. This survey published in 2018 included 68 companies out of a total of 271 companies that were approached, the majority being small- and medium-sized enterprises (SMEs) (65%). The results showed that challenges were quite variable, most often related to country-specific requirements (16%), manufacturing (15%), and clinical trial design (8%).

The low number of ATMPs that made it to market also prompted regulatory authorities to develop support programs. The Directorate General Health and Food Safety of the European Commission together with EMA initiated a number of initiatives to improve the regulatory environment for ATMPs thereby facilitating the development and authorization of ATMPs in the EU for the benefit of patients [64]. As part of this supportive action, EMA has included in the section "Guidance on ATMP Development" of the overview page on ATMPs [26] checklists and flowcharts for preclinical and clinical development, and for quality of products in development: an extract of most important requirements for the preclinical and clinical development, and for quality, is presented in Tables 10.3, 10.4 and 10.5.

Table 10.3 The most important regulatory requirements during the preclinical development phase of cell-based medicinal products (EMA, ATMP)

What are the potential risks associated with the clinical use of ATMP	Perform a risk based approach, including addressing any safety concerns from previous clinical studies of similar products
What is the intended patient population?	Identify specific patient eligibility criteria based on safety, pharmacokinetic and efficacy data
What are the toxicological and safety effects?	Perform general safety and toxicity studies, including studies based on risk-based approach
What is the therapeutic window? What should be the starting dose and dosing scheme in humans	
What is the efficacy? What is the mechanism of action?	Carry out a proof of concept study
What are the pharmacokinetic characteristics?	Perform a pharmacokinetic study investigating, among others, distribution and persistence Investigate the inadvertent germline transmission

Data from reference [26]

Table 10.4 The most important regulatory requirements during the clinical development phase of cell-based medicinal products (EMA, ATMP)

Does the drug reach the site of action?	Investigate the feasibility of the route of administration and pharmacokinetic characteristics such as biodistribution and elimination
Does the compound cause its intended pharmacological effects? And what are the undesired pharmacological effects?	Demonstrate the mechanism of action and off-target pharmacological effects
Does the compound have Beneficial effects on the disease or its pathophysiology?	Investigate the effect on The disease and relevant Pathophysiological systems
What are the sources of variability in drug response in the target population?	Determine sources of variability in Drug response (e.g. concomitant Medication, disease status, prognostic factors) and if dose adjustment is required
What is the therapeutic window?	Determine the starting dose of the first in human study and determine the optimal dose regimen based on all safety and efficacy data
Are there off-target Pathophysiological effects?	Investigate safety and tolerability

Data from reference [26]

Table 10.5 The most important regulatory quality-related requirements of cell-based medicinal products (EMA, ATMP)

Is the development of the potency assay on schedule?	Perform a potency study
Are the products comparable across all studies Will future changes in the manufacturing process (including upscaling) or product be needed?	Consider a comparability exercise Describe control strategy of materials and manufacturing process
What is the location of the manufacturing site	Ensure the manufacturing adhere to the Suropean GMP regulations Read the rules that apply to importing products into the EU after production outside EU
Have you started preparing the marketing authorization dossier	Define the active drug substance and the final drug product and determine if it is a new active substance Identify raw materials and starting materials Check the community register of orphan medicinal product to see if a similar medicinal product for the same therapeutic indication has been granted market exclusivity protection

Data from reference [26]

Conclusions and Perspectives

After incidental transplants in the past, xenotransplantation received a boost three decades ago, combining then newly available immunosuppressants with genetic modification of animals some years later. Today, the field has made substantial breakthroughs and periods of stabilization like any other young discipline in medicine. For xenogeneic encapsulated islets a small clinical trial has been conducted in New Zealand [33, 65], for which a long process proved necessary to receive Ministerial approved [6]. In the first days of 2022, a first-in-human exploratory study was conducted with a heart from a pig with 10 gene modifications in a patient with terminal heart failure [66]. This study was approved by the FDA [67, 68] following the conditions of expanded access ("compassionate use") [69]. Earlier, the FDA approved a phase 1/2 clinical trial testing vital skin from miniature swine with 1 gene knock-out modification in patients with severe burn [70, 71].

Market entry of xenotransplantation products has not yet been realized. In Europe, clinical trials have not yet been initiated, but a number of groups have been in Scientific Advice meetings with regulatory agencies discussing products at the advanced nonclinical level.

Xenotransplantation products are innovative and new for regulators [72]. Today there is a spectrum of regulatory documents, which form the basis for clinical trial applications by sponsors of ATMPs. Most of these regard safety, i.e., the risk of transmission of endogenous or exogenous infectious pathogens. Noteworthy, with

the exception of a Guideline for xenogeneic CBMPs [23], there is no regulatory document that specifically addresses xenotransplantation products. For CBMPs the presently available regulatory oversight developed for autologous, syngeneic and allogeneic cells seems suitable to provide oversight for these xenotransplantation products, but oversight of xenogeneic organs might request additional regulatory documentation.

Since there is very little experience in evaluating xenotransplantation products by regulatory agencies, mutual experience needs to be built with sponsors, in which in-depth discussions between the parties, regulators and sponsors, are needed and highly recommended. Besides IXA [12] the International Society for Cell & Gene Therapy should be mentioned as medium in these translations, considering the mission of this society [73]. Xenotransplantation products are complex regarding their oversight, and the complexity regards not only efficacy and safety but also compatibility in physiology and function. This latter point has received little attention but needs to be addressed in studies preparing for clinical trials, and later market entry. Experience in long-term survival of porcine islets in diabetic monkeys serves to illustrate this issue [38].

There are a number of points that need discussion between regulators and sponsors. One of these regards the potential transmission of endogenous infectious agents: this is not only of relevance for the patient receiving a xenotransplantation product, but also is a potential public health issue. To this end, lifelong patient monitoring and storage of samples from porcine donor and human recipient has been requested. The logistics in realizing this demand needs discussion between sponsor, potential human recipients, and health institutions.

Besides these complexities, xenotransplantation has still many opportunities to bring innovative new medicinal products to clinical medicine. There have been—and still are—hurdles in development, and there might be still a long way to go, but with the present perspectives to initiate or perform exploratory clinical trials there are major achievements anticipated.

Acknowledgement The author gratefully acknowledges the stimulating discussion about regulatory affairs of xenotransplantation products with Nancy Veulemans (4C Partner bvba, Mechelen, Belgium) and Karin Hoogendoorn (Leiden University Medical Center, Leiden, The Netherlands).

Conflict of Interest Henk-Jan Schuurman is director at SchuBiomed Consultancy and provides consultancy in the biomedical sector worldwide.

References

1. Food and Drug Administration. Xenotransplantation. Current as of 03/03/2021. https://www.fda.gov/vaccines-blood-biologics/xenotransplantation. Accessed 23 Aug 2022.
2. European Medicines Agency. Concept paper on the development of a committee for proprietary medicinal products (CPMP) points to consider on xenogeneic cell therapy. November 16, 2000. https://www.ema.europa.eu/en/documents/scientific-guideline/

concept-paper-development-cpmp-points-consider-xenogeneic-cell-therapy_en.pdf. Accessed 23 Aug 2022.
3. Think Tank, European Parliament. What if xenotransplantation was the answer to the donor organ shortage? At a Glance. 13-01-2022. https://www.europarl.europa.eu/thinktank/en/document/EPRS_ATA(2022)697212. Accessed 23 Aug 2022.
4. Food and Drug Administration: source animal, product, preclinical, and clinical issues concerning the use of xenotransplantation products in humans guidance for industry. 2003, revised December 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/source-animal-product-preclinical-and-clinical-issues-concerning-use-xenotransplantation-products. Accessed 23 Aug 2022.
5. Huang C-P, Yang C-Y, Shyr CR. Utilizing xenogeneic cells as a therapeutic agent for treating diseases. Cell Transplant. 2021;30:9636897211011995. https://doi.org/10.1177/09636897211011995.
6. Cozzi E, Tallacchini M, Flanagan EB, et al. The international xenotransplantation association consensus statement on conditions for undertaking clinical trials of porcine islet products in type 1 diabetes—chapter 1: key ethical requirements and progress toward the definition of an international regulatory framework. Xenotransplantation. 2009;16:203–14. https://doi.org/10.1111/j.1399-3089.2009.00540.x.
7. Capella-Monsonís H, Zeugolis D. Decellularized xenografts in regenerative medicine: from processing to clinical application. Xenotransplantation. 2021;28:e12683. https://doi.org/10.1111/xen.12683.
8. Cozzi E, White DJ. The generation of transgenic pigs as potential organ donors for humans. Nat Med. 1995;1:964–6. https://doi.org/10.1038/nm0995-964.
9. Cooper DKC, Hara H, Iwase H, et al. Justification of specific genetic modifications in pigs for clinical organ xenotransplantation. Xenotransplantation. 2019;26:e12516. https://doi.org/10.1111/xen.12516.
10. Längin M, Mayr T, Reichart B, et al. Consistent success in life-supporting porcine cardiac xenotransplantation. Nature. 2018;564:430–3. https://doi.org/10.1038/s41586-018-0765-z.
11. Cooper DKC, Hara H, Iwase H, et al. Pig kidney xenotransplantation: progress toward clinical trials. Clin Transpl. 2021;35:e14139. https://doi.org/10.1111/ctr.14139.
12. Cooper DKC, Cowan P, Fishman JA, et al. Joint FDA-IXA symposium, September 20, 2017. Xenotransplantation. 2017;24:e12365. https://doi.org/10.1111/xen.12365.
13. Niu D, Wei HJ, Lin L, George H, et al. Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9. Science. 2017;357:1303–7. https://doi.org/10.1126/science.aan4187.
14. Patience C, Takeuchi Y, Weiss RA. Infection of human cells by an endogenous retrovirus of pigs. Nat Med. 1997;3:282–6. https://doi.org/10.1038/nm0397-282.
15. Netting J. Novartis axes UK transplant centre. Nature. 2000;407:547. https://doi.org/10.1038/35036712.
16. The Advisory Group on the Ethics of Xenotransplantation. Animal tissue into humans. London: The Stationary Office Publications Centre; 1996. ISBN 0113218664.
17. Nuffield Council on Bioethics. Animal-to-human transplants: the ethics of xenotransplantation. London: Nuffield Council on Bioethics; 1996. https://www.nuffieldbioethics.org/wp-content/uploads/xenotransplantation.pdf. Accessed 23 Aug 2022.
18. U.S. Department of Health and Human Services, Secretary's Advisory Committee on Xenotransplantation. Informed consent in clinical research involving xenotransplantation. Draft June 2004. https://www.tts.org/images/stories/ixa/regulatory_documents/8_SACX_Informed_consent_US_DHHS_June_2004.pdf. Accessed 23 Aug 2022.
19. US Public Health Service guideline on infectious disease issues in xenotransplantation. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2001;50:1–46.
20. World Health Organization, Department of communicable disease surveillance and response. WHO Guidance on xenogeneic infection/disease surveillance and response: a strategy for international cooperation and coordination. Document WHO/CDS/CSR/EPH/2001.2, 2001. https://apps.who.int/iris/handle/10665/68888. Accessed 23 Aug 2022.

21. Hawthorne WJ, Cowan PJ, Bühler LH, et al. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China. December 12–14, 2018. Xenotransplantation. 2019;26:e12513. https://doi.org/10.1111/xen.12513.
22. World Health Organization. Fifty-seventh World Health Assembly, Agenda Item 12.14, May 22, 2004. Resolution 57.18. http://www.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf. Accessed 23 Aug 2022.
23. European Medicines Agency, Committee for medicinal products for human use (CHMP). Guideline on xenogeneic cell-based medicinal products. EMEA/CHMP/CPWP/83508/2009. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-xenogeneic-cell-based-medicinal-products_en.pdf. Accessed 23 Aug 2022.
24. Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf. Accessed 23 Aug 2022.
25. Regulation (EC) No 1394/2007 of the European Parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance). https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF. Accessed 23 Aug 2022.
26. European Medicines Agency. Advanced therapy medicinal products: overview. https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview. Accessed 23 Aug 2022.
27. European Medicines Agency. Reflection paper on classification of advanced therapy medicinal products. Document EMA/CAT/600280/2010 rev.1. May 21, 2015. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf. Accessed 23 Aug 2022.
28. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: https://www.ich.org/. Accessed 23 Aug 2022.
29. Ten Ham RMT, Hoekman J, Hövels AM, et al. Challenges in advanced therapy medicinal product development: a survey among companies in Europe. Mol Ther Methods Clin Dev. 2018;11:121–30. https://doi.org/10.1016/j.omtm.2018.10.003.
30. Bloom ET. Xenotransplantation: regulatory challenges. Curr Opin Biotechnol. 2001;12:312–6. https://doi.org/10.1016/s0958-1669(00)00218-4.
31. Onions D, Cooper DK, Alexander TJ, et al. An approach to the control of disease transmission in pig-to-human xenotransplantation. Xenotransplantation. 2000;7:143–55. https://doi.org/10.1034/j.1399-3089.2000.00047.x.
32. Fishman JA, Scobie L, Takeuchi Y. Xenotransplantation-associated infectious risk: a WHO consultation. Xenotransplantation. 2012;19:72–81. https://doi.org/10.1111/j.1399-3089.2012.00693.x.
33. Wynyard S, Nathu D, Garkavenko O, et al. Microbiological safety of the first clinical pig islet xenotransplantation trial in New Zealand. Xenotransplantation. 2014;21:309–23. https://doi.org/10.1111/xen.12102.
34. Gazda LS, Collins J, Lovatt A, et al. A comprehensive microbiological safety approach for agarose encapsulated porcine islets intended for clinical trials. Xenotransplantation. 2016;23:444–63. https://doi.org/10.1111/xen.12277.
35. Cooper DKC, Ye Y, Rolf LL Jr, et al. The pig as potential organ donor for man. In: Cooper DKC, Kemp E, Reemtsma K, White DJG, editors. Xenotransplantation: the transplantation of organs and tissues between species. 2nd ed. Berlin: Spring-Verlag; 1997. p. 481–500. ISBN-13: 978-3642644603.
36. Sachs DH. The pig as a potential xenograft donor. Vet Immunol Immunopathol. 1994;1994(43):185–91. https://doi.org/10.1016/0165-2427(94)90135-x.
37. Kobayashi T, Taniguchi S, Ye Y, et al. Comparison of bile chemistry between humans, baboons, and pigs: implications for clinical and experimental liver xenotransplantation. Lab Anim Sci. 1998;48:197–200.

38. Graham ML, Bellin MD, Papas KK, et al. Species incompatibilities in the pig-to-macaque islet xenotransplant model affect transplant outcome: a comparison with allotransplantation. Xenotransplantation. 2011;18:328–42. https://doi.org/10.1111/j.1399-3089.2011.00676.x.
39. Kim MK, Lee JJ, Choi HJ, et al. Ethical and regulatory guidelines in clinical trials of xenocorneal transplantation in Korea; the Korean xenocorneal transplantation consensus statement. Xenotransplantation. 2013;20:209–18. https://doi.org/10.1111/xen.12036.
40. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02010L0063-20190626&from=EN. Accessed 23 Aug 2022.
41. European Medicines Agency, committee for advanced therapies (CAT). Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. EMA/CAT/GTWP/671639/2008 Rev. 1 – corr. November 12, 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en-0.pdf. Accessed 23 Aug 2022.
42. 810.21. Federal Act on the transplantation of organs, tissues and cells. http://www.admin.ch/ch/e/rs/810_21/index.html. October 8, 2004. Accessed 23 Aug 2022.
43. 810.213. Verordnung über die Transplantation von tierischen Organen, Geweben und Zellen. http://www.admin.ch/opc/de/classified-compilation/20051808/index.html. March 16, 2007. (This document is only available in german, french and italian language). Accessed 23 Aug 2022.
44. Spillman MS, Sade RM. Clinical trials of xenotransplantation: waiver of the right to withdraw from a clinical trial should be required. J Law Med Ethics. 2007;35:265–72. https://doi.org/10.1111/j.1748-720X.2007.00135.x.
45. Rothblatt M. Commentary on achievement of first life-saving xenoheart transplant. Xenotransplantation. 2022;29(3):e12746. https://doi.org/10.1111/xen.12746.
46. Standing H, Lawlor R. Ulysses contracts in psychiatric care: helping patients to protect themselves from spiralling. J Med Ethics. 2019;45:693–9. https://doi.org/10.1136/medethics-2019-105511.
47. Walker T. Ulysses contracts in medicine. Law Philos. 2012;31:77–98. https://www.jstor.org/stable/41348267. Accessed 23 Aug 2022.
48. European Medicines Agency. Committee for Advanced Therapies (CAT), September 2011 meeting. https://www.ema.europa.eu/en/documents/committee-report/committee-advanced-therapies-cat-september-2011-meeting-monthly-report_en.pdf. Accessed 23 Aug 2022.
49. Schuurman H-J. Regulatory aspects of clinical xenotransplantation. Int J Surgery. 2015;23:312–21. https://doi.org/10.1016/j.ijsu.2015.09.051.
50. European Medicines Agency. Guidelines relevant for advanced therapy medicinal products. https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products. Accessed 23 Aug 2022.
51. European commission, Directorate-General Health and Consumer Protection. human organ transplantation in Europe: an overview; 2003. https://ec.europa.eu/health/ph_threats/human_substance/documents/organ_survey.pdf. Accessed 23 Aug 2022.
52. Directive 2010/45/EU of the European Parliament and of the council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010L0053&from=EN. Accessed 23 Aug 2022.
53. European Directorate for the quality of medicines & healthcare, council of Europe. Guide to the quality and safety of organs for transplantation 7th Edition. 2018. https://www.edqm.eu/en/-/new-release-7th-edition-guide-to-the-quality-and-safety-of-organs-for-transplantation. Accessed 23 Aug 2022.
54. Schuurman H-J, Hoogendoorn K. Solid organ xenotransplantation at the interface between research and clinical development: regulatory aspects. Xenotransplantation. 2020;27:e12608. https://doi.org/10.1111/xen.12608.
55. Godehardt AW, Tönjes RR. Xenotransplantation of decellularized pig heart valves—regulatory aspects in Europe. Xenotransplantation. 2020;27:e12609. https://doi.org/10.1111/xen.12609.

56. European Medicines Agency. From laboratory to patient: the journey of a medicine assessed by EMA. February 10, 2020. https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf. Accessed 23 Aug 2022.
57. Paul Ehrlich Institut, advanced therapy medicinal products (ATMP). https://www.pei.de/EN/medicinal-products/atmp/atmp-node.html;jsessionid=08CB2BEE77C34912F7105E375C6CB914.intranet222. Accessed Aug 2022.
58. European Medicines Agency, Committee for Advanced Therapies (CAT). https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat. Accessed 23 Aug 2022.
59. European Medicines Agency. Advanced therapy classification. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification. Accessed 23 Aug 2022.
60. European Medicines Agency. Scientific advice and protocol assistance. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance. Accessed 23 Aug 2022.
61. European Medicines Agency, Scientific Evidence Generation Department. European medicines agency guidance for applicants seeking scientific advice and protocol assistance. EMA/4260/2001 Rev. 13, 31 March 2022. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf. Accessed 23 Aug 2022.
62. Salmikangas P. Challenges during the development of ATMPs. Dresden: CAT-DGTI Workshop; 2014. https://www.ema.europa.eu/en/documents/presentation/presentation-challenges-during-development-advanced-therapy-medicinal-products-paula-salmikangas_en.pdf. Accessed 23 Aug 2022.
63. Barkholt L, Voltz C. ATMP Development Challenges – from scientific advice to marketing authorisation. https://www.ema.europa.eu/en/documents/presentation/presentation-advanced-therapy-medicinal-product-atmp-development-challenges-scientific-advice-market_en.pdf. Accessed 23 Aug 2022.
64. European Commission and European Medicines Agency. European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs. October 20, 2017. https://www.ema.europa.eu/en/documents/other/european-commission-dg-health-food-safety-european-medicines-agency-action-plan-advanced-therapy_en-0.pdf. Accessed 23 Aug 2022.
65. Matsumoto S, Abalovich A, Wechsler C, et al. Clinical benefit of islet xenotransplantation for the treatment of type 1 diabetes. EBioMedicine. 2016;12:255–62. https://doi.org/10.1016/j.ebiom.2016.08.034.
66. Griffith BP, Goerlich CE, Singh AK, et al. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med. 2022;387:35–44. https://doi.org/10.1056/NEJMoa2201422.
67. Hawthorne WJ. World first pig-to-human cardiac xenotransplantation. Xenotransplantation. 2022;29:e12733. https://doi.org/10.1111/xen.12733.
68. Denner J, Schuurman H-J. Early testing of porcine organ xenotransplantation products in humans: microbial safety as illustrated for porcine cytomegalovirus. Xenotransplantation. 2022;29(6):e12783. https://doi.org/10.1111/xen.12783. in press
69. Food and Drug Administration. Expanded Access. https://www.fda.gov/news-events/public-health-focus/expanded-access. Current at August 24, 2022. Accessed 23 Aug 2022.
70. Evaluation of safety, tolerability and efficacy of xeno-skin® for temporary closure of severe burn wounds. https://clinicaltrials.gov/ct2/show/NCT03695939?cond=Burns&cntry=US&phase=04&draw=3&rank=13. Accessed 23 Aug 2022.
71. First application of genetically modified, live-cell, pig skin to a human wound. https://www.eurekalert.org/news-releases/667682. October 11, 2019. Accessed 23 Aug 2022.
72. Jorqui-Azofra M. Regulation of clinical xenotransplantation: a reappraisal of the legal, ethical, and social aspects involved. Methods Mol Biol. 2020;2110:315–58. https://doi.org/10.1007/978-1-0716-0255-3_20.
73. International Society for Cell & Gene Therapy. https://www.isctglobal.org/about/about-us. Accessed 23 Aug 2022.

Regulatory Considerations and Oversight: A Japanese Perspective

11

Takaaki Kobayashi and Shuji Miyagawa

Introduction

World Health Organization (WHO) and International Xenotransplantation Association (IXA) held a joint meeting of the Global consultation on Regulatory Requirements for Xenotransplantation Clinical Trials at Changsha in 2008, where Changsha Communique was presented [1]. At the second meeting at Geneva in 2011 [2], a report was given on the legal developments in each country. The Japanese Ministry of Health, Labor and Welfare (MHLW) was of the opinion that even with the WHO's recommendation (i.e., Changsha Communique), there was no need to establish legally binding laws and regulations in light of the Japanese situation (verbal opinion, i.e., personal communication of which no written document exists). At that time, sufficient preclinical results in primates had not been obtained, even using genetically modified pigs. Because the issues of controlling immune response and infectious diseases had not been resolved, no applications of clinical trials were filed except intra-peritoneal alginate-encapsulated porcine islet xenotransplantation in New Zealand [3]. Thus, effective regulations that have a legal basis with powers were not yet in place in many countries.

Later, clinical xenotransplantation trials began to be officially planned and conducted not for organs, but for skin and cornea as well as pancreatic islets in the world [4]. In Japan, cell transplants including islet xenotransplantation came to be stipulated in the framework of the "Regenerative Medicine Promotion Act" [5]. In addition, since advancements in genome editing technology, which have made

T. Kobayashi (✉)
Department of Renal Transplant Surgery, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan
e-mail: takaaki.kobayashi@aichi-med-u.ac.jp

S. Miyagawa
Department of Pediatric Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_11

possible numerous genetic modifications and development of effective immunosuppressive therapies such as co-stimulatory blockade, have improved the preclinical results of organ transplants using non-human primates, updating the original Changsha Communique has been discussed [6].

Islet

Islet xenotransplantation guidelines were reported at IXA in 2009 and revised in 2016 [7], after preparation at the 12th Congress of IXA (Osaka, Japan) in 2013 and discussion at second International Conference on Clinical Islet Xenotransplantation (ICCIX) (San Francisco, USA) in 2014. Two important meetings between the MHLW (Health Policy Bureau, Research and Development Division) and Japanese Society for Xenotransplantation were held on January 29, 2014 and June 24, 2015. After recommendation for the creation of a regulatory framework to establish porcine islet transplantation for treatment of diabetes mellitus, application for approval of islet xenotransplantation were made possible by the inclusion in the "Act on the Safety of Regenerative Medicine" (enacted on November 25, 2014) [8]. It was confirmed that there is no problem to implement clinical research as class I regenerative medicine.

The "Revised Pharmaceutical Affairs Act" essentially regulates the manufacturing, sale, and safety measures of pharmaceuticals, quasi-drugs, cosmetics, and medical devices, and ensures their appropriateness for marketing purposes, and was revised to allow corporate participation (enacted on November 25, 2014) [8]. Consequently, this Act can cover xenogeneic cells as well. At present, the issue of organ xenotransplantation has not been stipulated in the above Acts.

Regarding infectious issues, "Guidelines for Public Health Infectious Disease Issues in Xenotransplantation" (2001 version) was reviewed by MHLW Science Special Research Project and reported on May 27, 2016 [9].

Organ

The MHLW (Minister's Secretariat, Health Policy Bureau, Health Service Bureau and Pharmaceutical Safety and Environmental Health Bureau) and the Japan Society for Xenotransplantation held a virtual conference on February 18, 2022. The following issues were presented and discussed, although no formal agreement or policy resulted about, (1) preclinical experiments in organ xenotransplantation and update of clinical xenotransplantation including recent clinical studies in the U.S., (2) WHO and IXA, three joint meetings for Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials in 2008 (Changsha), 2011 (Geneva) and 2018 (Changsha), (3) current (preparation) status in Japan, (4) legal development for islet xenotransplantation (above-mentioned), and (5) need of effective regulations for organ xenotransplantation.

A new discussion is needed to bring xenogeneic organs into the category of regenerative medicine, including genetically modified pigs. It was reconfirmed that there is no place to apply for or deliberate on clinical studies/trials of organ xenotransplantation. The MHLW will work on a detailed study of the situation in Japan and decide on the direction regarding the legislation.

Future Issues

Clinical organ transplantation is still developing in Japan. The number of deceased organ donors (per million population) is less than 1, which is 20–50 times lower than in other advanced countries such as Europe and U.S [10]. In the area of kidneys, documents of the United States Renal Data System (USRDS) also show that more than 90% of patients with end-stage renal failure choose hemodialysis [11]. Even under these circumstances, reports of experiments in the U.S. were sensational and succeeded in making xenotransplantation known to the general public, although it is actually undeniable that it became a temporary topic of conversation because of 2-month death report.

Furthermore, even here in Japan, we have heard informally that applications for clinical study of xenotransplantation are being prepared in some academia.

The WHO and IXA's Changsha Communique states that it must be supported by appropriate preclinical data. There are neither the effective genetically modified pigs nor a clean facility capable of conducting clinical studies using designated pathogen free (DPF) source pigs (even in the U.S., there is only one such facility in March 2022) [12].

However, if the interpretation that when the efficacy and safety of genetically modified pigs have already been proven at other facilities, no pre-clinical study using non-human primates is required at each facility, will be justified, clinical studies/trials will be readily conducted worldwide after import of such genetically modified pigs or cells for nuclear transfer. If there is no place for discussion once the application is submitted, then it is a problem. We hope that the MHLW will understand such an urgent issue even in Japan who is behind other countries in transplantation, because there are patients who need it.

References

1. First WHO global consultation on regulatory requirements for xenotransplantation clinical trials: Changsha, China, 19-21 November 2008. The Changsha Communique. Xenotransplantation. 2009;16(2):61–3.
2. WHO. Second WHO global consultation on regulatory requirements for xenotransplantation clinical trials. Geneva: WHO; 2011. https://apps.who.int/iris/handle/10665/341817
3. Garkavenko O, Durbin K, Tan P, Elliott R. Islet transplantation: New Zealand experience. Xenotransplantation. 2011;18:60.
4. Human Xenotransplant Registry. https://humanxenotransplant.org/

5. Shimoda M, Matsumoto S. Update regarding xenotransplantation in Japan. Xenotransplantation. 2019;26(1):e12491.
6. Hawthorne WJ, Cowan PJ, Bühler LH, et al. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China December 12–14, 2018: "the 2018 Changsha Communique" the 10-year anniversary of the international consultation on xenotransplantation. Xenotransplantation. 2019;26(2):e12513.
7. Hering BJ, Cozzi E, Spizzo T, Cowan PJ, Rayat GR, Cooper DK, Denner J. First update of the International Xenotransplantation Association consensus statement on conditions for undertaking clinical trials of porcine islet products in type 1 diabetes--executive summary. Xenotransplantation. 2016;23(1):3–13.
8. Regenerative Medicine Promotion Act [Legislation by Diet members.] https://www.mhlw.go.jp/english/policy/health-medical/medical-care/dl/150407-01.pdf
9. Document of 10th Meeting of the Health Sciences Council, Subcommittee for Evaluation of Regenerative Medicine (in Japanese). https://www.mhlw.go.jp/stf/shingi2/0000125766.html
10. International registry in organ donation and transplantation. https://www.irodat.org
11. USRDS 2018 annual data report volume 2, end-stage renal disease Chapter 11: International Comparison. https://www.usrds.org/previous-adrs/2010-2019/
12. Reardon S. First pig-to-human heart transplant: what can scientists learn? Nature. 2022;601(7893):305–6.

Regulatory Considerations and Oversight: A Chinese Perspective

12

Lisha Mou and Zuhui Pu

History and Current Status

Currently, the National Health Commission of the People's Republic of China regard organ xenotransplantation technology as medical technology of Class III—a high tier category that includes medical technologies with major ethical issues as well as safety and effectiveness concerns [1]. The 2008 and 2018 Changsha Communiqué stimulated the efforts in China in the following areas: (a) xenozoonosis; (b) regulatory; (c) biorepository; (d) transgenic pig facilities; (e) biomaterials and encapsulation; and (f) immunosuppression and tolerance induction [2, 3]. Also, the General Offices of the CPC Central Committee and the State Council released a set of guidelines to Strengthen the Governance over Ethics in Science and Technology on March 20, 2022 [4]. These guidelines clarified the principles and requirements of science and technology including xenotransplantation ethics principles and governance requirements, governance system and governance system guarantee. According to the guidelines, it is important that scientific activities serve humanity, respect people's rights to life, adhere to fairness and justice, control risks appropriately, and maintain openness and transparency. All the above efforts reflect the state of xenotransplant science and support in China.

There are three guidelines and expert consensuses related to xenotransplantation. Firstly, the Chinese Medical Association of Organ transplantation Xenotransplantation group released the Clinical Research Guidelines on xenotransplantation on Nov 15, 2018 (2018 Expert Recommendations, see Table 12.1) [5]. Secondly, the above association released the Clinical Trial Expert Consensus

L. Mou (✉) · Z. Pu
Imaging Department, Shenzhen Institute of Translational Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, Guangdong, China

MetaLife Center, Shenzhen Institute of Translational Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_12

Table 12.1 Key points of the Clinical Research Guidance on xenotransplantation (2018 Expert Recommendations) [2]

No.	Contents
1.	Clinical research should be approved and controlled by the health commission of province or nation
2.	This guidance includes: general principles, project application and review, technical standards, ethical requirements, biosafety, project management, donor requirements, recipient selection, project implementation, follow-up, etc.
3.	Donors are limited to pigs without specific pathogens (SP), including wild-type and genetically modified pigs. Samples should be stored for more than 50 years
4.	The cell transplantation center require compliance with current good manufacturing practices (cGMP)
5.	Collected data of the project should be reported to the authorities regarding the information of implementation

Table 12.2 Key points of the expert consensus in clinical research on islet xenotransplantation (2019 Expert Recommendations) [3]

No.	Contents
1.	Clinical research should be approved and controlled by the National Health Commission (NHC)
2.	Islet cells from genetically modified pig (or devices containing islet cells) should be approved by the National Medical Products Administration
3.	This guideline include: general principles, application and approval of clinical research for islet xenotransplantation, donor requirements, ethical requirements, technical and related equipment standards for clinical research, biological safety standards, project implementation, project management, etc.
4.	The cell transplantation center require compliance with current good manufacturing practices (GMP)
5.	Collected data of islet xenotransplantation should be controlled by NHS and public open source permitted by law
6.	Donors should be specifically cultured without designated pathogen free (DPF). Samples should be stored for more than 30 years

on islet xenotransplantation on Nov 15, 2019 (2019 Expert Recommendations, see Table 12.2) [6]. The quality standards and ethical requirements of islet xenotransplantation are stipulated, which facilitate the development of clinical islet xenotransplantation technology. Thirdly, the China Organ Transplantation Development Foundation released the "Expert Consensus on Clinical Trials of Human Xenotransplantation in China" on April 6, 2022 [7]. The "Consensus" states that xenotransplantation is essential and that its academic findings can contribute in the advancement of the transplantation field. The "Consensus" stated that the technological preparations, ethics, and development of regulations are still lacking compared with globally advanced levels.

The above guidelines came as a result of advanced allotransplantation efforts in China. Especially, most of the experts who release the guidelines are from the allotransplantation field. The guidelines were prepared by a subcommittee of experts from regulatory, clinical, and scientific research specializations. The guidelines will guide the further development and standardization of clinical research on xenotransplantation.

References

1. National Health Commission of the People's Republic of China. The third category of medical technology catalog; 2013. http://www.nhc.gov.cn/wjw/ywfw/201306/4d1b9d11323342dcacedd31e893efac0.shtml. Accessed 28 Mar 2022.
2. First WHO global consultation on regulatory requirements for xenotransplantation clinical trials: Changsha, China, 19–21 November 2008. The Changsha Communiqué. Xenotransplantation. 2009;16(2):61–3.
3. Hawthorne WJ, Cowan PJ, Bühler LH, Yi S, Bottino R, Pierson RN 3rd, Ahn C, Azimzadeh A, Cozzi E, Gianello P, Lakey JRT, Luo M, Miyagawa S, Mohiuddin MM, Park CG, Schuurman HJ, Scobie L, Sykes M, Tector J, Tönjes RR, Wolf E, Nuñez JR, Wang W. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China December 12–14, 2018: "the 2018 Changsha Communiqué" the 10-year anniversary of the international consultation on xenotransplantation. Xenotransplantation. 2019;26(2):e12513. https://doi.org/10.1111/xen.12513.
4. China releases guidelines to strengthen governance over ethics in science, technology. http://english.www.gov.cn/policies/latestreleases/202203/21/content_WS6237b179c6d02e5335328099.html. Accessed 12 Jun 2022.
5. Chinese Medical Association of Organ transplantation, Xenotransplantion group. Guidance for clinical research on xenotransplantation (2018 recommended version). Organ Transplant. 2018;9(6):405–8.
6. Chinese Medical Association of Organ transplantation, Xenotransplantion group, Wei W, Kefeng D, et al. Experts consensus on islet xenotransplantation clinical trial (2019 Expert advice edition). Organ Transplant. 2019;10(6):672–7.
7. How far is the clinical success of xenotransplantation? http://www.news.cn/2022-04/07/c_1128537299.htm. Accessed 16 Jul 2022.

Part III

Religious Aspects

Religious Viewpoints: Protestant and Catholic

13

Daniel J. Hurst, Daniel Rodger, Vanessa K. Pizutelli, and Veronica Danser

Introduction

The demand for human organs for transplant consistently outpaces the need. In the United States (US) alone, there are currently around 100,000 persons waiting for a kidney transplant, with the median wait-time approaching 4 years [1]. Many of these patients—17 each day in the US—will die on the waiting list [1].

Because of this great need for additional organs for transplant, research into the use of non-human animals for transplantation has been conducted for decades. Xenograft heart valves, primarily from pigs have been used successfully since the 1960s [2], but the use of solid organ xenografts presents a more significant challenge. Recently, in 2021, there has been a flurry of activity in animal-to-human solid organ transplant, known as xenotransplantation (XTx). This activity has created excitement for continued advancement and researchers are quickly moving in the direction of formal human clinical trials [3–5]. Much has been written on the ethical issues that may present in XTx [6–8], as well as some commentary on theological issues and positions that exist [9–12]. This chapter seeks to provide a summary of the landscape of Christian—both Protestant and Catholic—viewpoints towards XTx, the dominant arguments made in support and opposition to the practice, and the growing body of empirical evidence. While XTx refers to any cross-species transplant, this chapter will largely focus on solid organ transplants. The chapter concludes with an appeal for additional empirical studies focused on specific areas in need of further exploration.

D. J. Hurst (✉) · V. K. Pizutelli · V. Danser
Rowan-Virtua School of Osteopathic Medicine, Stratford, NJ, USA
e-mail: hurst@rowan.edu; pizute72@rowan.edu; danser@rowan.edu

D. Rodger
London South Bank University, London, UK
e-mail: daniel.rodger@lsbu.ac.uk

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_13

Xenotransplantation and the Initial Role of Theologians

Various forms of XTx using different animals have been attempted since at least the seventeenth century with very little success [13]. In the modern era, a major landmark in XTx took place in 1984 with the case of Baby Fae. Stephanie Fae—better known as Baby Fae—was born prematurely in October 1984 with hypoplastic left heart syndrome (HLHS). HLHS is a rare congenital heart defect that, if left untreated, will typically be fatal within the first weeks of life. Treatment consists of either multi-step surgical procedures or heart transplant. Shortly after her birth, Dr. Leonard Bailey at Loma Linda University Medical Center in California judged that surgical treatment was very risky with approximately a 50% mortality. He is also recorded as rejecting the prospect of a heart allograft due to no documented successes. Bailey, who had performed hundreds of experimental animal transplants, suggested transplanting the heart of a young female baboon into the merely days old infant [14, 15]. The XTx was performed and while the baboon heart functioned well for 2 weeks, rejection soon occurred and Baby Fae died on day 20 after the surgery [16]. The case of Baby Fae was not so much a landmark for XTx in terms of helping science advance, but rather Baby Fae would place XTx squarely in the media and in the eyes of theologians.

Prior to Baby Fae there is only sparse mention of XTx in theological writings. However, Baby Fae would change this and oftentimes it was the viewpoints of clergy members who were quoted in media accounts. As one example, following Baby Fae a leading Vatican theologian—Rev. Gino Concetti—issued a report in *L'Osservatore Della Domenica* (a weekly publication of the Holy See) outlining six conditions under which transplanting a non-human animal organ into a human could be justified:

1. that the patient needed it
2. that no suitable human or artificial organ was available
3. that the surgical team was properly qualified
4. that the hospital had the right equipment
5. that the patient or guardians agreed, and
6. that a "broadly positive outcome" was foreseeable [17].

Concetti did not specify which condition had not been met in the case of Baby Fae, though it seems likely that the sixth condition loomed large in his viewpoint. Following Baby Fae, theological—particularly Christian—viewpoints on XTx began to be reported on at greater length.

Transplantation in Christian Thought

One way to think through the ethical issues of XTx would be to see it as an extension of allotransplantation. However, to see non-human-to-human transplant as *simply* an extension of human-to-human transplant is limited. XTx brings forth novel

ethical issues as well as presenting old debates in a new light. Nonetheless, beginning with a discussion of how allotransplantation has been viewed from a Christian viewpoint is a good starting point, as much has been written and deliberated on.

A principal viewpoint in the extant Christian literature on allotransplantation is positive and endorses transplant as an act of selfless love from one person (alive or deceased) to another, though nuances exist [18, 19]. Norman Geisler's view is emblematic of the general positivity, seeing transplant as in accordance with the biblical principle of love [20]. As Jesus emphasized, "Greater love has no one than this, that someone lay down his life for his friends" (John 15: 13). One of the most prolific Protestants to have written on issues of medical ethics, Paul Ramsey, stated emphatically that once it has been determined that a patient has died then "the corpse itself can certainly be used as a 'vital organ bank'" [21]. Similarly, Helmut Thielicke, referring to allotransplantation, stated, "I see no reason why [organ transplant] should involve any ethical or religious problems" [21].

Lutheran bioethicist Gilbert Meilaender presents a more nuanced view of living organ donation, on the one hand, seeing humans as stewards—rather than owners—of our bodies, and that whilst donating a kidney is a bodily-gift, it remains morally complex [22]. For instance, donating a kidney requires exposing oneself to the intrinsic risks involved with undergoing general anesthesia, major surgery, and a life with just one kidney, none of which is insignificant. After all, as Meilaender notes, "[I]t is one thing to aim at my neighbor's good, knowing that in so doing I may be harmed; it is another to aim at my own harm in order to do good to my neighbor" [22] (p. 89). In contrast to the theological and moral themes of allotransplantation as a bodily *gift* to another, XTx requires using animals as a means to an end by using them to benefit humankind.

Xenotransplantation in Christian Thought

Perhaps the most thorough discourse on XTx from a Christian perspective has come from the Catholic Church's Pontifical Academy for Life. The Pontifical Academy for Life, a group of persons appointed by the Pontiff to promote the Church's consistent life ethic that frequently comments on scientific and bioethical matters, released a guidance document on scientific and ethical considerations for XTx in 2001 [23]. The Academy included anthropological and ethical aspects of XTx that should be considered, including: human intervention in the created order, the use of animals for the good of humankind, and how XTx may affect the identity of the graft recipient. Each of these aspects will be considered.

In the Catholic tradition, humankind is created in the image and likeness of God—the *imago Dei*. This is a basic tenet not only of Catholicism but of Christian doctrine in general. Humankind is both the centerpiece and the pinnacle of God's creation, per the Academy. Certain duties proceed from this. In Genesis 1: 26 and 28, God tells humans to exercise dominion over the things of the earth [24]. While there is significant debate on what the exercise of this dominion looks like, it has historically been understood to entail that the use of animals for food, clothing, and

work is morally licit, a view held by Augustine and Thomas Aquinas [25]. Dominion, of course, should not to be understood as permitting despotism, exploitation, and abuse, but rather care, responsibility, and stewardship [26]. However, what this looks like in praxis remains contested. More to this point, Pope John Paul II writes in his encyclical *Laborem Exercens*, "Man is the image of God partly through the mandate received from his Creator to subdue, to dominate, the earth. In carrying out this mandate, man, every human being, reflects the very action of the Creator of the universe" [23]. Hence, in Catholic doctrine and even Christian doctrine more broadly, human intervention in the created order is mandated in order to hold dominion over the rest of the created world, further affirming that this dominion is not to be reduced to lording over creation in a destructive manner. Rather, it points to guiding creation towards the good of humankind [23]. If animals can be used to glorify God and bring about his Kingdom through humans, then Catholic theology seems to allow for their use. Several Catholic pronouncements affirm these positions, including documents from the Second Vatican Council (1962–1965).

As seen above, generally the use of animals to support and promote humankind is permissible in Catholic theology, making the exception that encephalon and gonad transplantation cannot be considered morally licit [23]. The Pontifical Academy for Life examined not only this basic question but the more specific questions of: (1) whether animals can be used to improve humankind's chances of survival or to improve their health, and (2) if it is acceptable to breach the barrier between humans and non-human animals. To answer the first question, the Academy re-emphasizes the role of humans over the created world and that the rest of the created order is meant to serve humanity:

> [T]he sacrifice of animals can be justified only if required to achieve an important benefit for man, as is the case with xenotransplantation of organs or tissues to man, even when this involves experiments on animals and/or genetically modifying them [23].

Certain criteria should still be adhered to when using animals for these purposes, such as, among others, preventing unnecessary animal suffering. On the second question regarding whether it is acceptable to breach a barrier between humans and non-human animals by transplanting a xenograft into a human, the Academy notes that there is no doctrinal basis that would preclude XTx.

Catholic theology also approaches the topic of XTx from an anthropological position, that is, in relation to the identity of the xenograft recipient. Would XTx alter a person's identity or what it means to be human? Would it change humanity on an ontological level or a psychological level? This is a primary question for the Church that must be answered in order to assess the moral legitimacy of XTx. For instance, Pope John Paul II, in a 2000 address to the International Congress of the Transplant Society, upheld the moral legitimacy of XTx if it held to the following conditions that, "the transplanted organ does not affect the psychological or genetic identity of the person who receives it" and "that there exists the proven biological possibility of carrying out such a transplant with success, without exposing the recipient to excessive risks" [23]. Empirical studies have tried to assess whether persons believe that XTx would affect the psychological identity of the transplanted

person [9]. The Catholic Church notes that in the early stages of XTx then psychological experts should assess "probable repercussions that the recipient could undergo in their psyche." [23].

A final criterion that the Pontifical Academy advises to assess the moral legitimacy of XTx is health risk. On this point, the Academy notes that the probability and extent of damage that could occur define the acceptability of such risk [23]. In addition, the Academy notes that it is an ethical requirement for researchers to proceed with utmost caution, but the document is silent on how to evaluate when an acceptable risk threshold is low enough to proceed.

There has been limited explicit theological engagement with XTx from Protestants. Some of the earliest engagement came from the German speaking world, specifically the Evangelical Church (Protestant) in Germany in partnership with the German Bishops Conference (Catholic) who formed a working group in 1998 [27]. Together they recommended the importance of ethical dialogue and identified several ethical and legal challenges posed by XTx, though with little in-depth theological analysis. These included consideration of (1) the moral status of non-human animals and humankind's legal and moral responsibility towards them, (2) the risks posed by the possibility of xenozoonotic disease and how an individual patient can give informed consent for a potential global risk, and (3) the potential for negative psychosocial sequelae from receiving a xenograft.

Paris and colleagues reported on religious viewpoints presented at a symposium of the 2017 International Xenotransplantation Association [10]. In the section on Christian perspectives then three relational aspects of the Christian tradition applied to XTx were considered. These three relational aspects include the need to treat the whole, the appropriate use of animals, and the potential impact that a given treatment would possibly have on the larger community. However, outside these few theological viewpoints, there is little literature from a Christian—specifically an explicitly Protestant perspective—on XTx.

XTx, therefore, finds itself in the midst of a contemporary theological and ethical debate. If the use of non-human animals for food is theologically permissible,[1] then it ought to be prima facie permissible to use non-human animals for XTx. In fact, the case is even stronger for the latter given that the necessary sustenance for the body can be achieved without killing animals. However, some Christians may argue that eating animals is not permissible, or at least is not morally and theologically ideal given that God did not permit humankind to kill non-human animals in their prelapsarian state (Gen 2: 16). Only in humankind's postlapsarian state does God first give qualified permission to eat non-human animals for food (Genesis 9: 3). Rather than addressing the case for and against the killing of non-human animals for consumption, there does not seem to be any scriptures or doctrine that implicitly or explicitly rule out the use of non-human animals for the benefit of humans; though, in light of the stewardship and responsibility to creation given to humankind, it

[1] Animals are frequently killed for sacrifices and food throughout the Old Testament (Lev. 7: 12–18; 1 Chron. 29:21, 22; Deut. 12:15; Lev. 17:13; Lev. 4) and premumably entailed some degree of animal pain and suffering.

would be a mistake to conclude from this that it permits non-human animals to be instrumentalized and treated without any moral regard. Nevertheless, it does seem exegetically consistent to view XTx as an extension of the acceptable uses of non-human animals that is already permitted in Scripture. This position is similarly internally consistent with the creation narrative and the dominion given to humankind by God, which seemingly gives them the right to put their interests above those of non-human animals.

Nevertheless, it is worth noting that this perspective is not without challenge. Vic McCracken points out that embracing XTx could be understood as another example of human hubris, whereby humankind once again attempts to become like God [28]. After all, part of what is unique about the human condition is that despite our propensity to abuse creation and the mandate given to us by God, we are able to transcend our nature, for good or ill. What remains unclear is whether or not XTx should be understood as constituting a violation of our responsibility towards creation or an acceptable expression of it.

This permissive approach does, however, leave many difficult ethical questions unresolved. For example, will XTx be practiced in a way that reflects the Christian moral values that follow from being God's image bearers and having dominion over non-human animals? This is unclear, since non-human animals such as pigs—whom are social animals with significant cognitive and emotional capacity [29–31]—will be genetically engineered, bred, isolated, and kept in biosecure, pathogen-free environments where they will live in a manner that is atypical and perhaps deprived. Therefore, if XTx is permissible from a Christian view we should be supportive of attempts to minimize the pain and suffering of any non-human animals involved. Moreover, a point that has been rarely, if ever, discussed is whether or not it is always necessary to kill a non-human animal to access their organs for XTx. It is at least conceivable in some cases, that a single pig kidney could be removed whilst leaving one functioning kidney in the pig from which to continue to live in a separate and freer, but albeit secure, environment. There are obvious downsides to this approach, the most obvious being the economic and time costs associated with the number of additional surgeries required, and the provision of suitable postoperative care. Greatly increasing this pig population could, theoretically, have deleterious effects on an ecosystem where they are kept. However, something akin to this may help to make XTx more acceptable to those with theological and ethical concerns with the permissibility of raising and harming non-human animals only for human benefit.

Despite the more recent positive advancements, it is worth cautioning that the scientific realization of XTx is not necessarily inevitable. It may well be the case that the necessary efficacy of non-human animal organs is not achievable and that alternatives arise in its place. One alternative might be the use of induced pluripotent stem cells and the 3D printing of organs, which would have the benefit of preventing immunogenicity [32], and would not require killing non-human animals. However, *if* XTx can one day produce outcomes similar to a human organ this may have practical implications for other areas of transplantation ethics. For instance, will cadaveric organ donation be necessary if all the required organs can be accessed

through XTx, and what will the implications be for—hard and soft—presumed consent models of organ donation? Both practices have contributed to the misunderstanding that the human body is a mere collection of organs that can be used by whoever requires them, and arguably compromises a Christian anthropology of the body.

Empirical Data

In 2008, the World Health Organization (WHO) hosted a global consultation on the regulatory requirements for XTx clinical trials in Changsha, Hunan, China. Within the principles that were produced, the WHO stated that before any clinical trial is conducted there should be not only scientific assessment, but also include "ethical assessment and should involve the public." Researchers have interpreted this statement to signal that broad samples of the public should be consulted on ethical matters involved in XTx. Ethical assessment may be particularly important within the local communities in which XTx clinical trials are planned.

To date, there have been qualitative and quantitative studies conducted that have, to varying degrees, assessed theological viewpoints toward XTx. In addition, at least one symposium has been held with theologians [10]. Assessing theological viewpoints toward a particular issue, such as XTx, is complex. Religious viewpoints are oftentimes primary to the identity of a person. Adherents of the same religion or, as is the case in Protestant Christianity, even the same denomination, may espouse differing viewpoints on a topic. While the Catholic Church has the Pope as its ecclesiastical head, as well as the Magisterium as the official teaching body, Protestantism and other faith groups, with their various denominations, do not have a true cognate of this. Nonetheless, while theological arguments can certainly be made, as presented in the previous section, empirical studies can also aid in showing how persons who self-identify as Christians think through the issues at stake in XTx. Nonetheless, detailed theological viewpoints on XTx are limited.

Theological opinion on XTx can be found for centuries, as highlighted in the previous section. Studying the attitudes of persons toward XTx that do not specifically assess the role of religion on viewpoints have been studied since at least the 1990s [33]. Empirical studies on the viewpoints of persons toward XTx who identify as a member of a particular religious tradition are difficult to locate in the extant literature prior to around the turn of the twenty-first century [34, 35]. Ward makes brief mention of a questionnaire study sent to dialysis patients in Great Britain and stated that many of those who were unwilling to accept a xenograft objected either because of animal ethics concerns or for religious reasons, which were not detailed [36]. Schlitt and colleagues in Germany used a questionnaire to survey viewpoints of patients who either had received a transplant (n = 722) or were on the waiting list for various organ grafts at the time (n = 327) [34]. In the study, researchers did not find that a patient's self-identified religion (Protestant: 53%; Catholic: 26%)

influenced their viewpoints on accepting a xenograft, stating that concerns about the use of animal organs based upon religion were "very rare."

Hagelin and colleagues published a study in 2001 that assessed associations between religious beliefs and attitudes toward XTx in students from Kenya, Sweden, and the United States [35]. In their study, non-religious students approved of XTx at higher rates than religious students. In the religious students' cohort, Protestants were more likely to accept XTx than Catholics. However, this can vary from country to country. A study exploring the views of undergraduate and graduate theology students (n = 123) in South Korea found that despite having very positive views of human transplantation, the participants were found to have a neutral attitude towards XTx, with religious belief shown to be negatively correlated with a less favorable view towards XTx [37]. The researchers caution against deriving any causal relationship between religious belief and attitudes towards XTx, as the participants demonstrated a lack of understanding of transplant-related issues. It is also noteworthy that how favorably or unfavorably someone may view XTx is dependent on how much information they are given. For example, in a study (n = 327) from Canada, support for the use of pigs for XTx dropped by ~20% when participants were told that the pigs would need to undergo genetic engineering [38].

In 2006, Jeong et al., published a Delphi survey of respondents in South Korea regarding viewpoints on the societal impacts and implications of XTx [39]. The survey comprised many groups of persons, including a broad Christian faith group perspective that included ministers, priests, and monks. The core reservation identified toward XTx amongst this group was that XTx is a challenge to God. This perspective was not fully explained, though it was apparent that it was a negative outlook on the research.

In 2010, Jenkins and colleagues published a questionnaire survey of how different faith and cultural groups view the use of allogeneic and xenogeneic mesh for soft tissue repair [40]. Representatives from major faith groups were contacted and researchers concluded that many major Christian faith groups leave the decision of whether to accept a xenogeneic mesh product up to the individual.

Lastly, in 2019, Hurst and colleagues held a series of focus groups with various members of the community surrounding The University of Alabama at Birmingham, the site of a recent bilateral kidney XTx in a deceased person and where XTx clinical trials are being considered [3, 9, 41]. One focus group was comprised of 10 clergypersons—8 Protestant, 1 Catholic, and 1 Muslim. The Catholic participant—a deacon in the Church—stated his viewpoints aligned with the document produced by the Pontifical Academy for Life. A recurring concern amongst several of the Protestant clergypersons centered around the idea of hypocrisy and its connection to animal ethics. While none of the participants articulated a viewpoint that would eschew the use of animals for purposes such as food or clothing, there was concern for a species of pig merely bred for their organs. As was highlighted above, the topic of animal ethics and the proper stewardship of creation, including what dominion of creation entails, has occupied a central place in Judeo-Christian theology, and it is evident that XTx re-frames this old discussion.

Community Risk of Xenozoonosis Vs. Individual Benefit

A primary ethical concern with XTx has been the risk of xenozoonotic infection. Pigs naturally are hosts to certain viruses that could plausibly be transmitted to a human xenograft recipient. While this risk is now considered to be very low due to specifically breeding pigs in biosecure, pathogen-free environments, as well as "knocking out" certain viruses from the pig genome, some risk remains. In early 2022, the University of Maryland Medical Center transplanted a pig kidney into a living adult male who was not considered a candidate for a human heart due to medical non-compliance. He lived for about 2 months before dying. Following his death, it was revealed that he had acquired a cytomegalovirus—a communicable virus—which is thought to have come from the pig heart [42]. At the time of this writing, an official autopsy report is still pending, but it exhibits the individual risk.

When thinking about the issue of potential xenozoonosis spread throughout the community due to an infected xenograft through a Christian lens, there are certain Christian principles that may help guide this analysis. Christians are called to love their neighbor. When a lawyer asks Jesus what the greatest commandment is, Jesus responds:

> You shall love the Lord your God with all your heart and with all your soul and with all your mind. This is the great and first commandment. And a second is like it: You shall love your neighbor as yourself. On these two commandments depend all the Law and the Prophets. (Matthew 22: 37–40, ESV).

Pointing to this commandment to love one's neighbor as oneself has been used as justification for allotransplantation. That is, a Christian may show their love for another by providing for them in their need for an organ. However, in the context of XTx an opposing conclusion could be drawn. In the face of real risk of the potential for xenozoonotic spread, it could be argued that the loving action would be not to perform any action/undergo any therapy that could lead to risk for another, especially an unknown level of risk that the "neighbor" did not consent to. However, daily we undertake activities that place those around us at some risk–risk that was not consented to. We drive our cars and are accepting risk. If we have passengers—children, especially—we are accepting a risk for them, as they cannot consent to that risk. We place other drivers and pedestrians at risk. We bring up the aspect of "risk" because Christians are called to love their neighbors, as previously mentioned. Accepting a non-human organ carries the risk of becoming infected with a pig virus and then possibly exposing others (our neighbor) to that risk—a risk they did not consent to accept. The constant risk of spreading an infectious disease to loved ones (at least until the scientific community can be certain their source pigs are indeed pathogen-free) is a glaring issue and one that Christians may not want to assume currently due to the recent COVID-19 pandemic.

Ways Forward

As has been stated, very little has been written from the perspective of assessing XTx in light of Christian theology. The literature could benefit from additional resources that are accessible to parish clergy and to Christians globally. While XTx being a clinical option is still likely years in the future, it would be prudent for Christian theologians and moral philosophers to begin addressing these issues from their own denominational outlook to provide a helpful perspective and structure to think through the issues involved. It may be premature for clergy to be having conversations with their parishioners on XTx, yet beginning to think through how they might counsel persons on these issues in light of their religious commitments seems sensible.

From an empirical standpoint, we know from some data that while acceptance of XTx is generally high, there are some hesitations among persons with religious beliefs. Some Christian clergypersons have stated that they may feel "hypocritical" by supporting XTx [9]. These viewpoints merit further exploration. Furthermore, not much is known about Christian viewpoints toward XTx aside from the bifurcation of Catholicism and Protestantism. Minority Protestant denominations, as well as Orthodox viewpoints, may be especially underrepresented in the data that exists, which will need to be accounted for in future studies.

References

1. Health Resources & Services Administration. Organ donation statistics. https://www.organdonor.gov/learn/organ-donation-statistics
2. Manji RA, Lee W, Cooper DKC. Xenograft bioprosthetic heart valves: past, present and future. Int J Surg. 2015;23(Pt B):280–4.
3. Porrett PM, Orandi BJ, Kumar V, Houp J, Anderson D, Cozette Killian A, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;22(4):1037–53.
4. NYU Langone Health Performs Second Successful Xenotransplantation Surgery 2021. https://nyulangone.org/news/nyu-langone-health-performs-second-successful-xenotransplantation-surgery
5. Kotz D. UM medicine performs historic xenotransplantation, vol. 11; 2022. https://www.umaryland.edu/news/archived-news/january-2022/um-medicine-performs-historic-xenotransplantation.php
6. Hurst DJ, Padilla LA, Walters W, Hunter JM, Cooper DKC, Eckhoff DM, et al. Paediatric xenotransplantation clinical trials and the right to withdraw. J Med Ethics. 2020;46(5):311–5.
7. Padilla LA, Hurst D, Maxwell K, Gawlowicz K, Paris W, Cleveland D, et al. Informed consent for potential recipients of pig kidney xenotransplantation in the United States. Transplantation. 2022;106(9):1754–62.
8. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Scientific and psychosocial ethical considerations for initial clinical trials of kidney xenotransplantation. Xenotransplantation. 2022;29(1):e12722.
9. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021:e12684.

10. Paris W, Seidler RJH, FitzGerald K, Padela AI, Cozzi E, Cooper DKC. Jewish, Christian and Muslim theological perspectives about xenotransplantation. Xenotransplantation. 2018;25(3):e12400.
11. Daar AS. A survey of religious attitudes towards organ donation and transplantation. In: Collins GM, Dubernard JM, Land W, Persijn GG, editors. Procurement, preservation and allocation of vascularized organs. Dordrecht: Springer Netherlands; 1997. p. 333–8.
12. Sharifova RA, Al Breizat AKS, Kaabak MM, Maslikova UV, Yaremin BI. Ethical issues of xenotransplantation in the aspect of religious views. Bull Med Inst "REAVIZ" (Rehabilitation, Doctor and Health). 2022;1:117–30.
13. Cooper DKC. A brief history of clinical cross-species organ xenotransplantation. In: Cooper DKC, Byrne G, editors. Clinical xenotransplantation: pathways and Progress in the transplantation of organs and tissues between species. Cham: Springer; 2020. p. 3–26.
14. Jonasson O, Hardy MA. The case of Baby Fae. JAMA. 1985;254(23):3358–9.
15. Stafford N, Leonard L. Bailey: in 1984 he transplanted a baboon heart into a human infant known as "Baby Fae". BMJ. 2019;366:l4669.
16. Bailey LL, Nehlsen-Cannarella SL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA. 1985;254(23):3321–9.
17. Vatican Expert Views Surgery on Baby Fae. The New York Times. 1984 November 18, 1984; Sect. 1e.
18. Oliver M, Woywodt A, Ahmed A, Saif I. Organ donation, transplantation and religion. Nephrol Dial Transplant. 2011;26(2):437–44.
19. Thomasma DC. The quest for organ donors: a theological response. Health Prog. 1988;69(7):22–4, 8.
20. Geisler NL. Christian ethics: options and issues. Grand Rapids: Baker; 1989.
21. Ramsey P. The patient as person: exploration in medical ethics. 2nd ed. New Haven: Yale University Press; 2002.
22. Meilaender G. Bioethics: a primer for Christians. 2nd ed. Grand Rapids: Eerdmans; 2005.
23. Pontifical Academy for Life. Prospects for xenotransplantation: scientific and ethical considerations Vatican City: Vatican; 2001. http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html
24. Middleton JR. The liberating image. Grand Rapids: Brazos Press; 2005.
25. Bruton SV. Christian ethics and vegetarianism. In: Thompson PB, Kaplan DM, editors. Encyclopedia of food and agricultural ethics. Dordrecht: Springer Netherlands; 2013. p. 1–7.
26. Bruggermann W. Genesis. Louisville: John Knox Press; 1982.
27. Church Office of the Evangelical Church in Germany (EKD); Secretariat of the German Bishops' Conference (DBK). Xenotransplantation: an aid to ethical discernment. 1998. https://repository.globethics.net/bitstream/handle/20.500.12424/216250/BG16_Joint_PD_Xenotransplantation.pdf?sequence=1&isAllowed=y
28. McCracken V. Public attitudes toward xenotransplantation: a theological perspective. J Evid Based Soc Work. 2021;18(5):492–9.
29. Reimert I, Bolhuis JE, Kemp B, Rodenburg TB. Indicators of positive and negative emotions and emotional contagion in pigs. Physiol Behav. 2013;109:42–50.
30. Goumon S, Spinka M. Emotional contagion of distress in young pigs is potentiated by previous exposure to the same stressor. Anim Cogn. 2016;19(3):501–11.
31. Lawrence AB, Newberry RC, Špinka M. Positive welfare: what does it add to the debate over pig welfare? In: Špinka M, editor. Advances in pig welfare. Duxford: Woodhead Publishing; 2018. p. 415–44.
32. Soman SS, Vijayavenkataraman S. Applications of 3D bioprinted-induced pluripotent stem cells in healthcare. Int J Bioprint. 2020;6(4):280.
33. Mohacsi PJ, Blumer CE, Quine S, Thompson JF. Aversion to xenotransplantation. Nature. 1995;378(6556):434.
34. Schlitt HJ, Brunkhorst R, Haverich A, Raab R. Attitude of patients toward transplantation of xenogeneic organs. Langenbeck's Arch Surg. 1999;384(4):384–91.

35. Hagelin J, Hau J, Schapiro SJ, Suleman MA, Carlsson HE. Religious beliefs and opinions on clinical xenotransplantation--a survey of university students from Kenya, Sweden and Texas. Clin Transpl. 2001;15(6):421–5.
36. Ward E. Attitudes to xenotransplantation. Lancet. 1997;349:9067.
37. Sung SW, Jang K, Bargainer R, Cooper DKC, Paris W. South Korean theology student opinions about xenotransplantation. J Evid Based Soc Work. 2021;18(5):519–26.
38. Schuppli CA, Weary DM. Attitudes towards the use of genetically modified animals in research. Public Underst Sci. 2010;19(6):686–97.
39. Jeong D-Y, Kim Y-B, Chang S-O. Societal impacts and implications of xenotransplantation- a Delphi survey in Jeju, South Korea. Korean Soc Sci J. 2006;33(2):1–32.
40. Jenkins ED, Yip M, Melman L, Frisella MM, Matthews BD. Informed consent: cultural and religious issues associated with the use of allogeneic and xenogeneic mesh products. J Am Coll Surg. 2010;210(4):402–10.
41. Hurst DJ, Padilla LA, Cooper DK, Walters W, Paris W. The attitudes of religious group leaders towards xenotransplantation: a focus group study. Xenotransplantation. 2022:e12777.
42. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, et al. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med. 2022;387(1):35–44.

Religious Viewpoints: Sunni Islam

14

Mansur Ali, Usman Maravia, and Aasim I. Padela

> The human being was created like this: They took the wings of an angel, and tied them to the tail of a donkey, in hopes that the donkey—from the radiance and companionship of the angel—might become an angel, too. So what is so wonderful if this donkey became a human? God is able to do all things [1].

Introduction

In Islamic theological anthropology, humans are tied in a nexus of relationships—underneath but connected to God who is at the highest node, linked to human beings on an equal footing, and connected to animals who are the lower node in service to humankind. Humans are a constituent of two opposing forces: The spirit of God and dark mud. It is mentioned in the Qur'an that God created the first human Adam from dried clay formed from dark mud and then breathed His Spirit into him [2].[1] It is the

[1] All Qur'an translations are from 'The Qur'an. Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.'

M. Ali (✉)
Centre for the Study of Islam in the UK, School of History, Archaeology and Religion, Cardiff University, Cardiff, Wales, UK
e-mail: AliMM1@Cardiff.ac.uk

U. Maravia
Economic and Social Research Council (ESRC) Centre for Corpus Approaches to Social Science (CASS), Lancaster University, Lancaster, UK
e-mail: U.maravia@lancaster.ac.uk

A. I. Padela
Department of Emergency Medicine, Institute of Health & Equity, The Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: apadela@mcw.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_14

combination of the spiritual and the profane that makes human a paradoxical creature eloquently captured by Rumi in the epigraph above. Depending on their behaviour and conduct, humans have the potential to soar to the heights of the angels or alternatively fall to the depths of depraved creations even below animals. These fallen ones are branded in the Qur'an as spiritually unhearing, unspeaking, and unseeing and are likened to animals and at times worse than animals.

> We have created many jinn and people who are destined for Hell, with hearts they do not use for comprehension, eyes they do not use for sight, ears they do not use for hearing. They are like cattle, no, even further astray: these are the ones who are entirely heedless [3].

As a recipient of God's Spirit, the human is privileged with the title 'vicegerent' (caliph or *khalīfa* in Arabic). As God's vicegerent, the human is the 'instrument through which God's will is realized and crystalised in this world' [4] (p. 29). Consequently, for human comfort, as well for the purpose of bolstering their capacity to do good works, God has placed the entire creation at his service. But the caliphate is tempered with a reminder that the caliph in return is only a servant of God (known in Arabic as *ʿabd*). This bridles the caliph-cum-servant from exercising unfettered discretion over the creation. Thus, all those who wastefully squander God-given resources are termed the brothers of Satan in the Qur'an [5].

From a theological lens, animals have been created to benefit humanity. In the language of the Qur'an, this is known as *taskhīr* (subservience). All of nature is *musakkhar* (subservient) to the human who is the most privileged of creations. Thus, God permits humankind to hunt certain animals [6] and consume their flesh and milk (and honey) [7], to ride them [8], and to deploy them in service to benefit from their labour or products, such as wool [9]. Despite this servile status, humans are reminded that the primary obedience of animals lies with God; and there are many instances recounted in the Qur'an where animals have been employed by God to keep humans on the straight and narrow.

A crow taught the son of Adam, Cain, funerary rites [10]. Animals have been instrumental in implementing God's punishment [11] and cruelty to animals has triggered God's wrath [12] (See [13] for more examples). The Prophet reprimanded against purposeless killing of animals. He said, *'Whoever kills even a sparrow or anything smaller, without it deserving it, God will question him about it'* [14]. The Prophet extolled compassion towards animals. He exhorted, 'The Compassionate One has mercy on those who are merciful. If you show mercy to those who are on earth, He who is in the heaven will show mercy on you' [15]. During the slaughter of animals, he commanded that the knife be sharp and the cut swift to cause minimal pain. He forbade slaughtering one animal in front of another. Thus, he said,

> God has prescribed proficiency in all things. Thus, if you kill, kill well; and if you slaughter, perform it well. Let each of you sharpen his blade and let him spare the suffering of the animal he slays [16].

Illustrating the compassionate treatment of animals, the Prophet Muhammad recounted the story of a prostitute who went down into a well and filled her leather

sock to quench the thirst of a dying dog. God forgave her for this act of benevolence [17]. In contrast, he shared an incident about another woman who locked a cat in the house and starved it to death. That woman was decreed as hell-bound for her cruel behaviour [18].

This ethos of treatment of animals with care, compassion and God-consciousness (*taqwā*) is captured in the hortatory Prophetic counsel where he encouraged Muslims to recite a prayer from the Qur'an every time they mount a beast; to remind them that it is God who has subjugated (*taskhīr*) such magnificent animals for human ease.

> [It is God] who gave you ships and animals to ride on so that you may remember your Lord's grace when you are seated on them and say, 'Glory be to Him who has given us control over this; we could not have done it by ourselves. Truly it is to our Lord that we are returning,' [19].

These Qur'anic exhortations and Prophetic teachings led to Muslim culture taking animal welfare seriously. For example, Ibn al-Marzubān (d. 921), a medieval Muslim scholar extoled the loyalty of dogs in a book entitled, 'The book of the superiority of dogs over many of those who wear clothes' (*faḍl al-kilāb ʿalā kathīr min man labisa al-thiyāb*) [20].

This brief discussion is sufficient to demonstrate that while animals are not on par with humans from an Islamic lens, as stewards of the earth humans must not seek to dominate creation but to stand with it in a caretaking relationship of it, and with respect to animals be mindful of their welfare. This theological narrative informs our exposition on 'Sunni Islamic perspectives' on xenotransplantation. Xenotransplantation or xenografting refers to transplanting organs from one species (animals) to another (humans) [21] (p. 232). We will examine ethical issues related to this practice from an Islamic perspective grounded in the Sunni schools of law. While there may be significant overlap with Islamic perspectives based on Shia schools of law, we want to ardently avoid conflation of Sunni Islam with Islam. Similarly, our chapter offers a perspective but there can be multiple authentic 'perspectives' on the issue because even within the Sunni denominations there are a plurality of views vis-à-vis bioethics. We shall attempt to underscore some of this diversity in this chapter.

The chapter is divided into a number of subsections. We start by making some general observations on Sunni ethics; and follow it with some discussions on medication and therapy (*tadāwī bi al-muḥarramāt*). We next mine the Sunni ethico-legal tradition to build an accurate understanding of xenotransplantation ethics. Finally, we deliberate on some further afield ethical issues related to the impact of controversial therapies and Muslim self-image which will assist in understanding how Sunni perspectives on xenotransplantation are arrived at and received by the general Muslim population. We conclude the chapter by adopting precaution [21]. We view xenotransplantation to be a stop-gap treatment, and call for further research into preventative medicine and alternative therapies that avoid allografts and porcine xenografts.

Sources of Sunni Ethico-Legal Deliberation

Sunni Islam is primarily nomocratic, meaning that God's Will is to be worked out through the law. Whilst Sunni law has its foundation in two primary textual sources, the Qur'an and Prophetic practice (*sunna*), the bulk of it is found in the legal interpretations of these sources by jurists documented in Islamic law collections.

The gatekeepers of the law are the jurists (*fuqahāʾ*). They are scholars with the intellectual training and credentials needed to deduce laws from the primary sources. Their authority is constructed through an interaction between texts, discursive methods, and personified knowledge [22]. Thus, they are taken seriously as religious authorities only as long as they follow the rules of interpretation mapped out in Sunni legal theory (*uṣūl al-fiqh*). To maintain their authority, they must follow a system of precedents. New laws and deliberations need to be anchored to the Qur'an, *sunna* or commentaries of the ancient scholars similar to English common law.

While there were multiple interpretations and law schools in the formative period, by the tenth century these were reduced to four dominant Schools of Law: Ḥanafī, Shāfiʿī, Mālikī, and Ḥanbalī named after their eponymous founders. Henceforth, these legal schools function as sources of Islamic law in tandem with the primary sources. Even so, individual scholars deliberate on novel matters using analogical reasoning (*qiyās*) and other formal methods (*ijtihād*), and render non-binding legal opinions termed fatwas.

In the modern period, a new form of ethico-legal reasoning has emerged—collective legal deliberations (*ijtihād jamāʿī*) [23]. Groups of Islamic jurists and experts in other fields convene at international conferences to derive Islamic position statements, termed *qarārāt*, on novel issues. Although these *qarārāt* do not have any legal force, they have been used as the basis for law in some Muslim countries [24]. For some, these modern declarations are a substitute to the findings of the traditional schools of law, and thus transcend them [25].

Medication in Sunni Ethics and Law

Sunni perspectives on xenotransplantation ethics cannot be properly appreciated without some general discussion on medication and therapy in Islam.

While using medication and therapy is permitted by Islamic law, and according to some authorities encouraged, unlike life-saving sustenance such as food and drink it is not morally obligatory. This is unless there is a high probability that the therapy will be lifesaving [26]. At first blush, it may seem odd to even broach this topic. After all, are not diseases and seeking a cure from them an integral part of our lives? That may be the case; however, from a theological point of view, medication and therapy pose a dilemma: if everything happens in this world because God willed it, it follows that God willed illness on someone, which follows that trying to cure that illness may be viewed as challenging God's Will. Indeed, this is how some of the Companions of the Prophet understood medication when they asked him, 'Would not medication go against the Will of God?' The Prophet pacifyingly and

rhetorically responded, 'to use medication is also according to the Will of God' [15, 27]. Nevertheless, the fact that using medicine is not obligatory provides space to those who want to exercise a heightened level of spirituality by surrendering themselves to God's will. At the same time, the theological position that God can cure without the need for human intermediaries, must also be preserved within the law. Hence, it cannot be judged to be sinful to forego medication and therapy, and instead choose to rely on God alone.

The discussion above is somewhat theoretical since no Sunni jurist wholly objected to the pursuit of medication and therapy by a Muslim subject. Its primary purpose was to relieve the foregoing theological tension. However, opinions are divided on using medication and therapy that is based on normatively prohibited products (*tadāwi bi al-muḥarammāt*), such as alcohol and pork. In four different verses, the Qur'an details items which are forbidden to consume [28–31]; they include carcass, blood and pork amongst others. Despite the prohibition, these things are permissible to use in cases of dire necessity (*darura*). The Qur'an reads,

> You are forbidden to eat carrion; blood; pig's meat; any animal over which any name other than God's has been invoked; any animal strangled, or victim of a violent blow or a fall, or gored or savaged by a beast of prey, unless you still slaughter it [in the correct manner]; or anything sacrificed on idolatrous altars. […] but if any of you is forced by hunger to eat forbidden food, with no intention of doing wrong, then God is most forgiving and merciful [28].

This is further qualified in another verse, '*But if someone is forced by hunger, rather than desire or excess, then God is most forgiving and most merciful'* [30].

The above verses reveal that in cases of dire necessity one is allowed to utilise forbidden items commensurate to need. 'Necessity' has been defined by the Ḥanāfi scholar al-Jaṣṣāṣ (d. 981) as 'a [subjective] fear of injury or harm to the self or limbs,' [32] (p 1: 159).

The above Qur'anic verses are complemented or contradicted (depending on perspective) by a Prophetic statement, 'God sent down illness and its cure and he made a cure for every illness. Therefore, seek medication but do not seek what is forbidden (*ḥarām*) as medication' [33].

This narration could be interpreted in two ways:

1. A Muslim is permitted to seek all effective medical options as long as the therapy does not involve anything that would otherwise be prohibited.
2. A Muslim is permitted to use substances that may otherwise be prohibited if facing a dire need and this is the only viable option.

The first interpretation where prohibited items are not permissible for medication is supported by a case wherein a delegation from the cold Yemenite region of Himyar sought permission from the Prophet to drink alcohol made from wheat to help increase their body temperature [34] (p. 2: 69). Although not much detail is present in the account, some questions arise such as what alternatives were available? What

would have been the side effects? Was the only purpose to keep themselves warm or were there other motives? Bearing these questions in mind, the Prophet reminds them that the drink would still be intoxicating and by the admission of the delegation, the tribe was known to drink excessively, the side effect would be that the people would not be able to abstain from it beyond the reason stated i.e., thermoregulation.

The second interpretation is in line with the Qur'anic verses above on permission in dire necessity. The primary Prophetic precedence for this is the case of the people of ʿUrayna who could not adopt well to the environment of Madina and fell seriously ill. The Prophet instructed them to drink the milk and urine of camels upon which they were cured [35]. Another precedent for this interpretation is found in the case of ʿArfajah b. Saʿd, a Companion of the Prophet, whose nose had been cut off in the battle of al-Kulāb. ʿArfajah, knowing that the use of gold is prohibited for men, had a nose made of silver. However, the silver resulted in an unbearable stench. The Prophet then himself advised that ʿArfajah have a golden nose made [33]. As such, ʿArfajah himself did not desire a golden nose or show any desire to display any gold items for that matter. The fact that the Prophet advised him to seek a golden nose attests to the fact that therapy can be sought using substances that would otherwise be prohibited for use as long as it is for a genuine need. Likewise, in cases of dire need (*ḥājah*) the Prophet recommended silk, another forbidden item for men to wear, for ʿAbd al-Raḥmān b. ʿAwf and Zubair b. al-ʿAwwām who were both suffering from chronic pruritus [16].

Based on the above, many jurists, but not all, have extrapolated the following with regards to *tadāwī bi al-muḥarammāt* [36] (11: 115–124, entry '*tadāwī*') [37–38]:

1. It is permissible in cases of dire necessity (*ḍarūra*) or extreme need (*ḥājah*) providing that the usage is proportionate to the need.
2. And the cure is definite (*yaqīn*) or highly probable (*ghalabat al-ẓann*).
3. And a halal alternative is not found.

The way this extrapolation applies to xenotransplantation is that a pig-heart transplant might be the only life-saving option for some patients. Under such circumstances receiving a pig-heart would be permissible due to dire necessity (*ḍarūra*) or extreme need (*ḥājah*). The only concern jurists might have, however, is that a pig heart transplant is still considered experimental therapy.

Xenotransplantation and Its Relationship to Allotransplantation

Sunni scholars have been discussing allotransplantation (human to human transplantation) since the 1920s with a surge of fatwas appearing from the early 1950s. Two of the authors of this chapter (Ali and Maravia) have detailed seven different positions gleaned from a reading of over a hundred fatwas in multiple languages

[39]. What is clear from these fatwas is that those who permit organ transplantation view it through the lens of necessity or extreme need. In other words, it is tolerated but not preferred as a number of disliked activities are involved including invasive surgery, prolonging burial, etc. Organ transplantation is accommodated because it is a life-saving therapy, however in the presence of an alternative, that will always be preferred providing that it can fulfil similar functions of the body. Hamdy in her anthropological study of organ transplantation in Egypt [40] writes that her interviewees who were suffering from renal failures were reluctant to receive organs from live donors because they were concerned that donors would end up having renal failure in the future. Instead, they desired cloned or synthetic organs be made available.

If in future, xenotransplantation therapy becomes as effective as allotransplantation, we predict that Islamic jurists who now advocate human to human organ transplantation will retract their fatwas and opt for xenotransplantation as the preferred option.

Animal Use in Medication and Therapy in Sunni Ethics

The use of animal products such as bone, hide, and hair have been long discussed by classical Islamic jurists [36] (18: 335–338, entry '*ḥayawān*'; 20: 32–38 '*khinzīr*'). While xenotransplant in the true sense of the word was not discussed by medieval scholars, their discussion on the use of animal parts in medication provides the foundation upon which to build a Sunni perspective on xenotransplantation [41]. It is to these foundational principles that we now turn to. How these principles are applied to xenotransplantation is discussed below in section "A Sunni View on Xenotransplantation"

With regards to using animal parts in medication and therapy, Sunni scholars take several factors into consideration. These include the type of animal, type of limbs and organs used and whether the animal was dead or alive at the time the body parts were procured. Scholars categorise animals into three types: (1) the *ḥalāl* animal: an animal which is permissible to consume after ritual slaughtering, e.g. a goat, (2) the legally clean animal: an animal which is clean according to Islamic law but not permissible to consume, e.g. a cat (3) an intrinsically impure animal not permitted to eat and not clean, e.g. a pig (although there exists a difference of opinion on this matter as will be highlighted in the next section). The *ḥalāl* animal might either die on its own, be ritually slaughtered, or be killed non-ritually. Each of these methods of death implicate the legal permission on its usage. For the other two types of animals, the method of death does not matter. Finally, body parts are divided into those parts that have a steady supply of blood (e.g., organs) and those parts that do not (e.g., bones, hair, and nails) [36] (18: 335–338, entry '*ḥayawān*'; [42] (pp. 534–68).

All Sunni jurists agree that a severed limb or an organ of an animal which is still alive (irrelevant of the type of animal) is ritually impure (*najis*); and grafting the severed limb into a person will render all forms of ritual worship void. This is based on the Prophet's prohibition on his arrival to Medina when he observed

some people consuming camel humps and goat legs without slaughtering the animals. He counselled, 'The severed limb from a living animal is a carcass!' [15, 33]. This Prophetic reproach became the basis for Sunni scholars to declare severed limbs from living animals to be the same as a carcass. Also included among the category of 'carcass', and therefore ritually impure, are all dead animals with the exception of the ritually slaughtered *ḥalāl* animal. Hence it will not be permissible to utilise them in the absence of dire necessity (*ḍarūra*) or extreme need (*ḥājah*).

Returning to our discussion on pig heart transplants, the extracted heart of a pig is considered *najis* because (a) the pig cannot be slaughtered in a halal manner and (b) the heart is considered carcass once it has been extracted from the pig. However, as previously highlighted, dire necessity allows exceptions for such a heart to be utilised especially for the purpose of saving a life.

A Note on the Status of Pig in Islam

Since the primary source animal for xenotransplantation is a pig and porcine heart transplantation has recently been performed in a living adult [43–44], a few words related to how the pig is understood by Sunni scholars as well as its clinical need is in order. The Qur'an is clear that grazing animals are *ḥalāl* for consumption, and Islamic jurists rule that carnivores must be avoided. However, there was lack of clarity about pigs which from one perspective act like grazing animals, and from another behaved like animals of prey, i.e., they are omnivores. The Qur'an clarifies this status by associating pigs with carnivores and declaring its consumption to be forbidden except in a life-threating situation where an alternative is not available [30]. Based on this, the majority of Sunni scholars declared the pig to be inherently impure, including its hide, sweat and saliva, dead or alive. However, the Mālikī school as well as prominent jurists such as Ibn Taymiyya (d. 1328) [45] (1: 264), al-Shawkānī (d. 1834) [46] (2: 196), and Ibn ʿĀshūr (d. 1973) [47] (5: 22) held the view that the pig is clean and only its consumption was prohibited. As for benefiting from the pig in other ways, the Ḥanafī jurist Abū Yūsuf argued that pig leather could be used after tanning [48] (1: 86) and also argued that boar bristles could be used in shoemaking [48] (1: 63).

This legal position vis-à-vis the pig undergirds a Muslim culture of almost total avoidance. Muslims do not farm pigs, and in some Muslim sub-cultures, the utterance of the word 'pig' may be avoided altogether. Muslim patients and jurists commonly look to animals that are *ḥalāl* for consumption such as goats and cows to use in pharmaceutical testing and biomedical research.

Yet, several reasons are given, however, for preferring pig organs or indeed a pig heart for transplantation purposes. Mohiuddin explains:

> We have completely mapped the genome of a pig … We know how a pig differs from a human and what changes are needed to make its organs acceptable in our bodies. We don't know much about goats or cows [49].

Pigs are also the preferred choice for transplantation purposes because they reproduce frequently, they are easier to modify genetically, and their organs are similar in size to that of humans. Although chimpanzees, baboons, and gorillas are much closer matches to humans genetically, in addition to all (including pigs) carrying the risk of zoonotic viruses transferring to humans, non-human primates, especially chimpanzees, are declared to be endangered species. More important perhaps is that the dominant xenotransplantation model involves pig organs. Decades of research and millions of dollars have gone into making the pig model viable, other models have a much steeper hill to climb.

A Sunni View on Xenotransplantation

Given the restrictive conditions placed on therapy that uses normatively prohibited material (*tadāwī bi al-muḥarramāt*) and the strong sentiment against the pig borne out of an understanding of scripture, Sunni jurists advocate a hierarchy of animals that can be used for xenotransplantation, even in the case of dire necessity. Organs from a ritually slaughtered *ḥalāl* animal is the preferred, primary option. This is followed by organs from the legally clean animal such as non-human primates. Only as a last resort will Islamic scholars allow the use of porcine products [36] (11: 115–124, entry '*tadāwī*') [42]. But since porcine products are the only viable option available today, Islamic jurists cautiously allow it in cases of genuine medical necessity while recommending that effort and research should be exerted in trying to find *ḥalāl* alternatives. This nuance is illustrated by the Islamic Law Council (IFC-MWL) of Mecca declared at the end of its eighth session held in January 1985 that.

> The following are legally permissible *a priori*,[2] … to procure an organ from a ritually slaughtered *ḥalāl* animal without reservation and from non-*ḥalāl* animals in case of necessity for transplantation into the person who is in need of it [50] (p. 77).

Similarly, the Indian Islamic Law Council in its 1989 conference concluded that

1. It is permissible to use the organs of the ritually slaughtered halal animal for human transplantation.
2. In the case of dire necessity where one fears for one's life or limbs and no alternative is available, it is permissible to use the organs of non-halal animals or the halal animal which was not ritually slaughtered.
3. In cases of non-necessity, the use or porcine organs is not permissible [51] (1: 247).

Despite the above declarations, contentions about which patient-level conditions permit usage remain. Some jurists at the Indian assembly maintain that porcine

[2] The declaration has already discussed living donation from humans.

organs are also permissible to use in cases of extreme need (*ḥājah*), whilst others have opined that even in cases of dire necessity their use is not permissible [51] (1: 242–3). Similarly, the premier jurist al-Qaradāghi, Secretary General of the International Union of Muslim Scholars, declared that porcine transplant is permissible only in dire necessity (*ḍarūra*) and not extreme need (*ḥājah*) [52] (p. 489). Some Islamic Law Councils, like the Port Elizabeth Mujlis al-Ulama based in South Africa, declared that even in dire situations the use of porcine organs is not permissible [53] (p. 24).

Other jurists like the former rector of Al-Azhar University, Shaykh Gād al-Haqq (d. 1986) [54] (7: 356) and Shaykh ʿAtīyah Ṣaqar (d. 1996) have permitted bone xenotransplantation, with the latter arguing in favour of a pig pancreas [55] (10: 233). The late Mufti Muhammad Shafi who categorically prohibited organ donation also recommended xenotransplantation to be further developed as a suitable alternative to allotransplantation [56] (7: 52). The former chief mufti of Saudi Arabia, Sheikh Ibn al-ʿUthaymīn (d. 2001) emphasised that the most important factor to consider concerning clinical need is what is best for the patient—as such, if a synthetic valve does not agree with the patient but a pig valve does, then the latter could be used [57]. The Sheikh further highlighted that the prohibition mentioned in the Qur'an applies only to the consumption of pig flesh.

Where a xenotransplantation is a viable option, a Muslim patient must have the right to be well-informed about its benefits, risks, and any alternatives. The onus of providing sound information rests with (a) the medical experts to provide the pros and cons of the treatment in light of statistical and scientific data, and (b) Islamic jurists who could review the medical information at hand and advise in the best interest of the Muslim patient.

In summary then, the mainstream view among Islamic jurists appears to be that xenotransplantation from pigs is contingently permissible in cases of dire necessity (*ḍarūra*) or extreme need (*ḥājah*) providing that (1) the usage is proportionate to the need, (2) cure from the therapy is definitive (*yaqīn*) or highly probable (*ghalabat al-ẓann*), and (3) a *ḥalāl* alternative is not available.

The authors of this chapter agree with the contingencies, however, believe that a judgement of permissibility is non-ideal. In contrast, we opt for a tread-with-care and watch-this space approach recognizing that xenotransplant is 'a stop-gap intervention that is potentially life-saving' [41]. We base our cautious approach based on the following considerations.

Islamic Concerns: Potential Religious Objections to Xenotransplantation

As has been mentioned above, using prohibited substances for medical purposes is allowed under three circumstances: (1) dire or urgent need, (2) if there is a strong possibility of cure, and (3) no *ḥalāl* alternatives are found. Xenotransplantation may be objected to because it does not satisfy some of these conditions.

Since xenotransplantation is a medical therapy, it will fall under the general ruling of medicine in Sunni Islamic law; it is treated as permissible but not obligatory unless proven to be lifesaving [41]. Yet, the status of xenotransplantation as an experimental therapy intrinsically makes it of unknown efficacy even if it appears to be life saving to the laity. The recent example of an individual receiving a pig heart but dying within weeks illustrates that this cure is illusive, and the therapy of uncertain efficacy [44, 58]. This status leads to the question that if medication and therapy itself is not obligatory in Islam, does it logically follow that Islamic law would allow for violating a prohibition against porcine usage when the outcome of the proposed therapy is uncertain? It appears to us that the criterion of certainty, or dominant probability, of cure and/or life-saving status is not met. Said another way, we worry about resorting to arguments on dire necessity off-hand. We do not believe that the existence of a threat to life or severe distress automatically allows one to violate a normative prohibition. Rather the proposed outcome must be interrogated by assessing success rates and the like. Rather than permitting porcine xenotransplantation based on the patient facing a dire need or life-threat, we weigh more heavily on evaluating the probabilities of a therapeutic outcome.

Other concerns to the recipient must also be weighed. Even though the effects of hyperacute rejection have been mitigated by genetic modification of the source animal, how much do we know about the negative immunological responses to xenotransplant? Especially given the possible risk of zoonotic risk transmission found in basic laboratory science settings. Furthermore, graft versus host diseases in primates such as baboons is well known [59]. Transgenesis involving human DNA to be implanted into pig embryo throws up another problem related to experimenting with human DNA and creating human like embryos in pigs. These all must not only be disclosed to potential recipients but must be accounted for in Islamic ethico-legal deliberation, for harms must be repelled before procuring benefits.

Sunni law also seems to be stuck in a circular mode of reasoning. Alternatives to allotransplant are always preferred position, with human organ transplantation being permitted only due to dire necessity. If xenotransplant is deemed an alternative, then it should be the preferred method to adopt, yet we see there is hesitation to take from non-*ḥalāl* animals even during necessity. The condition that the use of *ḥarām* animal organs is possible only in the absence of alternatives brings the issue back round to allotransplant. At present there seems to be confusion on what is primary and what is alternative therapy based on the juridical statements. Further legal analysis is required to break this regress.

Additionally, it is always not a straightforward case as to which option one should opt for even in the presence of a *ḥalāl* alternative. As Shaykh al-ʿUthaymīn mentions above, this should be assessed on the basis of individual cases. For example, a person facing a choice of whether to use a mechanical heart valve or a porcine heart valve, the answer immediately not need be that the mechanical heart valve is the more Islamically reliable and safe position. A mechanical heart valve will require lifelong blood thinning medication in addition to immunosuppressant medication. These will further expose the patient to infection, which can be avoided if a porcine heart valve was used. However, a porcine heart valve will need to be

replaced after 10–15 years which may not be conducive with people of 65 years of age and above. A risk-benefit analysis will decide what the best Islamic option is for a patient. Hence, we believe individual level determinations are needed as to what is the best, and 'most Islamic' option for a patient.

Muslim Concerns: The Impact of Controversial Therapies

Muslim patients might refuse xenotransplant from pigs and similar therapies despite their clinical needs. Such decisions may be rooted in the Prophet's words, *"Allah has not kept cure for you in what he has made prohibited for you"* [35]. However, given the fact that the Prophet himself allowed for the use of nose moulded from gold and silk for men with severe itch conditions, both of which are normatively prohibited, Muslims may opt not to do so.

Even though the Qur'an explicitly permits—in dire situations—the use of alcohol, pork, as well as animals slaughtered non-ritually, Muslims have continued to seek alternatives. Perhaps, this drive is due to the condition in the verse *'as long as one does not desire it'* [30]. Muslim scientists, therefore, throughout history despite their immense passion for medical progress tried to avoid such therapies as much as possible and sought alternatives so as not to infringe on Islamic moral principles. Although such therapies may cure a Muslim physically, side effects could involve feelings of guilt or loathsomeness affecting their spiritual and emotional well-being [60]. As such, Muslim patients may feel dissatisfied with the outcome. Due to this negative impact of xenotransplantation on Muslim patients, health care professionals must keep them well-informed about alternatives [60].

We have seen above that in cases of necessity, scholars do permit the use of forbidden items and by extension xenotransplantation from *ḥarām* source animals. Despite this, people's self-image of their body and fear of a perception of altered subjectivity, may hinder them from using animals as sources for organs [60]. At one end is the Qur'anic understanding that humans are the most perfect of creations created in the image of God and on the other, the Qur'an is interpreted to view the pig as a pollutant (*rijs*) [30]. A juxtaposition of these two beliefs may result in viewing xenotransplantation as a confluence of the pure and the profane, the attaching of the wing of an angel on to the tail of a donkey, giving rise to a chimeric creature paradoxically human and animal. George Orwell eloquently conjures up this image

> Twelve voices were shouting in anger, and they were all alike. No question, now, what has happened to the faces of the pigs. The creatures outside looked from pig to man, and from man to pig, and from pig to man again; but already it was impossible to say which was which [61].

To add to the problem, the Qur'an mentions that an entire community was transformed into pigs and monkeys as a punishment for disobeying God [62]. While no scholars have taken this aspect into consideration while issuing their verdict on xenotransplant, the issue of altered subjectivity and metamorphosis as punishment

from God may cause trepidation in some people to accept animal to human transplant for themselves or their loved ones.

Finally, whereas in the case of allotransplant, there is a sense of community and an understanding of volitional gifting, such things are missing in the case of xenotransplant. This may lead some people to feeling guilty that defenseless animals have been exploited for their selfish gains.

Conclusion

In Islamic theological anthropology, animals are servile to human beings within a relationship of stewardship where humans seek not to dominate animals. Many Prophetic reports extol the seriousness of humane treatment of animals. It is within these strict parameters and only out of dire necessity have Sunni scholars allowed the use of xenograft. In fact, they believe that more resources need to be spent in developing xenotransplantation therapy since this is the lesser of two harms, the greater harm being violating the dignity of a human donor. Based on this, most Sunni jurists do not object to xenotransplantation from pigs in cases where there is a patient-level dire necessity, no alternatives are present, and the posited treatment is efficacious. These conditions are unevenly met by xenotransplantation. Moreover, Islamic jurists advocate a hierarchy of preferred animals as follows; animals that are permitted to consume followed by animals such as primates that are judged to be clean though not for consumption, followed by juridically impure animals such as the pig. Research models for xenotransplantation should be advised of this preference in Islamic law.

Juridical views are only one out of numerous motivators of Muslim healthcare behaviours and ethical decision-making. Other factors influencing Muslims include uncertainty about negative immunological responses to the therapy, and the fear of cross-species virus transmission. Social concerns such as self-image and the perception of altered subjectivity may hinder them from receiving a xenograft irrelevant of how many fatwas permitting it is out there. Because of the uncertainty that the conditions for a dire necessity argument are met and patients may feel spiritually ill at-ease with the therapy, we view porcine xenotransplantation to be a stop-gap treatment to the problem of organ failure [21]. We advocate that the root causes of organ failure be addressed such that the need for organ replacement therapies is reduced, and that alternative animal models as well as synthetic models be researched such that allografts and porcine xenografts are not needed.

References

1. Rumi J. Fīhī mā fīhī. Translated as discourses of Rumi by Arberry AJ. London: RoutledgeCurzon; 2009.
2. Qur'an 15: 28–29. Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
3. Qur'an 7:179. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.

4. Hossein N. A young Muslim's guide to the modern world. Cambridge: Islamic Text Society; 2010.
5. Qur'an 17:27. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
6. Qur'an 5:4. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
7. Qur'an 16: 69. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
8. Qur'an 16:8. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
9. Qur'an 40:79-80. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
10. Qur'an 5:31. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
11. Qur'an 105. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
12. Qur'an 91. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
13. Tlili S. Animals in the Qur'an. Cambridge University Press; 2012.
14. Al-Nasāʾī A. In: Af G, editor. Sunan al-Nasāʾī. Aleppo: Maktab al-Maṭbūʿāt al-Islāmiyya; 1986.
15. Al-Tirmidhī M. Sunan al-Tirmidhī. 1st ed. Beirut: Dār al-Maghrib al-Islāmī; 1996.
16. Muslim ibn Al-Ḥajjāj. Ṣaḥīḥ Muslim. Edited by Al-Baqi MF. Beirut Dār al-Iḥyāʾ al-Turāth al-ʿArabī; 1991.
17. Al-Bukhārī MI. Ṣaḥīḥ al-Bukhārī; kitāb al-musāqāt; bāb faḍl saqy al-māʾ. Beirut: Dār Ṭawq al-Najā; 2001.
18. Al-Bukhārī MI. Ṣaḥīḥ al-Bukhārī; kitāb aḥādīth al-anbiyāʾ; bāb ḥadīth al-ghār. Beirut: Dār Ṭawq al-Najā; 2001.
19. Qur'an 43:13-14. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
20. Ibn al-Marzubān MIH, Smith GR, Haleem MA. The book of the superiority of dogs over many of those who wear clothes. Aris & Phillips; 1978.
21. Veatch RM, Ross LF. Transplantation ethics. 2nd ed. Washington: DC Georgetown University Press; 2015.
22. Mandaville P. Globalization and the politics of religious knowledge: pluralizing Authority in the Muslim World. Theory Cult Soc. 2007;24(2):101–15.
23. ʿAbdullāh S. Al-ijtihād al-jamāʿī wa ahmiyatuh fī nawāzil al-ʿaṣr. Majallat al-Majmaʿ al-Fiqhī al-Islạmī. 2010; 25: 47–74.
24. AlBar MA. Al-Mawqif al-fiqhī wa al-akhlāqī min Qaḍiyat Zarʿ al-Aʿḍāʾ. Damascus: Dar al-Qalam; 1994.
25. Ali M. ORGAN-ised rejection: an Islamic perspective on the dead donor rule in the UK–revisited. Journal of British Islamic Medical Association. 2021;7(3):12–20.
26. Al-Qaraḍāwī Y. Fatāwa Muʿāṣirah. 4th ed. Kuwait: Dar al-Qalam; 2004.
27. Ibn Mājah MY. Sunan Ibn Mājah. Beirut Dār al-Jīl; 1998.
28. Qur'an 5:3. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
29. Qur'an 2:173. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
30. Qur'an 6:145. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
31. Qur'an 16:115. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.
32. Al-Jaṣṣāṣ AB. Aḥkām al-Qurʾān. Beirut: Dār Iḥyāʾ al-Turạth al-Arabi; 1992.
33. Abū Dāwūd. Sunan Abī Dāwūd. Edited by ʿAwwāma M. Beirut: Muʾassisat al-Rayyān; 1998.
34. Ibn Abī Shayba. Musnad Ibn Abī Shayba. Riyad: Dar al-watan; 1997.
35. Al-Bukhārī MI. Ṣaḥīḥ al-Bukhārī; *kitāb al-Ṭibb*. Beirut: Dār Ṭawq al-Najā; 2001.
36. Encyclopaedia of Islamic jurisprudence. Kuwait: Ministry of Islamic Affairs Kuwait; 1988–2006.
37. Padela AI, Furber SW, Kholwadia MA, Moosa E. Dire necessity and transformation: entry-points for modern science in Islamic bioethical assessment of porcine products in vaccines. Bioethics. 2014;28(2):59–66.
38. Ebrahim AFM, Padela AI. The Islamic juridical principle of dire necessity (al-darura) and its application to the field of biomedical interventions. In: Padela A, editor. Medicine and sharia: a dialogue in Islamic bioethics. Notre Dame University, Notre Dame University of Notre Dame Press; 2021. p. 57–70.
39. Ali M, Maravia U. Seven faces of a fatwa: organ transplantation and Islam. Religions. 2020; 11 (2) (99): 1–22.

40. Hamdy S. Our bodies belong to god: organ transplants, Islam, and the struggle for human dignity in Egypt. Berkeley: University of California Press; 2012.
41. Padela AI, Duivenbode R. The ethics of organ donation, donation after circulatory determination of death, and xenotransplantation from an Islamic perspective. Xenotransplantation. 2018;25(3):1–12.
42. Bakrū K. Ḥukm al-intifāʿ bi aʿḍāʾ al-bashariyya wa al-ḥayawaniyya. Aleppo: Dār al-khayr; 2001.
43. Galchen R. The medical miracle of a pig's heart in a human body. The New Yorker. 2022; https://www.newyorker.com/magazine/2022/02/28/the-medical-miracle-of-a-pigs-heart-transplant-in-a-human-body
44. Schlich T, Lutters B. Historical perspectives on xenotransplantation. Lancet. 2022;399(10331):1220–1.
45. Taymiyya I. Al-Fatāwa al-Kubrā; masʾalat al-kalb hal huwa Ṭāhir am najis? Dar Kotob al-Ilmiyah; 1987.
46. Al-Shawkānī MA. Fatḥ al-Qadīr; Sūrat al-anʿām (6: 145). Damascus: Dār Ibn Kathīr; 1993.
47. Ibn ʿĀshūr, M. Al-Taḥrīr wa al-tanwīr; Sūrat al-māʾida. Beirut; 2000.
48. al-Kāsānī A. Badāʾiʿ al-Ṣanāʾiʿ fī Tartīb al-Sharāʾiʿ. Beirut Dar al-Kotob al-Ilmiyah 1986.
49. Cited in Saad H. Are Muslims ready to accept pig organ transplants? TRT 2022. https://www.trtworld.com/magazine/are-muslims-ready-to-accept-pig-organ-transplants-51344
50. IFC. Resolution of the Islamic Fiqh council in its 8th session (1985). Majallat al-Majmaʿat al-Fiqhī al-Islāmī. 2003;1(1):77–80.
51. Al-Qāsmī MI. Jadīd Fiqhī Mabāḥith. Karachi: Idarat al-Qur'an; 1994.
52. Al-Qaradāghī AM, Al-Muḥammadī AY. Fiqh al-Qaḍāyā al-Ṭibbiyya al-Muʿāṣira. Beirut: Dar al-Bashāʾir al-Islamiyya; 2006.
53. Ebrahim AFM. Organ transplantation, euthanasia, cloning and animal experimentation an Islamic view. Markfield: Leicester the Islamic Foundation; 2001.
54. Gād al-Haqq, A. Fatāwa Dār al-Iftāʾ al-Maṣriyya; aḥkām mutafarriqāt: naql al-aʾḍāʾ min insān ilā ākhar. https://ketabonline.com/ar/books/77(7: 356)
55. Ṣaqar, A. Fatawa Dar al-Iftāʾ al-Maṣriyya; min aḥkām mutafarriqāt: naql juz min al-khinzīr ilā al-insān. https://ketabonline.com/ar/books/77(10: 233)
56. Shafi M. Aʿḍāʾ Insānī kī Pewandkārī. In: Shafi M, editor. Jawāhir al-Fiqh. 7, vol. 7. Karachi: Maktaba Darul Uloom Karachi; 2010. p. 17–74.
57. Ibn A-ʿUM. Ḥukm zarʿ sharyān min qalb al-khanāzīr fi qalb al-insān. Official website of Shaykh Muḥammad b. Ṣāliḥ al-ʿUthaymīn. https://binothaimeen.net/content/13594
58. News BBC. Man given genetically modified pig heart dies [internet]. BBC News BBC News. 2022; [cited 2022 Mar 28]. https://www.bbc.co.uk/news/health-60681493
59. Nuffield Council on Bioethics. Animal-to-human transplants: the ethics of xenotransplantation. London: London Nuffield Council on Bioethics; 1996.
60. Haddow G. 'Dirty pigs' and the xenotransplantation paradox. Med Humanit. 2021;47(4):417–24.
61. Orwell G. Animal farm. Oxford: Oxford University Press; 2021.
62. Qur'an 5:60. Translated by Abdel Haleem, M.A.S. Oxford: Oxford University Press; 2010.

Religious Viewpoints: Shia Islam

15

Kiarash Aramesh

Introduction

For Shia Muslims, xenotransplantation is not a merely theoretical issue. Shortly after the invention and commercialization of the porcine heart valve replacement in the United States in the late 1960s and early 1970s, Iranian heart surgeons began to use this procedure for their patients [1]. For many Muslim patients and doctors, the question arose of whether the Islamic law (*Shari'at*) allows transplanting a part of a pig to a Muslim. The seriousness of this question was partly because of the strict Islamic rules commanding the avoidance of pigs and not consuming their meat and other products. There is a consensus among Muslim jurists that the pig is inherently unclean (*najis*), and consuming its products is forbidden (*haram*). The debate about xenotransplantation has started among Shia jurists since then and has developed new dimensions with the subsequent advances in this biomedical field. As described below in this chapter, the problem was not only the permissibility of using porcine tissue to treat a medical condition in a Muslim, but also the status of the transplanted tissue in the body of the recipient. In other words, whether the transplanted tissue (or organ) is still a porcine (and unclean) tissue, or if it becomes a part of the human body.

This chapter describes the perspective of Shia Islam on these issues. Since it is a bioethical topic, it falls under the domain of Islamic and Shia bioethics. Therefore, this chapter begins with a brief introduction to this branch of religious bioethics. Then, it explains how Shia bioethics seeks guidance from its main sources to shed light in an emerging practical issue such as xenotransplantation. This chapter ends with a brief discussion of a flaw in this approach.

K. Aramesh (✉)
Bioethics Institute, PennWest University, Edinboro, PA, USA
e-mail: karamesh@pennwest.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_15

Shia Bioethics

Since the first appearance of the term "bioethics" in the 1970s, religious bioethics has contributed significantly to creating and developing this field. The first parts of the bioethical literature were created by Catholic bioethicists. It is not surprising that other religions, including Judaism and Islam, rushed to join the efforts and developed their own branches of bioethics. The first question before the founders of different branches of religious bioethics was as follows: What are our principles of bioethics? And, in which part of our body of religious knowledge, should we seek and find those principles?

Each branch of bioethics, regardless of being religious or secular, appeals to certain sources to derive its normative principles. Among Muslims, Islamic Jurisprudence (*fiqh*) has been the main source of guidance for creating and developing what is called Islamic bioethics. Muslim jurists (*ulama* or f*uqaha*) issue decrees (*fatwas*) about emerging ethico-legal issues, including the bioethical ones. The current field of Islamic bioethics, since its first appearance, has mostly focused on deliberating on the theoretical bases, interpretations, and practical implications of such fatwas [2, 3].

The appeal to Islamic Jurisprudence as the main source of bioethics is common among Shia and Sunni scholars. Shia *fiqh* has been the main source of Shia bioethics. After the 1979 revolution in Iran, Shia *fiqh* has become the main source of the laws and regulations in the country. Over time, many bioethical issues arose, and the jurists tried to address them by appealing to the traditional *fiqh*. Transplantation and xenotransplantation have not been an exception. This special status as being the main source of the laws and regulations in a country has had a multitude of impacts on Shia bioethics, among them being its fast growth in the field of bioethics and its flexibility to deal with practical issues compared to other accounts of Islamic bioethics [4, 5].

The Principle of Necessity

The main sources of the Shia branch of Islamic jurisprudence are (1) The Qur'an, (2) *Hadith* (what the prophet and imams said, did, or agreed upon), (3) *Ijma'* (consensus among jurists), and (4) reason (*aql*) [6]. Shia jurists derive many jurisprudential principles from these sources to guide them through addressing the new-emerging issues [7, 8].

The most important one among the above-mentioned sources is the Qur'an. However, the Qur'an was written in the seventh century CE; therefore, it is obvious that there is nothing about xenotransplantation in it. However, some more general guidance provided by the Qur'an had helped the jurists to shed light on the problem of xenotransplantation [9].

Surah An-Nahl, Verse 115, reads:

> He has only forbidden you to eat carrion, blood, swine, and what is slaughtered in the name of any other than Allah. But if someone is compelled by necessity—neither driven by desire nor exceeding immediate need—then surely Allah is All-Forgiving, Most Merciful. (Qur'an, 16: 115)

Also, Surah Al-Ma'idah, Verse 3 reads:

> Forbidden to you are carrion, blood, and swine; what is slaughtered in the name of any other than Allah; what is killed by strangling, beating, a fall, or by being gored to death; what is partly eaten by a predator unless you slaughter it; and what is sacrificed on altars. You are also forbidden to draw lots for decisions. This is all evil. Today the disbelievers have given up all hope of ˹undermining˺ your faith. So do not fear them; fear Me! Today I have perfected your faith for you, completed My favour upon you, and chosen Islam as your way. But whoever is compelled by extreme hunger—not intending to sin—then surely Allah is All-Forgiving, Most Merciful. (Qur'an, 5: 3)

The last sentence of the above verse clearly permits consuming the forbidden food in the face of necessity.

Although with such a clear and straightforward guidance from the Qur'an, no more advice would be necessary, there are quotes from the Shia Imams that assert the same concept. For example, a Hadith from Imam Sadiq reads:

> If it becomes necessary for a person's survival to consume the meat of a dead body, blood, or pork, and he refuses to do so and dies as a result, he dies as a heretic [10].

What the Shia jurists understand from the above-mentioned quotes from the Qur'an and Hadith (and a multitude of similar ones that can be found in the scripture), is that even the forbidden (*haram*) acts, such as consuming a dead body or pork, can be permitted in the face of an overwhelming necessity. In other words, if saving the life of a person requires consuming such a forbidden food, it is allowed to do so and save one's life or save them from unbearable hardship.

The third source of Shia jurisprudence (reason) also agrees with this conclusion that a *haram* act or food should be allowed when it is necessary for a justifiable purpose, such as saving a person's life. They appeal to some versions of the principle of double effect (that the good effect of preserving life is intended even though the haram act is foreseen as an unintended side effect) to explain this conclusion.

In a wider perspective, both the scripture and reason imply a jurisprudential principle, called *dharura* or *idhtirar*. This principle entails that a forbidden (*haram*) act or food becomes allowed if it is necessary to save a life or to prevent unbearable hardship. It is from this principle and with the background explained above that Shia jurists conclude that it is allowed to transplant a part of a dead body or an animal if it is necessary for saving one's life to treat one's serious disease or alleviate one's unbearable suffering [9, 11, 12].

The Principle of No Harm

Another principle that has been appealed to support the permissibility of xenotransplantation is the principle of "no harm and no harassment" (*la dharar wa la dhirarr fi al-din*). This principle can simply translate into the avoidance of any harm to one's self or others and avoidance of any acts that reciprocally cause such harms [8, 12].

Muslim jurists appeal to this principle to justify not observing otherwise obligatory commands in cases where they may cause serious harms. Accordingly, using the otherwise *haram* foods or *najis* materials is permitted if they are needed to prevent serious harms such as unbearable suffering or death. For such an application, xenotransplantation using dead bodies or porcine tissues is a perfect example [7, 9, 11].

There are some Quranic verses and *Hadith*s that support this principle. Among them, there is a *hadith* from which the title of this principle originates, and has been quoted by both Shia and Sunni jurists. This *hadith* holds that the prophet once said, "Neither harming nor reciprocating a harm to a Muslim is allowed" [8].

The Principle of Original Permissibility

The principle of permissibility or *ibaha* maintains that everything is permissible unless it has been declared as forbidden [13]. There have been some controversies about this principle and the areas of human life to which it applies. However, at least among Shia jurists, it seems that there is almost a consensus on accepting some versions of this principle. This principle is mostly backed by reason. However, some Qur'anic verses and hadiths have been cited to support it. Among them, the first sentences of the 29th verse of Surah *Al-Baqarah* reads:

> He it is Who created for you all that there is on the Earth; He then turned to the sky and ordered it into seven heavens. And He has full knowledge of everything (Qur'an, 2: 29).

Shia jurists appeal to this verse and other similar ones to argue that everything on Earth is created for human beings, therefore, they are allowed to use them, with two exceptions: first, when there is a harm in using them; second, when there is an explicit ban in the scripture.

Accordingly, all the animals are created for human beings, including the clean and unclean ones. Therefore, when a question arises about the permissibility of using a part of animals, one needs to see whether there is any noticeable harm or a religious ban against it. If not, especially when there are possible benefits in using them, as it is evident in the case of xenotransplantation, then using them is permissible [9, 13].

Even from a Pig?

Although no religious authority has issued a fatwa against the permissibility of xenotransplantation (see below), some scholars have raised doubts about it. They claim that there is no good use to the *Haram*. In other words, if something is called forbidden in the scripture, it means that there is no justifiable use to it, even if it seems so initially [14]. This perspective holds that because the ultimate reason of such bans are hidden from people, they shouldn't violate those bans based on their own understanding of the consequences. They argue that if consuming pork or wine is forbidden in Islam, it means that nobody can benefit from using them whatsoever. Even if one finds therapeutic benefits in them, the ultimate harm, that is hidden and undiscovered, overwhelms such therapeutic benefits.

Such arguments caused serious doubts about the therapeutic uses of wine recommended by medieval Muslim physicians at that time. However, in the presence of numerous Qur'anic verses and *hadith*s in favor of the principles of necessity and no harm, they have not been able to change the fatwas about life-saving treatments such is xenotransplantation [9].

Fatwas

There is a consensus among Shia jurists that xenotransplantation, even from inherently unclean animals such as the pig, is permissible should its necessity be confirmed by healthcare providers, scientists and/or regulatory bodies. In Shia jurisprudence, the jurists who are educated enough to issue religious decrees are called *mujtahid*. The most senior ones among them who usually have numerous followers among the believers are called grand *Ayatollah*. All the grand Ayatollahs who have been asked about xenotransplantation and have issued decrees (*fatwa*s) about it, with no exception known to the author of this chapter, have recognized its permissibility. Also, they unanimously believe that the transplanted organ or tissue becomes a part of the recipient's body and should be regarded as human tissue and it is not inherently unclean anymore.

For instance, Ayatollahs Khomeini and Vahid Khorasani (one of the most conservative Shia authorities) have issued fatwas that explicitly allow xenotransplantation even from unclean animals [9]. Although there are serious doubts about the eligibility of Ayatollah Khamenei to be considered a grand Ayatollah, his opinions as the supreme leader of the Islamic Republic of Iran are of practical importance because the part of the government that is in charge of health care generally follows them. Ayatollah Khamenei also has explicitly permitted xenotransplantation [15].

As mentioned above, there is no fatwa against xenotransplantation in the literature. However, one should notice that all these fatwas have been issued in reply to questions made by the followers, and those questions entail an emphasis in the necessity of the procedure as a prerequisite and not being accompanied by any other banned deeds. Therefore, all those fatwas are applicable to the cases that meet these two important conditions.

The Problem of Daily Prayers: The Status of the Transplanted Tissue

Another issue that may arise is about doing daily prayers. In Islam, it is mandatory that all Muslims do certain prayers, called *namaz* or *salat*, five times a day. There are certain rules for the type of dress a Muslim is allowed while doing those prayers. For example, no part of an animal that is killed without observing the related Islamic ritual (*zibh*) or an animal whose meat is forbidden (*Haram*) or is unclean (*najis*) should be included in the dress while doing the mandatory daily prayers. Therefore, if a Muslim holds a piece of pig's skin, meat or bone in their hand or pocket or as a part of their clothing, they are not allowed to do their mandatory prayers. Considering this mandate, the question arises of whether the transplanted tissue is still animal tissue or not. For example, in the case of porcine heart valve transplantation, what is the status of the transplanted tissue? Is it still a part of a pig? If so, the recipients cannot do their daily prayers! The same would be true for patients who have received an organ transplant from a human cadaver.

Shiite authorities, however, assert that attributes such as being unclean or haram or dead apply to the bodily parts without a human soul. A transplanted tissue or organ becomes a part of the recipient's body. Therefore, it is alive by the soul of the recipient. Therefore, it cannot be considered a part of a dead animal's body. Therefore, it is allowed to do daily prayers while having an alive transplanted tissue or organ, even from an unclean animal or whose meat is forbidden to be consumed.

A Flaw

Various branches of Islamic bioethics face serious challenges regarding a variety of issues such as human rights, rights of non-Muslims, and gender equality. Xenotransplantation is not among them. As described above, the position of Shia scholars toward xenotransplantation is compatible with common morality. However, a minor theoretical problem is still noteworthy. The notion of soul as understood by Shia jurists is adopted from the Medieval accounts of human biology and medicine. The Shia holy scripture (the Qur'an and Hadith) was developed and collected between the seventh and ninth centuries CE. It is not surprising that their description of the human body and soul is compatible with the knowledge of their time. Later, Shia jurists, even the contemporary ones, continued appealing to those Medieval accounts in interpreting the scripture. There are many examples of such a practice, including the discussions about abortion and reproductive technologies. The extension of human life through the human soul into the transplanted organ or tissue is also based on the Medieval understanding of the soul and cannot be explained based on the current scientific understanding of the human anatomy and physiology. Although this flaw does not have any detrimental role in the xenotransplantation debate, it might be so in other areas such as the status of human embryo and abortion debates [16].

Conclusions

Xenotransplantation has been one of the issues that raised almost no controversy among Shia jurists. The permissibility of xenotransplantation is supported by all the sources of Shia jurisprudence, the Qur'an, tradition, reason, and consensus. Also, all the applicable principles support such permissibility, among them the principles of necessity, no harm, and original permissibility are the most cited ones. All the fatwas issued on this subject are unanimous in declaring its permissibility. These fatwas have permitted xenotransplantation with two conditions, first, medical necessity; second, not being accompanied by other forbidden acts. If these conditions are met, there won't be any differences between the animals that are killed with Islamic rituals and the ones that are not. Neither are there any difference between unclean animals and *halal* ones. The theoretical premises on which Sha jurisprudence relies, especially in the realm of human physiology, in some cases are obsolete. Although this problem has minimal practical consequences in the case of xenotransplantation, it should be explored and addressed separately.

References

1. Tabriz University of Medical Sciences (2019). The history and current situation of Heart transplantation surgery in Tabriz University of Medical Sciences. Tabriz University of Medical Sciences. Accessed 8 Apr 2022.
2. Aramesh K. Normativity in Islamic bioethics. In: Gielen J, editor. Dealing with bioethical issues in a globalized world. Cham: Springer; 2020. p. 13–30.
3. Padela AI. An introduction to Islamic bioethics: its producers and consumers. In: Padela AI, editor. Medicine and Shariah. Notre Dame: University of Notre Dame Press; 2021. p. 1–38.
4. Aramesh K. The influences of bioethics and Islamic jurisprudence on policy-making in Iran. Am J Bioeth. 2007;7(10):42–4.
5. Larijani B, Zahedi F, Malek Afzali H. Medical ethics in the Islamic Republic of Iran. East Mediterr Health J. 2005;11(5–6):1061–72.
6. Atighetchi D. Islamic bioethics: problems and perspectives. Dordrecht: Springer; 2007.
7. Mohaghegh Damad SM. Medical Fiqh. Tehran: Hoghughi; 2012.
8. Sachedina A. No harm, no harassment: major principles of health care ethics in Islam. In: Guinn DE, editor. Handbook of bioethics and religion. New York: Oxford University Press; 2006. p. 265–89.
9. Moradi Y, Keykha MR, Khakpoor H. Barresiye Peyvand -e- A'zaye Heyvan -e- Zajis-ul-ein va Mordar Ben Ensan. Fiqh-e-Pezeshki. 2016;8(28 & 29):161–78.
10. Sadouq M. Al-Khisal. Qom: Jame'eye Mdarresin; 1984.
11. Hatami S, Amini R. Xenotransplantation from the perspective of medical jurisprudence and law viewpoints. Religion and Health. 2017;5(1):61–9.
12. Sachedina A. Islamic biomedical ethics. New York: Oxford University Press; 2009.
13. Kamali MH. The principle of original permissibility (Ibahah). In: Shariah and the Halal Industry. New York: Oxford University Press; 2021. https://doi.org/10.1093/oso/9780197538616.003.0003.
14. Paris W, Seidler J, Fitzgerald K, Padela A, Cozzi E, Cooper DKC. Jewish, Muslim, and Christian theological views of xenotransplantation. Xenotransplantation. 2018;25(3):e12400. https://doi.org/10.1111/xen.12400.

15. Shafaqna.com (2015). Answer of Ayatollah Khamenei to a Question about Transplantation from a Haram Animal to a Human. Shafaqna. https://fa.shafaqna.com/news/64623/پاسخ-حضرت-آیت-الله-خامنه-ای-به-پرسشی-در-29/. Accessed 5 May 2022.
16. Aramesh K. Shiite perspective on the moral status of the early human embryo: a critical review. J Relig Health. 2018;57(6):2182–92. https://doi.org/10.1007/s10943-017-0518-6.

Religious Viewpoints: Judaism

16

Ira Bedzow

Introduction

Xenotransplantation is no longer the medicine of the future. It is already here. In September 2021, a surgical team at University of Alabama at Birmingham successfully transplanted two kidneys from a genetically modified pig into a person who was declared dead according to neurological criteria. A surgical team at New York University also performed a successful porcine kidney xenotransplantation in September and then again in November of 2021. In January 2022, a surgical team at University of Maryland Medical Center successfully transplanted a genetically modified pig heart into a living patient.

The reason that the pig's genes must be altered is to decrease their chances of rejection by the recipient. Even in human organ transplantation, organ recipients are at risk of their body rejecting the transplant as a foreign, and thus harmful, intrusion in the body. Traditionally, a patient would receive immunosuppressants to prevent organ rejection, yet such medication leaves the person more susceptible to other diseases, as the body is less able to fight viral and bacterial infections. Without genetic modification, xenotransplantation may be at higher risk for rejection and for

I. Bedzow (✉)
Center for the Study of Law and Religion, Emory University School of Law, Atlanta, GA, USA
e-mail: ira.jay.bedzow@emory.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_16

hyperacute rejection since the organ itself is so genetically different from the recipient's that it causes the person's immune system immediately to produce antibodies against it [1]. Genetic modification of the pig allows for its organs to be more compatible with their human recipients [2]. Genetic modification is also used to modify the animal's organs so that they only grow to a size appropriate for a human body and function effectively given human physiology [3].

The benefits of transplanting genetically modified pig organs into humans are consequential. In the United States alone, there were 24,669 kidney transplants performed in 2021 and 22,817 in 2020 [4]. There were also 3817 heart transplants in 2021 and 3658 in 2020 [1]. As of September 2021, 97,200 people were on the waitlist for a kidney transplant and 3500 people were on the waitlist for a heart transplant [5]. The ability for genetically modified pigs to serve as a ready supply of organs would greatly reduce both the wait time for people to receive organs and the number of people who die while waiting for a transplant. It would also reduce the ethical challenges that surround policies and practices related to organ donation, procurement, distribution, and allocation. Of course, these challenges will not be solved immediately. It took about two decades from the first successful human heart transplant for transplant centers to become commonplace [6]. While medical technology may move at a faster pace for xenotransplantation given the current speed of medical progress, it will still be a few years before xenotransplantation will be considered a routine procedure.

Transplanting whole pig organs is different from implanting a porcine heart valve into a human patient or using pigs to make insulin and blood thinners, since the risks and complications of transplanting whole organs is much greater and different than using pigs (or other animals) for other medical purposes. For example, one may assume that a porcine heart valve is comparable clinically to a porcine heart, just a little smaller. Yet, all porcine valves are treated to avoid rejection before they are implanted. Porcine valve implantation therefore does not come with the same risks of rejection nor the same needs to take immunosuppressive medication. Nor do the pigs who "donate" these valves require genetic modification.

There are those, such as Bruno Reichart—a cardiothoracic surgeon who performed Germany's first successful heart transplant and who is a strong xenotransplantation advocate—who argue that there should be no stigma or ethical concerns regarding porcine xenotransplantation [7]. However, stigma and seemingly ethical concerns may arise in those communities who believe that pigs are unkosher and anathema to their religious tradition.

I will not discuss at length in this chapter the Jewish medical ethics considerations regarding whether a patient should participate in a risky procedure or the debates surrounding using (and genetically modifying) animals for the purpose of medical treatment. These topics are discussed at length elsewhere, though I will make a few points on the matter. This chapter will focus primarily on the permissibility according to Jewish medical ethics of using pigs as a source of organs for xenotransplantation. First, I will give a quick word on the relationship between Jewish (medical) ethics and Jewish law.

The Relationship Between Jewish (Medical) Ethics and Jewish Law

While the relationship between Jewish law and Jewish ethics is similar to a certain degree across various denominations of Judaism, the divergence between denominations in how they respectively describe the relationship is based on how each denomination conceives of the divinity of the Jewish canon and its immutability or evolution. I write from the perspective of Orthodox Judaism. As such, both the Jewish philosophers of law and legal decisors brought in this chapter, and the way they will be interpretated, will be primarily from that vantage point.

Unlike the relationship between secular medical ethics and law, where the two domains are separate yet inform each other in terms of how to analyze medical ethics cases [8], how to determine standards of proper conduct [9], and how to create good health policy and practices [10], Jewish medical ethics and Jewish law (or Halakha) are isomorphic. In the words of Rabbi Immanuel Jakobovits, "[T]he Jewish concept of medical ethics is the very reverse of that commonly accepted in civilized countries of the world" [11]. One reason for this overlapping relationship is theological. The Torah is perceived as a divine document that lays out moral ways to live; ethics is, therefore, not a separate domain of inquiry but part of Jewish law itself (Iggrot Moshe Even HaEzer 2: 11). Another reason is that, even if one wants to imagine an ethics that is separate from Jewish law, the moral values inherent in the Torah are expressed through discussion of the Halakha and its application to contemporary (medical) situations [12]. As such, analysis of an issue through the lens of Jewish (medical) ethics will necessitate reference to Jewish legal and other canonical sources.

Participating in Risky Procedures

A patient considering a heart transplant is most likely in a halakhic category where it would be permissible to undergo a treatment that may extend his or her life beyond 12 months but nevertheless has a risk of hastening death. Of course, as the probability of success increases and the risk of the procedure decreases, there is greater rabbinic consensus towards permissibility (Responsa Tzitz Eliezer 10: 25; Responsa Ahiezer Yoreh Deah 16: 6; Iggrot Moshe Yoreh Deah 2: 58 and 3: 36). Because those with kidney failure can undergo dialysis for years, there is less consensus among the rabbinic decisors over the permissibility of undergoing a kidney transplant. However, if the patient desires the transplant to improve his or her quality of life, it is permitted (Responsa Tzitz Eliezer 4: 13: 2). This is especially the case as heart and kidney transplantations have become "routine" and the probability of success is now quite high. As of 2014, the International Society of Heart and Lung Transplantation indicates a current 1-year survival rate of 84.5% and a 5-year survival rate of 72.5% for heart transplantation [13]. Currently, the survival rate for kidney transplant recipients is 95% at 1 year and around 90% at 3–5 years [14]. While the survival rates for porcine xenotransplantation are unavailable today as it

is still an experimental procedure, as xenotransplantation becomes more commonplace and as survival rates reach the levels equivalent to other more common procedures, the ethical permissibility of undergoing such a procedure will also be more acceptable among the rabbinic decisors.

Using (and Genetically Modifying) Animals for the Purpose of Medical Treatment

In the realm of Jewish medical ethics, concern over genetically modifying animals and using their organs for transplantation would fall under the discussion of *tza'ar ba'alei hayyim*, i.e., causing pain to animals. There is a dispute among the rabbinic decisors as to whether the halakhic prohibition is Torah mandated or a rabbinic enactment (BT Bava Metzia 32b-33a). Typically, the distinction between the two is in the severity of punishment warranted for one who transgresses and in how to evaluate a situation where transgression is only a potential outcome rather than a definitive one. Regardless of the disagreement over category, the Talmud nevertheless warns that *tza'ar ba'alei hayyim* is a grave sin and warrants severe punishment (BT Bava Metzia 85a).

Despite the importance of this prohibition, one does not violate *tza'ar ba'alei hayyim* if the harm to the animal serves a benefit. For example, it is permissible to kill animals for food and to use them for labor (Terumat HaDeshen II: 105). Benefit should not be construed as simple enjoyment, since one of the reasons for the prohibition is to engender in people the trait of mercy (Teshuvot HaGeonim [Harkavy] I: 375), and, as such, activities such as hunting for pleasure is typically deemed reprehensible (Nodah b'Yehudah Yoreh Deah 6). Yet, treating animals in ways that, though potentially harmful, provide tangible benefit to humans and that limits unnecessary pain to the animal is deemed acceptable according to Jewish law. Moreover, Rabbi Moshe Isserles states explicitly in his gloss to the *Shulhan Arukh* that anything that is needed for medical treatment sets the transgression of *tza'ar ba'alei hayyim* aside (Shulhan Arukh Even HaEzer 5: 14). In the case of genetically modifying pigs to harvest their organs for transplant, there should be no prohibition related to *tza'ar ba'alei hayyim* if the animals are not subject to unnecessary pain and suffering in the process. All procedures that are necessary for the eventual treatment of human beings needing the transplant, such as killing the animals in order to harvest their organs, would also be permissible (Shevut Ya'akov Yoreh Deah 3: 71).

Pigs Are Not Kosher, and So Not Jewish

The Torah states that a person may eat any animal that has split hooves and chews its cud (Leviticus 11: 1–7). So as not to misinterpret the permission to include animals that have one criterion but not the other, the Torah continues to state that those animals which chew their cud yet do not have split hooves or which have split

hooves yet do not chew their cud are forbidden to be eaten. For the latter category, the Torah gives the explicit example of the pig.

The explicit mention of the pig as a prohibited animal is only part of the reason for the revulsion that people who aspire to live within the norms and values of the Jewish tradition have for the animal. For example, one does not see the same revulsion for the camel, the rock-badger, or the hare, which are the three animals explicitly mentioned in the Torah that a person is prohibited to eat because they chew their cud yet do not have split hooves.

Jewish pig revulsion and the status of the pig as anathema to Jewish identity is seen both in Jewish sources that view pork as a specific marker of non-Jewish cuisine and identity and in Greek and Roman sources, where the absence specifically of pork indicates Jewish cuisine and identity [15]. The relationship between consumption and identity, akin to the common expression, "You are what you eat," speaks not only to the symbolic aspect of what one chooses to put into one's body. It also encompasses the social aspect regarding with whom one may eat given dietary restrictions [16]. The pig as a symbol of otherness is therefore both a personal and social marker.

Rabbinic sources provide a few reasons for why the pig has such an antithetical status to Jewish identity to the point where one avoids even mere mention of its name when possible. In the Talmud, to reference a pig, a rabbi would sometimes call the animal a *davar aher*, i.e., "other thing," rather than use its proper name (BT Shabbat 129a, Pesahim 3b). One source provides a historical reason. The Talmud relates that when two members of the Hasmonean monarchy were fighting, one brother besieged the city of Jerusalem. At first, the brother would allow, despite the siege, for the purchase of sheep for the daily sacrifices in the Temple. However, to weaken the spiritual resolve of the city inhabitants, one day he delivered a pig instead of the required sheep for the sacrifice. The offense to the religious devotion of the Jewish people was so great that the Talmud relates that the land of Israel quaked over an area of 400 parasangs by 400 parasangs. At that time, the Sages placed a curse on those who would raise pigs (BT Bava Kamma 82b). This incident has continued throughout the centuries to be mentioned in rabbinic literature as a disgraceful attempt to mock the religiosity of the Jewish people, and the pig continues to serve as a symbol of religious sacrilege. Other rabbinic sources maintain the theme of sacrilege, yet the pig becomes a display of hypocrisy rather than open rebellion. The pig as a symbol of religious hypocrisy comes from the image of a pig displaying its split hooves. The rabbinic literature uses such an image to conceive of the pig as pretending or signifying that it is kosher while knowing that it is not (Genesis Rabbah 65: 1). The power of the pig as a symbol of non-Jewish or hypocritic Jewish identity is evident in the derogatory term, Marrano, meaning "pig," which was used to refer Jews in fifteenth-century Spain who were forced to convert to Christianity but may have secretly lived or at least identified as Jews.

A contemporary example that speaks to the case of how pig revulsion, as an expression of Jewish identity, can influence how a person may respond to the possibility of porcine xenotransplantation can be seen by the 2006 episode, "Save Me," from the popular television show, *Grey's Anatomy*. When Drs. Burke and Karev tell

a couple that their daughter needs a heart valve replacement, they suggest using a porcine valve, since it is considered the standard of care for her condition. The mother responds, "I don't care what you have to do. Save my daughter's life." When the daughter is told that they will be using a porcine valve, she adamantly refuses, saying, "You're letting them put a pig, a freaking non-kosher, *traif* mammal, into my chest, into my heart! The very essence of my being!" [17]. The daughter's visceral response against using a porcine valve is based on her feelings that incorporating a part of a pig into her body will somehow affect her religious being more deleteriously than death itself. At the end of the episode, the doctors settled on using a bovine valve instead of a porcine one. However, according to the rules of *kashrut* (dietary restrictions), eating an improperly slaughtered cow has the same gravity of transgression as eating a pig. Therefore, if the daughter is concerned about putting a "non-kosher, *traif* mammal," into her chest, she should detest the idea of the bovine valve as much as a porcine one. Yet she doesn't. While this example clearly makes certain assumptions regarding different denominations of Judaism, it does provide a clear example of how the symbol of the pig as anathema to Jewish identity can influence a person's understanding of whether using a porcine valve or a pig organ would be appropriate or disdained within the framework of their own religious tradition.

However, despite one's potential revulsion to the pig, from the perspective of Jewish law and Jewish medical ethics, the prohibition against its consumption is not because the animal is disgusting or antithetical to Jewish identity. The Talmud states,

> The Sages taught: "You shall do My ordinances (*mishpatai*)." [This refers to] matters that [even] had they not been written, [it would have been] logical that they be written… "And you shall keep my statutes (*hukotai*)." [This refers to] matters that Satan would challenge [because the reason for these commandments is not known or subject to reason.] These are [the prohibitions] against eating pork… And lest you say these are meaningless acts, the verse states: "I am the Lord," i.e. I am the Lord, I decreed these and you have no right to doubt them (BT Yoma 67b).

Another rabbinic source similarly states, "Rabbi Elazar ben Azariah says that one shouldn't say, 'I abstain from pork because I don't like it.' Rather [he should abstain] because of God's commandment" (Sifra Kedoshim 9). The difference between abstaining from consuming pork because one recognizes the divine command prohibiting its consumption and abstaining from pork because of a desire not to embody—both in the archaic/literal sense and the contemporary/metaphorical sense—an anti-Jewish identity is a significant distinction when it comes to xenotransplantation and Jewish medical ethics.

Pigs Are Not Kosher, but…

Halakhic discussion over whether one is permitted to use a prohibited object in an atypical fashion begins with two recorded statements made by Rabbi Yohanan in the Talmud. The first statement said in the name of Rabbi Yohanan is, "With regard to

all prohibitions in the Torah, one may be flogged for violating them only if he eats the prohibited item in its usual manner of consumption." The example the Talmud provides for what this statement excludes is prohibited fat eaten raw. The reason for the exemption is that it is not the usual way to eat prohibited fat; therefore, the person is not punished for its transgression. This implies that Rabbi Yohanan's statement refers to consumption prohibitions. Rabbi Yohanan's second statement is, "With regard to all prohibitions in the Torah, one is flogged for violating them only if he derives enjoyment from the prohibited item in the usual manner." The Talmud notes that this excludes both placing the fat of an ox that the court determined should be stoned to death (and thus one is prohibited to derive any benefit from the animal) on one's wound and, *a fortiori*, eating prohibited fat that is raw. There is no difference between the two statements when considering those substances that are prohibited to eat, such as pork, eaten in an atypical way. Yet the second statement is more expansive than the first in that it exempts from punishment not only direct consumption when such consumption is atypical, but it also exempts from punishment any form of enjoyment when using a prohibited substance in an abnormal way (BT Pesahim 24b).

Maimonides rules that the second formulation of Rabbi Yohanan's statement is authoritative. He writes in his *Mishne Torah*, "One is not liable for partaking of any of the prohibited foods unless one partakes of them in a manner in which one derives enjoyment…" (Mishne Torah Forbidden Foods 14: 10). One should note that when the Talmud states that a person is exempt from punishment, it typically means that the action is still prohibited but that the court cannot exact a penalty. It also means that the prohibition itself (and not just the punishment) may be pushed aside if there is a conflicting value or need, such as to fulfill the commandment of preserving one's health. Therefore, Maimonides writes, "When is this the case that we only heal ourselves with the substances that are prohibited in a situation of danger? When they are used in the manner of their enjoyment. For example, we feed the sick person insects or creeping animals, or *chamets* [leavened bread] on Passover or we feed him on Yom Kippur. But [if] it is not used in the way of its enjoyment, for example, we make a bandage or plaster from *chamets* [leavened bread] or from *orlah* [fruit from a tree in its first three years], or we give him to drink something bitter mixed with forbidden foods, since, there is no enjoyment to his palate, it is permissible even not in a situation of danger…" (Mishne Torah Foundations of the Torah 5: 8). The permissibility to override a transgression is measured by weighing both the relative severity of the transgression and the relative gravity of the situation.

Rabbi Yosef Karo rules in accordance with Maimonides' position. He writes that in a situation of danger one may use a prohibited food substance in a manner through which one derives enjoyment and, in situations that are less serious, in a manner through which one does not derive enjoyment. For those substances that are prohibited even to derive benefit, in situations of danger one may still use them in ways that do not derive enjoyment (Shulhan Arukh Yoreh Deah 155: 3). Rabbi Zechariah Mendel ben Aryeh Leib cites rabbinic authorities who make a distinction between consuming a prohibited food for the sake of medical treatment in a way that is not enjoyable and using the substance in other ways. He writes that one who inhales

something prohibited to eat through his nostrils is not liable even if he benefits from a *kazayit* [an olive-size amount] since it is not the way of eating (Be'er Heitiv Yoreh Deah 84: 37). Even though someone in need of an organ transplantation would be in such a position of danger that it would be permissible to receive a pig organ, given Rabbi Leib's distinction, receiving a pig organ for transplant is not even considered to be "consumption" of a prohibited food, let alone enjoyment.

Despite its permissibility, a patient may nevertheless be concerned that receipt of the pig organ would lead to spiritual pollution, i.e. *timtum halev* [polluted heart], which itself may cause the person to develop a bad character. The concept of *timtum halev* is derived from the verse, "You shall not draw abomination upon yourselves through anything that swarms; you shall not make yourselves impure therewith and thus become impure" (Leviticus 11: 43). In the Talmud, the school of Rabbi Yishmael teaches regarding this verse, "Sin pollutes the heart of a person who commits it, as it is stated: "And do not impurify yourselves with them, so that you should not be thereby impure." Do not read that term as: 'be impure [*venitmetem*]'; rather, read it as: 'be polluted [*venitamtem*]'" (BT Yoma 39a). This concept of spiritual pollution is codified by Rabbi Moshe Isserles in his gloss on the *Shulhan Arukh*, "The breastmilk of an Egyptian is like that of a Jewess, yet one should not have their child suckle from an Egyptian if it is possible to suckle from a Jewess since the breastmilk of an idolator will pollute the heart and cause him to have a bad nature. So shouldn't a Jewish nursemaid eat prohibited food nor should a child himself [eat prohibited food] because it will cause [spiritual/character] damage in his old age" (Shulhan Arukh Yoreh Deah 81: 7). The suckling child would not be consuming prohibited food, nor would the child, due to his age, be transgressing a commandment when eating food prohibited to others. Yet there is still a concern over the milk's or the food's influence on the spiritual nature and/or character of the child. Rabbi Zylberstein, however, has noted that such spiritual defilement may only result when the food sustains a healthy person and not when consumed medicinally. He also states that when used not in a manner of oral consumption, one need not worry about *timtum halev* (Shi'urei Torah l'Rof'im II: 84). A patient receiving a pig organ through a transplant would therefore not need to worry that the transplant may lead to spiritual pollution.

If a patient is nevertheless repulsed by the idea of receiving a pig organ, Jewish medical ethics and American medical ethics begins to part ways regarding how one may respond. According to American law and medical ethics, a competent patient has a right to refuse treatment, even if such refusal may lead to the patient's death and even if the patient knows that such treatment will lead to his or her death (Superintendent of Belchertown State Sch. v. Saikewicz). Moreover, a fundamental component of patient autonomy—both according to U.S. law and secular medical ethics—is the right of informed consent and refusal. As the American Medical Association Code of Ethics states, "Patients have the right to receive information and ask questions about recommended treatments so that they can make well-considered decisions about care" (Code of Medical Ethics Opinion 2.1.1). While American medical ethics once held that there were rare times when physicians may invoke therapeutic privilege, which is the decision to withhold information from a

patient for fear that disclosure may cause serious mental or physical harm to them, this is no longer a morally justifiable position according to the American Medical Association (Code of Medical Ethics Opinion 2.1.1).

According to Jewish law, however, patients have traditionally not had a right to refuse treatment and may be forced to be treated if necessary (Teshuvot HaRadvaz 4:1139; Magen Avraham Orakh Hayyim 328: 2). This is especially the case if refusal is based on misguided piety (Mor Uketziah 328). In situations where treatment will nevertheless lead to a prolonged life of pain and suffering, the patient has religious sanction to determine whether to undergo treatment (Iggrot Moshe Hoshen Mishpat 2: 74). Moreover, if being pressured to be treated may lead to significant negative psychological or other effects, deference to patient wishes may be acceptable (Iggrot Moshe Hoshen Mishpat 2: 74). Rabbi Feinstein also rules that actual coercion is never an acceptable treatment option (Iggrot Moshe Hoshen Mishpat 2: 74). Because Jewish law prioritizes compliance with Jewish law, including the commandment to preserve life and health, over misguided piety, there are some rabbinic authorities that deem it permissible not to reveal to the patient that the organ comes from a pig (Shi'urei Torah l'Rof'im II: 84). However, whether a physician may rely on this suggestion in practice depends on whether it is also permitted not to reveal such information according to the jurisdiction in which the physician practices.

Jewish Pig Farms for Organ Transplant

The pig heart and kidneys that were used in the recent xenotransplantations came from Revivicor, a subsidiary of United Therapeutics, a Maryland-based biotech company. The viability for transplant of such genetically modified pig organs means that other companies will also begin to raise pigs for the purpose of harvesting their organs for transplant. The Mishna, however, rules unequivocally that a Jew may not raise pigs (Mishna Bava Kamma 7: 7). The Talmud explains that the reason for the prohibition is the Sages' curse on those who raise pigs, made after the dispute between the members of the Hasmonean monarchy (BT Bava Kamma 82b). The Mishna also rules that, in general, one may not engage in the business of trading non-kosher animals (Mishna Shevi'it 7: 3). Rabbenu Tam notes that the Mishna specifically mentions pigs, even though it mentions all non-kosher animals elsewhere, because one may raise other non-kosher animals to engage in trade for nonculinary purposes, such as trading their hides. However, one may not raise pigs even when the intent is to engage in nonculinary business (Tosafot BT Bava Kamma 82b). The distinction noted by Rabbenu Tam is recorded in the *Shulhan Arukh* and its commentaries. Rabbi Yosef Karo writes, "It is forbidden to do business in anything that is specifically for eating and Biblically prohibited, even though it is not forbidden to derive benefit from it." (Shulhan Arukh Yoreh Deah 117: 1). Rabbi Shabbatai ben Meir HaKohen comments that this rule excludes horses, donkeys, and camels which are generally used for work, even if people may eat them. It also includes animals that, while typically raised as food, are specifically being raised for nonculinary purposes. He then cites Rabbi Karo's reference, in his commentary,

Bet Yosef, to Rabbenu Tam who excludes pigs from this leniency (Shakh Shulhan Arukh Yoreh Deah 1). For this reason, Rabbi Zylberstein recommends that Jews do not engage in the business of raising pigs for the purpose of harvesting their organs for transplant even when Jewish patients may receive them for transplant. The reason is that religious prohibitions may be pushed aside for the sake of saving a life, but it is not certain that raising these pigs will definitively lead to saving a life as one does not know if any particular pig will be an organ donor. Rabbi Zylberstein does, however, state that if not raising genetically modified pigs for transplant would lead to a potential danger, such as if biotech companies would not give these organs to Jews, then it would be permissible for Jews to engage in raising pigs to have a supply of organs for transplant (Shi'urei Torah l'Rof'im II: 84).

Conclusion

For a patient who aspires to live within the norms and values of the Jewish tradition, it would certainly be permitted to receive a pig organ if such a xenotransplantation could save his or her life. Yet the challenge for such patients may not only be in whether Jewish law permits it. It may also include how their aversion to consuming pig speaks to their Jewish identity. For such patients, it is important to understand how their own conceptions of Jewish identity impact their aversion and how rabbinic sources in the Jewish tradition can help allay the abhorrence they may have. In such cases, it is best to explain how pig organs are not kosher, but we can use them for xenotransplantation.

References

1. Ekser B, Cooper DK. Overcoming the barriers to xenotransplantation: prospects for the future. Expert Rev Clin Immunol. 2010;6(2):219–30.
2. Hryhorowicz M, Zeyland J, Słomski R, Lipiński D. Genetically modified pigs as organ donors for xenotransplantation. Mol Biotechnol. 2017;59(9–10):435–44.
3. Kemter E, Schnieke A, Fischer K, Cowan PJ, Wolf E. Xeno-organ donor pigs with multiple genetic modifications–the more the better? Curr Opin Genet Dev. 2020;64:60–5.
4. United network for organ sharing. Transplant trends. https://unos.org/data/transplant-trends/
5. Armstrong M. Statista. Organ transplant waiting lists in the U.S. https://www.statista.com/chart/26574/number-of-people-us-waiting-for-organ-transplant-by-type/
6. Stolf NA. History of heart transplantation: a hard and glorious journey. Braz J Cardiovasc Surg. 2017:423–7.
7. de Quetteville H. The telegraph. Why putting animal organs inside people could be the future of medicine. https://www.telegraph.co.uk/health-fitness/body/putting-animal-organs-inside-people-could-future-medicine/
8. Schneider CE. Bioethics in the language of the law. Hastings Cent Rep. 1994;24(4):16–22.
9. Foster C, Miola J. Who's in charge? The relationship between medical law, medical ethics, and medical morality? Med Law Rev. 2015;23(4):505–30.
10. Campbell AT, Sicklick J, Galowitz P, Retkin R, Fleishman SB. How bioethics can enrich medical-legal collaborations. J Law, Med Ethics. 2010;38(4):847–62.

11. Jakobovits I. The role of Jewish medical ethics in shaping legislation. In: Rosner F, editor. Medicine and Jewish Law. Northvale: Jason Aronson; 1990. p. 1–18.
12. Lichtenstein A. Abortion: a halakhic perspective. Tradition: J Orthodox Jew Thought. 1991;25(4):3–12.
13. Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, Dobbels F, Goldfarb SB, Levvey BJ, Meiser B, Yusen RD. The registry of the international society for heart and lung transplantation: thirty-first official adult heart transplant report—2014; focus theme: retransplantation. J Heart Lung Transplant. 2014;33(10):996–1008.
14. Briggs JD. Causes of death after renal transplantation. Nephrol Dial Transplant. 2001;16(8):1545–9.
15. Rosenblum JD. "Why Do You Refuse to Eat Pork?": Jews, food, and identity in roman palestine. Jew Q Rev. 2010;100(1):95–110.
16. Ohnuki-Tierney E. Rice as self. Princeton University Press; 1994.
17. Grey's Anatomy. "Save Me." https://greysanatomy.fandom.com/wiki/Save_Me/Transcript

Religious Viewpoints: Hinduism

17

Joris Gielen

Introduction

In October 2014, during a function to celebrate the renovation of an important hospital in the Indian city of Mumbai, Narendra Modi, the Prime Minister of India, made a remarkable statement:

> We can feel proud of what our country achieved in medical science at one point of time. […] We worship Lord Ganesh[a].[1] There must have been some plastic surgeon at that time who got an elephant's head on the body of a human being and began the practice of plastic surgery [1].

In his speech, the Prime Minister mentioned the Hindu God Ganesha, who has a boy's body and an elephant's head. Since even Hindu Gods may normally not be born with an animal head, it makes sense to assume that some kind of "surgeon" took care of the change of heads. Whether a "plastic surgeon" may be able to accomplish a surgery as complex as a head transplant on his or her own, as the Prime Minister suggested, might be open for debate, but the statement seems to suggest, at least, a Hindu attitude that is open towards xenotransplantation. If Gods may transplant an entire animal head onto a human body, humans might conclude that they may transplant animal organs, tissue or cells onto humans. Yet, how open is Hinduism to xenotransplantation? Is this story of Ganesha an outlier in Hindu mythology? Can it really be used to derive the attitude of Hinduism to xenotransplantation? What are the Hindu views on xenotransplantation exactly?

[1] In this chapter, scientific transliteration will be used for Sanskrit concepts (e.g. *ahiṃsā*). Scientific transliteration is not used for names of persons, Gods and places that are common in English (e.g. Krishna, Ganesha).

J. Gielen (✉)
Center for Global Health Ethics, Duquesne University, Pittsburgh, PA, USA
e-mail: gielenj@duq.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_17

These are important questions to answer. Hinduism is a major religion. In 2011, the most recent year for which census data from India are available, there were over 1.2 billion people in India 966 million out of which (79.8%) identified as Hindu [2]. Attracted by economic opportunities, Hindus have migrated in large numbers to countries all over the world. While in the US only 0.7% of the population is Hindu [3], this percentage still amounts to a total of well over 2 million Hindus living within the US. Moreover, within the healthcare workforce, Hindus are overrepresented in comparison to their share of the overall US population. In 2005, a national survey of the religious characteristics of US physicians found that 5.3% of these physicians identified as Hindu [4]. More recent data indicate that that this percentage has gone up since then [5]. As a consequence, in a future in which xenotransplants become more widely available, there will be Hindu patients who will be eligible for these transplants in the US, and there will be Hindu physicians and other Hindu healthcare professionals caring for these patients. Therefore, it is important to explore Hindu attitudes towards xenotransplantation as this will prepare healthcare professionals and organizations for communication with Hindu patients who will be eligible for xenotransplants and with Hindu physicians, nurses and other healthcare professionals who will care for these patients.

However, due to the novelty of xenotransplantation, there is not much literature on Hindu attitudes to this practice. A study among 556 persons of South-Asian origin in the UK indicated that Hindus may generally be open to receiving xenotransplants. Only 14.3% of Hindus said they "would not take xenotransplant." This percentage was significantly lower than that of Muslims (59.3%) and Sikhs (24.2%)—another religion that originated on the Indian subcontinent—[6]. This shows that the Hindu respondents were much more open to the practice. While these numbers are interesting, they do not reveal why Hindus would, or would not, approve of xenotransplantation. In order to understand Hindu attitudes to this issue, we need to study stories and concepts that are influential within Hinduism and that may inform these attitudes. From this perspective Hindu stories of divine beings who combine human and animal forms seem particularly relevant.

Divine Human-Animal Beings

A first story on such a divine being that we need to take a look at is obviously the story of the Hindu God Ganesha, who was mentioned by the Indian Prime Minister, Narendra Modi. As per certain stories of Ganesha's origin, he was not born with an elephant head. The stories tell how the Goddess Parvati, the wife of the God Shiva, created Ganesha from scurf of her own body while her husband was in deep meditation on a mountain far away from home. As a consequence, Shiva was unaware of the 'birth' of his son. After ending his meditation, Shiva wanted to be with his wife. However, when he attempted to enter her premises, Ganesha prevented him from entering. His mother was taking a bath and had asked him to let no one enter. When Ganesha persistently refused to let Shiva in, Shiva cut of Ganesha's head. Parvati was understandably furious because of the beheading of her son. In order to appease

her, Shiva promised that he would give Ganesha the head of the first living being that he would come across. That living being turned out to be an elephant. The elephant's head was put on Ganesha's body and Ganesha was resuscitated (Śiva Purāṇa, Rudrasaṃhitā 4.13–17) [7].

As per Hindu mythology, this was not the first time that Shiva was involved in the act of putting an animal head on a human-shaped body. Before marrying Parvati, Shiva had been married to the Goddess Sati. Sati's father Daksha, however, had never approved of that marriage. One day, Daksha organized a huge sacrifice to the Gods without inviting his daughter and her husband, Shiva. Sati felt so offended and humiliated that she immolated herself. When Shiva heard that news his wrath descended upon Daksha and his followers. In the ensuing violence, Daksha was beheaded. Shiva was merciful, though. He restored Daksha back to life and gave him the head of a goat (Śiva Purāṇa, Rudrasaṃhitā 2.14–42) [7].

Daksha and Ganesha are not the only instances of divine human-animal beings in Hindu mythology. The God Vishnu is said to have descended upon the earth in the form of a man-lion to save his devotee Prahlad. Prahlad's father was the mighty demon Hiranyakashipu, who was not only vehemently opposed to devotion to Vishnu, but had, also, been granted the boon from the God Brahma that he could neither be killed by a human or an animal. One day, Hiranyakashipu was so enraged by his son's devotion to Vishnu that he attempted to kill him. Before he could do that, Vishnu appeared in the form of a man lion. Because of his ambiguous human-animal nature, the man-lion was able to kill Hiranyakashipu (Bhāgavata-Purāṇa 7.8) [8].

It might be tempting to conclude from these stories that xenotransplantation may be unproblematic from a Hindu perspective. As already suggested above, if Gods transplant an animal head onto a human body, as in the cases of Daksha and Ganesha, or take on a human-animal form, as in the case of Vishnu, surely, transferring live cells, organs or tissues from animals to humans appears acceptable. Especially for people who are familiar with Christian modes of religious reasoning, this conclusion may sound convincing. After all, since Christianity's very beginnings, Christians have believed that a good moral life means imitating Christ [9]. As Son of God and God Himself, Christ exemplified a moral life and, therefore, committed Christians ought to live following His example. So, following the example of the Hindu Gods, are Hindus permitted to chop off human heads and replace them with animal heads, if medical science were to enable them to do so? Or, maybe slightly more prosaic, would the divine example at least permit humans to transfer animal tissue, cells, or organs into another human?

There is no straightforward answer to that question, because, at times, Hindu Gods do things that, at first sight, might seem immoral. Humans would obviously not be expected to imitate an immoral example. For instance, as per many stories Krishna, an avatar or incarnation of the God Vishnu, indulged in an adulterous affair with Radha and other milkmaids in the North Indian town of Vrindavan. Hindus have not interpreted this affair as a justification for adultery. Hindu commentators have explained and justified the relationship between Radha and Krishna in various ways and some have argued that what Gods do is not always appropriate for humans

and, thus, Krishna's adulterous example should not be followed [10, 11]. The stories of Krishna's dalliances with Radha should rather be seen as a devotional metaphor. For some commentators, love that transgresses the bonds of marriage is ultimately selfless because these adulterous lovers have to make great sacrifices in the pursuit of their desire. From this perspective, Radha's love is a metaphor for the self-sacrificing love that devotees should feel towards God or Krishna [12, 13].

Likewise, the stories about the God Shiva cutting off human heads and replacing these with animal heads are not exactly treatises about the morality of head transplants. These stories are intended to illustrate God's greatness so that believers will direct their devotion toward Him. The idea that was at the basis of these stories was that nothing is impossible for a God who can replace a human head with an animal head. Arguably, at the time when these stories originated many centuries ago, Hindus could not have imagined that, one day, xenotransplants would not be the subject of religious mythology, but a treatment that doctors offer to patients. Similarly, the story about the man-lion was about the extraordinary things God can do to protect His devotees [14]. Prime Minister Narendra Modi's speech was not about the morality of xenotransplantation either. The goal of the speech was to glorify India's technological and scientific greatness in a mythical past.

When the stories about divine human-animal beings are interpreted within their socio-religious and historical context, it becomes clear that they do not provide much insight into how Hindus ought or may be expected to think about xenotransplantation. At best, the stories could be seen as an indication that Hindus may not necessarily reject the practice on the basis of the assumption that humans have been created in the "image of God." In the Bible it is said that God created mankind in His "image and likeness," which sets humans apart from animals. As a consequence, from a Christian or Jewish perspective, xenotransplantation could be considered unacceptable because it compromises a human person's nature as created in God's image [15]. In 2003, S. Cromwell Crawford, argued in a book entitled *Hindu Bioethics for the Twenty-first Century,* that such a view does not align with Hindu perspectives. To substantiate his point, Crawford not only mentioned incarnations of Hindu Gods who take an animal form or a combination of animal and human form, such as the man-lion. He, also, noted that many Hindus view the cow as a Goddess and venerate the "monkey god, Hanumān" [16]. Crawford is of the opinion that these examples illustrate the Hindu "veneration of the natural world, and animals in particular." For him, this shows that, in the Hindu view, the animal realm is no less than the human realm. The human nature is not seen as superior to or more divine than the animal nature. From there, Crawford concludes that Hindus will accept xenotransplants, if the organ, tissue or cell can function effectively (pp. 127–128).

A possible objection to Crawford's analysis would be that sacrificing an animal to harvest its organs and save a human life may actually not be acceptable to Hindus, if, as Crawford argues, in the Hindu worldview human beings are not superior to animals. A xenotransplant would require the killing of one living being, the animal, to save another, the human who receives the transplant. This may not seem acceptable if both living beings are considered equally valuable. To this, Crawford

responds that in Hinduism it is believed that liberation from the cycle of death and rebirth can only be obtained during a human life. Therefore, in matters of life or death, a human life may be saved by sacrificing an animal and take its organ, cells or tissue (p. 128). While this argument seems elegant, it looks as if it is trying to have it both ways. On the one hand, Hinduism would not reject xenotransplants because there is no "sacred barrier" between humans and animals and humans are not superior to animals. On the other hand, when human life is in danger, an animal may be sacrificed because, somehow, the human life is still more valuable.

Clearly, the Hindu stories about divine human-animal beings do not give a clear unambiguous answer to the question whether or not xenotransplantation is morally acceptable to Hindus. If these stories do not tell Hindus how to think about xenotransplantation, what else does?

Karma

Another avenue to assess normative Hindu views on xenotransplantation is achieved by looking at religious concepts and beliefs that are shared by many or most Hindus and that may inform their attitudes to xenotransplantation. In this context, karma may be a relevant belief. Karma is a belief that is accepted in some form by most Hindus. Karma entails the conviction that every deed will have a consequence. If a person has done a morally good deed, the consequences will be good. If the deed has been morally bad, the consequences, too, will be bad. It is important to consider that in Hinduism, just as in Buddhism, Jainism, and Sikhism, three other religions of Indian origin, the consequences need not be experienced within this life. They may also be experienced in a future life because Hinduism accepts rebirth as a reality. In this way, karma can be used as an explanation for social and economic inequality: those who are born in a socio-economically less advantageous context may only have themselves to blame because their birth was determined by deeds they did in previous lives [17, 18]. The question that we then need to answer is: how can belief in karma be applied to the issue of xenotransplantation?

Within the context of xenotransplantation, there may be a double karmic effect. First, the animal providing the transplant may experience the karmic effect of 'donating' the transplant. Second, the person receiving the transplant and the clinicians involved in the transplant may experience the karmic effect of 'taking' the organ from another living being. For persons who are unfamiliar with religious traditions from India, it may sound strange that the animal may experience karmic effects just like humans. From the Hindu perspective, though, this is just the way karma operates. Humans, animals, and even plants are all subject to the karmic cycle of life and rebirth. An animal that, throughout its life, lives well by fulfilling its animal duties (*dharma*)—whatever these may be—may experience a good rebirth and may even be reborn as a human in a future life.

Obviously, donation of an organ, cells or tissue to help or even save another living being may be considered a meritorious act that may lead to good karma [19]. Since belief in karma distinguishes Hinduism and other religions that originated in

India from religions that originated elsewhere, such as Islam, this belief may explain why Hindus have been found to be more open to organ transplants than Muslims. A study in India among a group of 84 adults with an equal number of Hindu, Muslim, and Christian participants, found that Hindus were more likely to approve living donor transplants than Muslims [20]. A similar statistically significant difference was found in another study from India that included 863 outpatients in three tertiary hospitals. 63.6% of Hindus and 63.3% of Christians were willing to donate organs before or after death, while 52% of Muslims were willing to do this [21]. Likewise, a study in the UK that included 556 persons of South-Asian origin found that Hindus were more likely to "agree with organ donation" (92.2%) than Muslims (59.3%) [6].

While it is tempting to conclude that belief in karma explains the more favorable Hindu attitude to organ donation, we do not have hard empirical evidence to prove this conclusion. There are actually indications in the literature that religion may not be a major factor in Hindus' attitudes to organ donation. A study on the influence of religion on attitudes to organ donation in the UK found that the majority of the interviewed Hindus stated that they were not sure what their religion's position towards organ donation is [22]. While more data are needed to draw firm conclusions, the findings do seem to indicate that if belief in karma did influence the attitudes of Hindu study participants to organ donation, that influence was, at least ambiguous and, most likely unconscious.

Moreover, when analyzing the karmic effect of the 'donation' of a xenotransplant by an animal, there arises a further complication in that the animal does not really 'donate' the organ. It is taken. If the organ or body part is not freely given in an act of selfless altruism, can it lead to good karma? Can an animal experience the good consequences of an involuntary act? In Hindu texts and stories, we find indications that this may actually be possible. There is a famous story of a man who had led a dissolute life. He had been a gambler who had hurt his mother and killed a cow, a very grave sin because Hinduism considers cows sacred. After he had been killed by a tiger, his body was devoured by vultures. One of the vultures picked up a bone and flew away with it. Accidently, the vulture dropped the bone in the river Ganges while flying over it. Many Hindus believe that the Ganges has the power to wash away the sins of those who take a bath in it. As soon as the bone sank in the river, the wicked man's sins were wiped out and the man entered heaven [23].

There are several interesting parallels between this story and xenotransplants. Just like the evil man did not choose to take a bath in the river Ganges, the animal that provides the transplant does not choose to donate an organ, tissue or cells. And, just like the man was able to experience the good consequences of the involuntary bath that his bone took after he had died, so too, the animal may experience good karmic consequences when its organ, tissue or cells are transplanted into a human body after the animal's death. While the analogy is intriguing, it is important to remember that these stories have more of a devotional than a moral intent. This story concretely intends to show how merciful God is. If God has mercy upon a wicked person who is made to do a good religious act accidentally after his death, surely, He or She will be merciful to those who address all their devotion to Him or Her. Anyway, the story does illustrate the need to live a good religious life. The

animal who provides the transplant needs to live a moral life for which it may receive karmic reward, and so does the patient receiving the transplant and the clinicians involved in the transplant plant process. From there, we may ask the question what the karmic consequences of xenotransplantation will be for patients and clinicians.

From an ethical perspective, a major problem with xenotransplants is that they are only possible through violence. The animal that provides the transplant will be hurt in the process and be killed. Both the patient and the clinicians bear some indirect responsibility for that suffering. They are at least complicit in it. Therefore, they will have to experience the karmic consequences of the suffering that they caused to the animal. In order to steer Hindus away from violence and the karmic consequences that come along with it, Hindu texts and thinkers extol the concept of non-violence, or *ahiṃsā* in Sanskrit. This concept has a long and complicated history within the Hindu traditions and often there is a clear awareness that absolute non-violence is a mirage [24, 25]. Even Mahatma-Gandhi, who propagated non-violence in India's struggle for freedom from the British, recognized that there are particular circumstances that could warrant some level of violence, even killing. In his writings, Gandhi explored the criteria that had to be met in order to justify killing. These criteria could be an avenue through which killing an animal to harvest transplants could become acceptable. The problem is, however, that Gandhi posited that there be "no 'self-interest' involved in the decision to kill" [26]. We may accept that clinicians selflessly devote themselves to patient care, but it is hard to accept that the patient has no self-interest in requesting and accepting a xenotransplant.

The Hindu objections against harming and even killing animals in order to obtain transplants for humans may become even more acute if these transplants were to come from bovines. As already mentioned, in Hinduism the cow has a sacred status. Many Hindus consider contact with by-products of the cow purifying. At the same time, killing a cow is a sin. Therefore, Hindus may drink milk and eat curd and butter and even use cow urine and dung, but killing a cow in order to obtain products that could save human beings may be problematic [27]. For instance, Hindus may not accept the use of gelatin derived from bovines in intravenous fluids that are used in anesthesia or resuscitation [28]. Hindu patients and their families may actually not be aware of products containing materials derived from bovines that were killed in the process of procuring them. When informed about this, they may refuse administration of the product. This happened, for instance, when a Hindu family in the UK was informed that the surfactant Survanta (Beractant) is derived from bovines. The family subsequently declined to participate in a trial that involved this surfactant [29]. In 2006, Dr. Appupillay Balasubramaniam, who was the chairman of the Hindu Council of Australia at the time, explained in a letter to researchers investigating religious attitudes to the use of porcine and bovine surgical products, that surgery that involved bovine products is unacceptable to Hindus. The reason he mentioned was indeed that the product can only be obtained through killing of bovines [27].

While all this does indicate possible Hindu objections against xenotransplantation, this does not mean that Hindus will necessarily refuse a xenotransplant. The

empirical data that were cited at the end of the introduction to this chapter show that only a minority of Hindus are radically opposed to receiving a xenotransplant [6]. Most xenotransplants do not come from bovines and are, therefore, less problematic to Hindus, even though they still involve some degree of violence. As indicated above, non-violence is generally not an absolute demand in Hinduism, although it remains difficult to say or predict how individual Hindus will respond when offered a xenotransplant. Hindu traditions are diverse and that diversity is reflected in the Hindu approach to normative bioethics. Earlier research on normative bioethics in Hinduism has observed that a diversity in normative ethical conclusions is expected in Hinduism, because the Hindu approach to normative ethics "focuses on the ethical process rather than the outcome" or the ethical conclusion of that process. That process does not only integrate Hindu stories and concepts, such as karma and *ahiṃsā,* but also, broader ethical perspectives and questions, (e.g. whether or not the action under consideration is genuinely caring or whether or not God would approve the action). Due to the diversity within the Hindu traditions, individual Hindus may prioritize different components of the ethical process [30]. For example, not all Hindus may know the nuances of Gandhi's thought on *ahiṃsā,* or the story of the criminal whose bone fell into the river Ganges. As a consequence, a diversity of Hindu views on xenotransplantation is to be expected.

This may sound somewhat unsettling to persons who are looking for hard answers regarding how Hindu patients or healthcare colleagues might think about xenotransplantation. However, it is wise to remember that, in healthcare, ethical attitudes should never be assumed. The fact that a patient identifies as belonging to a particular religion, does not necessarily mean that that patient will agree with that religion's majority view on ethical issues. These issues ought to be explored with all parties involved in the ethical problem. From this perspective, organizations and healthcare professionals researching or offering xenotransplantation will need to make sure that they integrate cultural competence and cultural humility [31–33] throughout the transplantation process. Organizations and healthcare professionals who are willing to do this will need a good knowledge base regarding religious attitudes to xenotransplantation. This chapter has presented important stories and concepts that could inform Hindu attitudes to xenotransplantation. However, knowledge on its own is insufficient, and healthcare professionals and organizations must be aware of their limitations in this area. Organizations and healthcare professionals need the right attitudes and skills to explore the role that the stories and concepts may play in patients' views. They need to be careful not to impose preconceived notions on patients and their families and must be willing to learn from the patient in order to uncover the unique ethical perspective this person may have.

Conclusion

This chapter has studied religious stories, concepts and beliefs that may inform the attitudes of Hindus to xenotransplantation. The chapter showed that Hindu stories on divine human-animal beings such as the God Ganesha or the

appearance of the God Vishnu as man-lion may point at an openness to transplanting animal organs, tissue or cells into humans. On the other hand, the primary focus of Hindu stories such as those of Ganesha and the man-lion is devotional rather than moral and, therefore, the moral implications of the stories are ambiguous. The significance of the concept of karma is more clearly moral, although the concrete outcome of a Hindu argument on xenotransplantation based on the concept of karma remains ambiguous, too. While xenotransplantation may lead to good karma for the animal donating the organ, violence to the animal remains a part of the transplantation and may, thus, lead to bad karma for both the patient who receives the transplant and the healthcare professionals involved in the transplantation process. Given the ambiguity of Hindu arguments to xenotransplantation it is essential to thoroughly explore values and views with Hindu persons involved in a xenotransplant.

References

1. PM Modi takes leaf from batra book. Mahabharat genetics, Lord Ganesha surgery. The Indian Express; 2014.
2. Census of India website: office of the registrar general & census commissioner, ministry of home affairs, Government of Inida; https://censusindia.gov.in/
3. Center PR. Religious landscape study https://www.pewforum.org/religious-landscape-study/#religions
4. Curlin FA, Lantos JD, Roach CJ, Sellergren SA, Chin MH. Religious characteristics of U.S. physicians: a national survey. J Gen Intern Med. 2005;20(7):629–34.
5. Thompson K, Tak HJ, El-Din M, Madani S, Brauer SG, Yoon JD. Physicians' religious characteristics and their perceptions of the psychological impact of patient prayer and beliefs at the end of life: a national survey. Am J Hosp Palliat Care. 2019;36(2):116–22.
6. Karim A, Jandu S, Sharif A. A survey of south Asian attitudes to organ donation in the United Kingdom. Clin Transpl. 2013;27(5):757–63.
7. Shastri JL, editor. The Śiva-Purāṇa. Delhi: Motilal Banarsidass; 1950.
8. The Bhāgavata-Purāṇa. Delhi: Motilal Banarsidass; 1950.
9. Capes DB. Imitatio christi and the gospel genre. Bull Biblic Res. 2003;13(1):1–19.
10. Harman WP. The sacred marriage of a Hindu goddess. Bloomington: Indianapolis; 1989.
11. Gielen J. The theological bearing of purāṇic stories: an enquiry into the presence of feminine theology in the Brahma-vaivarta-purāṇa. Relig South Asia. 2008;2(2):177–93.
12. Goswami S. Rādhā: the play and perfection of rasa. In: Hawley JS, Wulff DM, editors. The divine consort, Rādhā and the goddesses of India. Delhi: Motilal Banarsidass; 1995. p. 72–88.
13. Kinsley D. Hindu goddesses. Visions of the divine feminine in the Hindu religious tradition. Delhi: Motilal Banarsidass; 1998.
14. Gielen J. God in India: diversiteit en devotie in de indische religies. Tielt: LannooCampus; 2013.
15. Ebner K, Ostheimer J, Sautermeister J. The role of religious beliefs for the acceptance of xenotransplantation. Exploring dimensions of xenotransplantation in the field of hospital chaplaincy. Xenotransplantation. 2020;27(4):e12579.
16. Crawford SC. Hindu bioethics for the twenty-first century. Albany: State University of New York Press; 2003.
17. Gielen J, Kashyap K. Belief in karma and mokṣa at the end of life in India. In: Selin H, Rakoff RM, editors. Death across cultures: death and dying in non-western cultures. Cham: Springer International Publishing; 2019. p. 19–39.
18. Klostermaier KK. A survey of Hinduism. Albany: State University of new York Press; 1994.

19. Wentzel Wolfe R, Gudorf CE, editors. Ethics and world religions: cross-cultural case studies. Maryknoll: Orbis Books; 2000.
20. Almeida N, Almeida A. Community attitudes toward kidney donation in India. Transplant Proc. 2013;45(4):1307–9.
21. Mithra P, Ravindra P, Unnikrishnan B, Rekha T, Kanchan T, Kumar N, et al. Perceptions and attitudes towards organ donation among people seeking healthcare in tertiary care centers of coastal South India. Indian J Palliat Care. 2013;19(2):83–7.
22. Randhawa G. An exploratory study examining the influence of religion on attitudes towards organ donation among the Asian population in Luton, UK. Nephrol Dial Transplant. 1998;13(8):1949–54.
23. Eck DL. Banāras, city of light. New York: Knopf; 1982.
24. Das V. Violence and nonviolence at the heart of Hindu ethics. In: Jerryson M, Juergensmeyer M, Kitts M, editors. The Oxford handbook of religion and violence. Oxford: Oxford University Press; 2013. p. 15–40.
25. Vidal D, Tarabout G, Meyer E. On the concepts of violence and non-violence in Hinduism and Indian society. South Asia Res. 1994;14(2):196–213.
26. Gielen J. Mahātmā Gandhi's view on euthanasia and assisted suicide. J Med Ethics. 2012;38(7):431–4.
27. Easterbrook C, Maddern G. Porcine and bovine surgical products: Jewish, Muslim, and Hindu perspectives. Arch Surg. 2008;143(4):366–70. discussion 70.
28. Sommerville A. Juggling law, ethics, and intuition: practical answers to awkward questions. J Med Ethics. 2003;29(5):281–6.
29. Adappa R, Benson R, Oddie S, Wyllie J. Use of animal surfactant: should we seek consent? Arch Dis Child Fetal Neonatal Ed. 2003;88(4):F351–F.
30. Gielen J. Normative bioethics in Hinduism. In: Gielen J, editor. Dealing with bioethical issues in a globalized world: normativity in bioethics. Cham: Springer International Publishing; 2020. p. 75–93.
31. Foronda C, Baptiste DL, Reinholdt MM, Ousman K. Cultural humility: a concept analysis. J Transcult Nurs. 2016;27(3):210–7.
32. Saha S, Beach MC, Cooper LA. Patient centeredness, cultural competence and healthcare quality. J Natl Med Assoc. 2008;100(11):1275–85.
33. Sue DW. Multidimensional facets of cultural competence. Couns Psychol. 2001;29(6):790–821.

Part IV

Social Aspects

Psychological Implications

18

Brittney Randolph, Jennifer Nosker, and Tina Jimenez

Introduction

The psychological considerations related to xenotransplantation are complex given the intraindividual, relational, and sociocultural factors that may influence a patient's consideration of this potentially life-saving procedure. Studies conducted on allotransplantation indicate that many psychosocial factors influence a person's decision to proceed with organ transplantation and these same factors can impact post-operative adjustment [1, 2]. Thus, psychological assessments have become increasingly common in the transplant evaluation and listing process [3–9]. Xenotransplant recipients are apt to experience challenges similar to those seen in allotransplantation; however, the medical, psychological, and social complexities associated with cross-species transplantation introduces a unique set of challenges and related psychosocial influences. As scientific advancements progress toward clinical trials, it is crucial to elucidate these factors in a way that informs adequate psychological assessment practices in xenotransplant candidate selection to ensure optimal outcomes for potential recipients.

From this perspective, the focus of this chapter is to identify areas of consideration in the psychological assessment of xenotransplant candidates. To achieve this aim, a brief review of the psychological factors pertinent to allotransplantation are provided followed by a discussion of the intraindividual, interindividual, and social

B. Randolph (✉) · J. Nosker
Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham Medical Center, Birmingham, AL, USA
e-mail: botruba@uabmc.edu; jnosker@uabmc.edu

T. Jimenez
Department of Mental Health, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_18

factors unique to xenotransplantation that may affect a recipient's identity and post-surgical adjustment. Finally, the ideal psychological state of potential xenotransplant recipients will be reviewed.

Psychological Factors in Allotransplantation

Psychological assessment in organ transplantation has been the topic of numerous investigations, and multiple studies have identified the psychological and social risk factors associated with poor transplantation outcomes [3–8]. Despite this, few evidence-based practice guidelines and consensus-based recommendations have been published regarding psychological assessment in organ transplantation. However, two recently published consensus guidelines proposed key risk factors and areas of consideration in the psychological assessment of organ transplant candidates [6, 7]. Based on a comprehensive review of literature, the following are contraindications or risk factors associated with poorer allotransplantation outcomes: (a) impaired cognitive status/capacity to give informed consent, (b) limited knowledge and understanding of the illness as well as treatment options, (c) past or current non-compliance of medical treatments and recommended health behaviors, (d) past or current mental health problems or addiction, (e) poorly developed coping skills, and (f) limited social support. Various psychosocial factors (e.g., employment, financial status, current stressors) have also been identified as potential risk factors for successful transplantation [6, 7].

The key domains for psychological assessment in allotransplantation will be equally important for xenotransplantation, particularly during clinical trials. However, given the novelty of cross-species transplantation, there are unique factors that have the potential to adversely impact xenotransplant recipients' identity and social functioning. As such, the psychological evaluation of xenotransplantation candidates will initially require additional assessment in the areas of intrapersonal, interpersonal, and social/community identity.

Intrapersonal Identity in Xenotransplantation

Intrapersonal identity is an important factor to consider in xenotransplantation. Intrapersonal identity refers to the cognitive, affective, and physical factors that contribute to one's sense of self over time. Interestingly, research has shown that intrapersonal identity is impacted by the process of organ failure and chronic illness, which diminishes a person's functional capacity and sense of autonomy over time [10]. Multiple investigations have shown that body image and social identity are frequently impacted among allograft transplant recipients, as well as other types of transplantation [11–15]. For example, some transplant recipients report viewing themselves differently post-operatively as a result of being transplanted with the organ of another human being [11, 16–18]. Fortunately, previous research conducted on various types of transplantation provides a foundation from which

to understand the potential psychological challenges xenotransplant recipients may experience.

In allograft psychological research, the "transplanted self" is a term that reflects the shift in identity experienced by many transplant recipients [10]. Although most allograft recipients effectively manage this identity transition, other patients struggle with this process [13, 19]. Studies have demonstrated that a small percentage of allograft recipients view their transplanted organ as foreign, which has been associated with psychiatric distress and poorer medical outcomes [13, 20–22]. In more extreme cases, patients have struggled to adjust to the point in which they stop taking immunosuppressants post-transplantation resulting in graft rejection [18, 23]. Although these studies do not indicate causality, they suggest that poor integration of the organ into one's identity can result in psychiatric distress and interfere with the ability to manage the necessary health behaviors required to maintain organ viability.

Given the findings of these studies, a proposed risk factor associated with failed identity integration post transplantation is psychological essentialism. Psychological essentialism is a cognitive process in which an individual believes that objects or items have their own stable identities. In other words, it is the belief that objects and items have their own inherent nature and behavior [24, 25]. Research conducted on psychological essentialism in the context of human organ transplantation has shown that some individuals believe they can receive the negative traits of the donor through the transplanted organ [13, 22, 26]. For example, the fear of developing depression if the donated organ was derived from a person who experienced mental health issues has been documented among transplant recipients [13, 22].

Across versus within-species transplantation might increase the likelihood of recipients experiencing the xenograft as foreign, thereby potentially increasing the likelihood of psychological essentialism to occur, as well as associated distress. Studies have already demonstrated that a similar trend towards psychological essentialism in cross-species transplantation may exist, as research participants have expressed beliefs that receiving a pig organ could lead to developing negative personality traits [27, 28]. Such perspectives are important considerations in the psychological evaluation of xenograft recipients, as they have the potential to impact candidates' cognitive and emotional adjustment to the transplanted organ [13, 18, 29].

Importantly, the presence of psychological essentialist characteristics should not preclude an individual from xenotransplantation, but rather, should be considered in the context of other factors. In contrast to negative associations with the porcine organ, which could have deleterious effects on post-surgical outcomes, the intersection of positive associations with psychological essentialism could result in a heightened solidarity and respect for animals, as well as increased commitment to caring for the xenograft post-transplantation [30]. Thus, attitudes towards animal use for science and perceptions of porcine transplantation are important factors for consideration if psychological essentialism is present in the potential xenotransplantation candidate.

Interpersonal Identity and Relational Factors of Xenotransplantation

Personal identity develops in social contexts through interpersonal relationships over time, and throughout childhood, adolescence, and adulthood [31]. As such, allotransplantation represents a complex social challenge that requires recipients to navigate their identity transformation within the context of their interpersonal relationships, and it is unsurprising that interpersonal factors have been implicated in both positive and negative organ transplantation outcomes. Specifically, research has shown that healthy relationships and social support are essential for successful post-operative outcomes [4, 17, 32], whereas poor adjustment post-transplantation has been shown to be related with a sense of inadequacy in relation to others, fear of social rejection, and reluctance to seek help from family and friends [17].

As xenotransplantation is still in experimental stages, it is difficult, if not impossible to understand how transplantation may affect the interpersonal relationships of xenograft recipients. However, recent studies have shown that future xenograft candidates may experience concerns regarding the effect of transplantation on their social relationships. Stadlbauer et al. [28] conducted a study on xenotransplantation attitudes among waitlisted kidney candidates, and the results showed that while many organ transplant candidates might consider a porcine organ if it was comparable to the efficacy of a human organ, a notable percentage of recipients (11%) expressed concern that their family and friends might have a negative reaction to their status as a xenograft recipient. Similarly, another study revealed participants' apprehensions that xenotransplantation would change their social interactions with others [27]. Although limited, these studies highlight the importance of the relationship between social support and successful adjustment following xenotransplantation.

Social and Community Influences on the Psychological Acceptance of Xenotransplantation

Decades of psychological and sociological research suggests that a person's identity is also shaped by the social context and communities in which an individual exists [33, 34]. Even though clinical trials have yet to commence, recent studies indicate that negative social attitudes and beliefs toward xenotransplantation have already developed [28, 35]. Social perspectives of xenotransplantation will likely have psychological implications for xenograft recipients, which will be an important area of future investigation and intervention. However, the social groups and communities to which xenotransplant recipients belong are apt to have a more profound impact on the immediate consideration of being transplanted, as well as post-surgical adjustment [36]. Recent research conducted has shown that theological beliefs and belonging to certain racial and ethnic groups, can shape a person's decision

regarding the acceptability of a xenograft. Religious and racial/ethnic differences in xenograft acceptance could further contribute to health disparities if potential candidates' concerns are not comprehensively addressed.

Regarding religion, for the past two decades religious leaders have hosted theological conversations regarding perspectives on xenotransplantation [35, 37, 38]. Among non-monotheistic religions, such as Hinduism and Buddhism, there is a broad consensus that the decision to accept a xenograft should be deferred to the individual, as religious teachings do not explicitly prohibit the use of animal organs to alleviate human suffering [37, 38]. Similarly, among monotheistic religions, xenotransplantation is not generally prohibited. Despite this, religious leaders have raised concerns regarding humans intervening in the order of creation, the acceptability of using animal organs for survival, and the possibility of xenograft recipients experiencing shame because of their religious views (e.g., porcine seen as impure or unclean) [37, 38]. Although the major world religions are not generally or explicitly prohibitive towards xenotransplantation, there is recognition that theological views of the self, soul, and body might result in adverse emotional responses to xenotransplantation [38] As such, the religious beliefs of transplant recipients, and perhaps of their primary support network, should be considered in the psychological assessment of xenotransplantation candidates.

Racial and ethnic perspectives on xenotransplantation may also influence decision-making regarding xenotransplantation candidacy and psychological adjustment post-surgery. Several recent studies have examined racial attitudes toward xenografting, showing notable differences across races in the acceptance of the procedure [27, 39, 40]. The results of these studies have revealed that Black and Latino participants had lower acceptance rates of cross-species organ transplantation compared to White participants [27, 40]. Hodge [39] postulated that these discrepancies may be partially due to the historical distrust of scientific clinical trials among underrepresented populations. For example, one study found that nearly 75% of Latino immigrants were not in favor of xenotransplantation and this was associated with a general negative attitude towards human organ donation [40].

While it is important to consider religious, racial/ethnic, and other cultural factors in xenotransplantation evaluations, further research is needed to elucidate the implications of these factors more explicitly. This is especially crucial considering many of these factors overlap with those implicated in current transplant health disparities [41], and could exacerbate these disparities if transplant teams do not understand potential recipients' underlying concerns and how to address them. Like many of the risk factors identified with allotransplantation, diversity factors should not be viewed as exclusionary or inclusionary. Quite the contrary, rather, teams should seek to understand and address the multiple factors that may influence a patient's understanding of and consideration for xenotransplantation and connect them with resources, if needed, to allow for an individualized and intersectional understanding of the implications of xenotransplantation.

The Ideal Psychological State for Xenotransplantation and Assessment Tools

During clinical trials, the selection of appropriate candidates for xenotransplantation requires careful psychosocial considerations to achieve positive post-operative outcomes. Consistent with allotransplantation psychological evaluations, xenotransplant candidates should have the capacity to provide informed consent or assent, which requires, to some extent, intact cognition [6]. Yet, organ failure and associated treatments can result in cognitive deficits [4, 42]. As such, it will be important for clinicians to assess cognition using objective cognitive screeners or neuropsychological tests [42]. If cognitive dysfunction is present, then clinicians should evaluate the extent to which the deficit(s) may impact the ability of the candidate to follow post-operative recommendations and procedures. While cognitive dysfunction should not preclude individuals from receiving a xenograft [43], the psychologist, psychiatrist, social worker and/or medical team should consider whether the patient will be able to follow post-operative requirements or whether they have a support system that can aid in managing post-operative care. Once cognitive capacity has been evaluated, potential recipients should be assessed for their knowledge and understanding of their illness, as well as treatment options available to them [6, 7]. Potential xenograft recipients should be able to demonstrate that they can comply with medical treatments and make health changes as necessary, which will be particularly important given the close medical monitoring that will initially be required.

Potential xenograft candidates should also be screened for mental health symptoms, as well as past or current addiction. Given the high rates of depression and anxiety in the general transplant population, xenograft recipients are apt to experience similar or exacerbated mental health difficulties due to the additional medical and social stressors associated with xenotransplantation [21, 32, 44]. Although psychological distress should not be solely used as an exclusionary criterion for xenotransplantation, candidates' coping skills should be carefully evaluated. Candidates should have the ability to cope with and manage stressors at all stages of the transplantation process, which will initially require careful medical observation and multiple medical appointments. Candidates should also be willing to learn new coping skills in order to navigate concerns from family members and friends, should these arise [10, 15].

Additionally, the ideal xenotransplant candidate should have the capacity to manage the identity transition that will occur as a result of being a xenograft recipient [13, 22]. As previously noted, psychological essentialism is a potential risk factor for poor psychosocial adjustment and providers should inquire about concerns or fears regarding xenograft transplantation and have open dialogue regarding any hesitations. The inclusion of a religious leader, counselor, or other identified healer could assist in facilitating these conversations. Social support will also be a critical component of the ideal xenotransplant profile, particularly given the negative societal attitudes that already exist towards cross-species organ transplantation [45].

Potential candidates should have social supports or possess willingness to seek assistance through alternative means, such as a xenotransplant support group, if available. Access to such resources should also be evaluated and referrals given if social support networks are limited.

Information on the domains previously mentioned can be attained through a clinical interview as well as measures commonly used in allograft transplantation, including the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) [45], Psychosocial Assessment of Candidates for Transplantation (PACT) [46], and the Transplant Evaluation Rating Scale (TERS) [47]. While more research is needed to determine the predictive validity of these measures on post-operative outcomes [16, 35, 48], they assess for psychological health, adaptive coping mechanisms, and other pertinent domains. Although developed for allograft recipients, these measures may be used in xenotransplantation until other tools are constructed. As xenograft science advances, standardized interviews and objective assessment measures specific to xenotransplantation with predictive validity for post-surgical adjustment are preferred and should be employed over subjective evaluative methods.

Conclusion

The psychosocial complexities of xenotransplantation parallel the scientific and medical challenges associated with the procedure. In addition to the factors considered in allotransplantation, the psychological assessment of xenograft candidates will require careful evaluation of the intraindividual, interindividual, and social identity factors that have the potential to influence decision-making and post-surgical adjustment. Although the medical field currently lacks assessment measures that predict post-operative success, a comprehensive psychological or psychosocial evaluation can inform transplant teams regarding candidates most suitable for transplantation during clinical trials. Most importantly, xenotransplant teams should consider employing models of care that are inclusive of underserved populations, which may require additional assessment, dialogue, and inclusion of other community resources and members. In this way, organ transplant teams can select approrpriate candidates during clinical trials and thereafter, while also providing tailored treatment recommendations.

References

1. AlHajri L, AlHebsi A, AlSuwaidi M. How context affects people's willingness to register for the deceased organ donation program. BMC Public Health. 2021;21:279. https://doi.org/10.1186/s12889-021-10753-5.
2. Baghernezhad M, Mani A, Ayoobzadehshirazi A, Roozbeh J, Zare M, Nikeghbalian S, et al. Psychologic evaluation in liver transplantation: assessment of psychologic profile of end-stage liver disease patients before and after transplant. Exp Clin Transplant. 2020;18(3):339–44.

3. Kumnig M, Jowsey GS. Preoperative psychological evaluation of transplant patients: challenges and solutions. Transpl Res Risk Manag. 2015;7:35–43. https://doi.org/10.2147/TRRM.S59268.
4. Bui Q, Allen L, Lemond L, Brambatti M, Adler E. Psychosocial evaluation of candidates for heart transplant and ventricular assist devices: beyond the current consensus. Circ Heart Fail. 2019;12(7):e006058. https://doi.org/10.1161/circheartfailure.119.006058.
5. Collins C, Labottt S. Psychological assessment of candidates for solid organ transplantation. Prof Psych: Res Practice. 2007;38(2):150–7.
6. Dew M, Dimartini A, Dobbels F, Teuteberg J, Yusen R, Zimbrean P, et al. The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation for adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support. J Heart Lung Transplant. 2018;37(7):P803–23. https://doi.org/10.1016/j.healum,2018.03/005.
7. Fidel Kinori S, Alcantara Tadeo A, Castan Campanera E, Costa Requena G, Diez Quevedo C, Lligona Garreta A, et al. Unified protocol for psychiatric and psychological assessment of candidates for transplantation of organs and tissues, PSI-CAT. Rev de Psiquiatr y Salud Men. 2015;8(3):130–6.
8. Mitchel C, Lipps A, Padilla L, Werkheiser Z, Cooper D, Paris W. Meta-analysis of public perception toward xenotransplantation. Xenotransplantation. 2020;27(4):e12583. https://doi.org/10.1111/xen.12583.
9. American Medical Association (2016, June). Guidelines for organ transplantation: code of medical ethics opinion 6.2.1. https://www.ama-assn.org/delivering-care/ethics/guidelines-organ-transplantation
10. Cormier NL, Gallo-Cruz SR, Beard RL. Navigating the new, transplanted self: how recipients manage the cognitive risks of organ transplantation. Socio l Health Illn. 2017;39(8):1496–513. https://doi.org/10.1111/1467-9566.12610.
11. Anthony SJ, Nicholas DB, Regehr C, West LJ. The heart as a transplant organ: unspoken struggles of personal identity among adolescent recipients. Can J Cardiol. 2019;35(1):96–9. https://doi.org/10.1016/j.cjca.2018.10.006.
12. Kristensen IV, Birkelund R, Henriksen J, Norlyk A. Living in limbo while one's identity is changing: patients' existential experiences 6 months after a kidney transplantation with a living donor. J Adv Nurs. 2020;77(3):1403–10. https://doi.org/10.1111/jan.14683.
13. Vamos M. Organ transplantation and magical thinking. Aust N Z J Psychiatry. 2010;44(10):883–7. https://doi.org/10.3109/00048674.2010.498786.
14. Swindle JS. Facial allograft transplantation, personal identity and subjectivity. J Med Ethics. 2007;33(8):449–53. https://doi.org/10.1136/jme.2006.017475.
15. Lee J. Face transplantation and identify: hidden identities, exceptions, and exclusions. Kennedy Inst Ethics J. 2019;29(2):125–58.
16. Appel JZIII, Always IP, Cooper DK. Xenotransplantation: the challenge to current psychosocial attitudes. Prog Transplant. 2000;10(4):217–25. https://doi.org/10.1177/152692480001000405.
17. Petre O, Cracium IC, Baba A. The experiences of living with a transplanted kidney from a deceased donor. J Ren Care. 2021;47:58–67. https://doi.org/10.1111/jorc.12349.
18. Errico M, Metcalfe N, Platt A. History and ethics of hand transplants. J R Soc Med Sh Rep. 2012;3(10):74. https://doi.org/10.1258/shorts.2012.011178.
19. Henneman K, Bauer-Hohmann M, Klewitz F, Tegtbur U, Pape L, Schiffer L, et al. Organ integration in kidney transplant patients- results of a KTx360 substudy. J Psychosom Res. 2021;145:110464. https://doi.org/10.1016/j.jpsychores.2021.110464.
20. Latos M, Lazar G, Horvath Z, Wittmann V, Szederkenyl E, Hodi Z, et al. Psychological rejection of the transplanted organ and graft dysfunction in kidney transplant patients. Transpl Res Risk Manag. 2016;8:15–24. https://doi.org/10.2147/TRRM.S104133.
21. Rosenberger E, Dew M, Crone C, DiMartini A. Psychiatric disorders as risk factors for adverse medical outcomes after solid organ transplantation. Curr Opin Organ Transplant. 2015;17(2):188–92.
22. Schlitt HJ, Brunkhorst R, Harmut HJ, Nashan B, Haverich A, Raab R. Attitudes of patients before and after transplantation various allografts. Transplantation. 1999;68:510–4.

23. Nassimizadeh M, Nassimizadeh A, Power D. Hand transplant surgery. Ann R Coll Surg Engl. 2014;96(8):571–4. https://doi.org/10.1308/003588414X13946184902767.
24. Olivola CY, Machery E. Is psychological essentialism an inherent feature of human cognition? Behav Brain Sci. 2012;37(5):499. https://doi.org/10.1017/S0140525X13003841.
25. Prentice DA, Miller DT. Psychological essentialism of human categories. Curr Dir Psychol Sci. 2007;16(4):202–6. http://www.jstor/stable/20183197.
26. Rhodes M, Leslie SJ, Saunders K, Dunham Y, Cimpian A. How does social essentialism affect the development of inter-group relations? Dev Sci. 2017;21(1):e12509. https://doi.org/10.1111/desc.12509.
27. Padilla L, Hurst D, Jang K, Rosales J, Sorabella R, Cleveland D, et al. Racial differences in attitudes to clinical pig organ xenotransplantation. Xenotransplantation. 2021;8(2):e12656. https://doi.org/10.1111/xen.12656.
28. Stadlbauer V, Stiegler P, Muller S, Schweiger M, Sereing M, Tscheliessnig K, et al. Attitude toward xenotransplantation of patients prior and after human organ transplantation. Clin Transpl. 2011;25(3):495–503. https://doi.org/10.1111/j.1399-0012.2010.01296.x.
29. Balkcom ER, Alogna VK, Curtin E, Halberstadt JB, Bering J. Aversion to organ donated by suicide victims: the role of psychological essentialism. Cognition. 2019;19:1–8. https://doi.org/10.1016/j.cognition.2019.104037.
30. Amiot C, Bastian B. Solidarity with animals: assessing a relevant dimension of social identification with animals. PLoS One. 2017;12(1):1–26.
31. Kroger J. Identity development in adolescence and adulthood. Oxford Research Encyclopedia of Psychology; 2017. https://oxfordre.com/psychology/view/10.1093/acrefore/9780190236557.001.0001/acrefore-9780190236557-e-54
32. Coglianese EE, Samsi M, Liebo M, Heroux AL. The value of psychosocial factors in patient selection and outcomes after heart transplant. Curr Heart Fail Rep. 2015;12:42–7. https://doi.org/10.1007/s11897-014-0233-5.
33. Greenfield E, Marks N. Religious social identity as an explanatory factor for associations between more frequent formal religious participation and psychological well-being. Int J Psychol Relig. 2007;17(3):245–59. https://doi.org/10.1080/10508610701402309.
34. Jensen LA. The cultural psychology of religiosity, spirituality, and secularism in adolescence. Adolesc Res Rev. 2021;6:277–88. https://doi.org/10.1007/s40894-020-00143-0.
35. McCracken V. Public attitudes toward xenotransplantation: a theological perspective. J Evid-Info Soc Work. 2020;18:1–9. https://doi.org/10.1080/26408066.2020.1814927.
36. Zurani N, Robson H, Razack A, Dublin N. Review paper: organ transplants: ethical, social, and religious issues in a multicultural society. Asia Pac J Public Health. 2010;22(3):271–68. https://doi.org/10.1177/1010539509357446.
37. Sykes M, d'Apice A, Sandrin M. Position paper of the ethics committee of the international xenotransplantation association. Transplantation. 2003;78(8):1101–7.
38. Ebner K, Ostheimer J, Sautermeister J. The role of religious beliefs for the acceptance of xenotransplantation. Exploring dimensions of xenotransplantation in the field of hospital chaplaincy. Xenotransplantation. 2020;27(4):e12579. https://doi.org/10.1111/xen.12579.
39. Hodge D. Xenotransplantation, trust, and trustworthiness: ethical issues for African Americans. Ethics, Med Public Health. 2018;7:59–67. https://doi.org/10.1016/j.jemep.2018.10.003.
40. Rios A, Lopez-Navas A, Martinez-Alarcon L, Ramir G, Hernandez A, Ayala MA, et al. Acceptance of organ xenotransplantation among Latin American immigrants residents in the United States. Xenotransplantation. 2016;23:269–78. https://doi.org/10.1111/xen.12250.
41. Wesselman H, Ford CG, Leyva Y, Li X, Chang CH, Dew MA, et al. Social determinants of health and race disparities in kidney transplant. Clin J Am Soc Nephrol. 2021;16:262–74. https://doi.org/10.2215/CJN.04860420.
42. Gupta A, Thomas T, Klein J, Montgomery R, Mahnken J, Johnson D, et al. Discrepancies between perceived and measured cognition in kidney transplant recipients: implications for clinical management. Nephron. 2017;138:22–8. https://www.karger.com/Article/Fulltext/481182
43. Friedman RL. Ethics of organ transplantation in persons with intellectual disability. J Pediatr. 2021;235:6–9. https://www.jpeds.com/article/S0022-3476(21)00497-2/fulltext

44. Schulz K, Kroencke S. Psychosocial challenges before and after organ transplantation. Transpl Res Risk Manag. 2015;7:45–58. https://doi.org/10.2147/TRRM.S53107.
45. Maldonado JR. Why it is important to consider social support when assessing organ transplant candidates? Am J Bioeth. 2019;19(11):1–8. https://doi.org/10.1080/15265161.2019.1671689.
46. Olbrisch ME, Levenson JL. Psychosocial assessment of organ transplant candidates: current status of methodological and philosophical issues. Psychosomatics. 1995;36(3):236–43. https://doi.org/10.1016/S0033-3182(95)71662-0.
47. Twillman RK, Manetto C, Wellisch DK, Wolcott DL. The transplant evaluation rating scale. A revision of the psychosocial levels system for evaluating organ transplant candidates. Psychosomatics. 1993;34(2):144–53.
48. Grover S, Sarkar S. Liver transplant -psychiatric and psychological aspects. J Clin Exp Hepatol. 2012;2(4):382–92. https://doi.org/10.1016/j.jceh.2012.08.003.

19 Challenges in Adequately Assessing the Social Attitudes and Perceptions of the Public Towards Xenotransplantation

Antonio Ríos and Marco Antonio Ayala-García

Xenotransplantation at Present

The shortage of organs for transplantation makes it necessary to look for definitive solutions that allow this activity to be carried out without long waiting lists, which often lead to morbidity and mortality. Potential options such as stem cells, bio-artificial organs and xenotransplantation involve a series of genetic manipulations and, in the case of xenotransplantation, the utilization of animals for human use, which have important ethical implications [1]. These considerations have a significant influence on how the population accepts this potential therapy.

Before analyzing the attitude and social perception towards xenotransplantation, it is important to consider the current status of xenotransplantation, a therapy that has not yet been fully accepted in some countries and is in preclinical experimental phases. Xenotransplantation is the most promising potential source of organs for transplantation [2–3]. In this regard, pigs are the most suitable donors, as they are easy to handle, omnivorous, have a similar physiology to humans, have organs of compatible size, have a short gestation period and can have multiple litters. However,

A. Ríos (✉)
Transplant Unit, Surgery Service, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Bio-Sanitaria (IMIB-Arrixaca), Murcia, Spain

Department of Surgery, Pediatrics, Obstetrics and Gynecology, University of Murcia, Murcia, Spain

Proyecto Colaborativo Internacional Donante ("International Collaborative Donor Project"), Murcia, Spain
e-mail: arzrios@um.es

M. A. Ayala-García
Proyecto Colaborativo Internacional Donante ("International Collaborative Donor Project"), Murcia, Spain

Clinical Surgery Coordination, Hospital General Regional No. 58 del Instituto Mexicano del Seguro Social, León, Guanajuato, Mexico

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_19

their use as organ donors depends on changes in their genome, such as the inactivation (knock out) of genes responsible for the production of some sugars that cause hyperacute rejection, and the addition (knock in) of human genes that produce substances capable of modulating chronic rejection. In addition, since 2017, 62 loci of porcine endogenous retroviruses (PERVs) have been inactivated, producing virus-free pigs [2]. These scientific in vitro and pre-clinical advancements have led to the recent human experiment, such as the xenotransplantation of a transgenic pig heart in 2022 at the University of Maryland School of Medicine (United States) [3]. However, significant immunological and infectious barriers still remain to be overcome, not to mention the legal, ethical and social issues that need to be addressed in the face of a possible clinical reality in the U.S.

Assessment of Attitudes and Social Perceptions

It should be remembered that an attitude is a learned predisposition to respond consistently in a favorable or an unfavorable way to an object or symbol [4]. In this sense, people have different attitudes to an aspect or situation. As a general rule, attitude is related to one's perception of everything surrounding the object in question. The traditional psychological definition of perception is the process of using the senses to become aware of objects, events, and relationships in the physical and social environment in order to interpret their significance and form knowledge and judgements. This process also involves learning, memory and symbolization [5].

Attitudes define the way one reacts to the world. The position taken regarding the situations that arise in life is determined by the feelings that a person may generate in favor of or against an object or situation. This suggests that an attitude is determined by the learning that different population groups acquire in the family, in the workplace and in academic training [6]. Therefore, when speaking of the attitude towards any subject, and in this case towards xenotransplantation, the following components should be considered:

1. *The cognitive component* is formed from a person's knowledge (cognitions) and perceptions that are acquired, by a combination of direct experience, with the object and/or situation, and information, obtained from various sources.
2. *The affective component* comprises the emotions and/or feelings of a person in a particular situation.
3. *The will component* involves the probability or tendency that an individual presents his/her behavior to a particular object or situation.

Social Information on Xenotransplantation

Public awareness about xenotransplantation is largely based on representations, generally inaccurate, obtained from the media, either traditional (television, radio, etc.) or online (social networks, internet, etc.) [7]. As a general

rule, the presence of medical and health issues in the media enables 'public education' and affects perceptions—generating opinions—on these health issues [7].

The lack of adequate public education on a given health topic largely conditions a population's attitude towards that topic. Indeed, the social perception of a topic such as xenotransplantation can be strongly conditioned by the predominant opinion groups in each society. In this sense, it should be remembered that population differences may be conditioned not by cultural aspects, but by the information to which they have access. In our research experience with multiple demographic and ethnic groups it appears that population attitudes may be conditioned not by cultural aspects, but by the information they have access to [13–17, 32–34].

For all the above-mentioned reasons, xenotransplantation has not been well assimilated by the population, and the potential risks it could entail are often unjustifiably increased.

Limitations in Understanding the Attitude and Social Perception Towards Xenotransplantation

It is difficult, if not almost impossible, to know the attitude and social perception towards xenotransplantation. There are several reasons for this phenomenon, and they must be taken into account when interpreting the available data. Broadly speaking, this lack of knowledge is due to the following facts:

Heterogeneous Studies with Different Tools to Measure This Situation

The great problem of studies that assess the attitude and social perception towards xenotransplantation is their heterogeneity. Specifically, these studies use questionnaires expressly designed and most are not validated to quantify and/or standardize the findings, something that does not occur in most of them [8]. The fact that most authors use different tools to perform this measurement makes it difficult to compare studies. Hence, it is not possible to determine the source of differences among populations: are they due to the selection of the groups or the questionnaire used in each case, or are there really population differences between the groups under study [8–10, 42].

Another aspect is the heterogeneity in the methodology used in each study. Some studies are conducted in person by direct interview, others are self-paced, others occur via telephone and, more recently, there has been an increase in the number of psychosocial studies conducted online. These methodologies increase the heterogeneity of the studies and makes it difficult to compare them.

Low Quality of the Studies

A high percentage of published studies have a high risk of bias and, therefore, a high probability that the results presented do not match reality [8, 43]. Thus, it is common to find problems of selection bias, insufficient samples, low completion rates, etc., in the published studies. In addition, there is a high percentage of publications in national journals that have low impact factors, are ranked in third or fourth quartiles and/or are not indexed.

This often leads to confusion and a lack of reliable information. There are often contradictory data among studies, perhaps due to study biases rather than to real differences in the attitude and social perception towards xenotransplantation.

There Are Few Studies That Analyze the Social Perception Towards Xenotransplantation

It is not possible to know the situation at the population level when the studies that analyze this situation focus on only a few groups. Mitchell et al. [8] performed a meta-analysis and found only 19 publications were of the minimum statistical information to be compared and to be included, and most were not population-based studies. This issue is important especially if cultural differences are taken into account. It should be remembered that although the world is becoming increasingly globalized, a relevant aspect that should be considered when analyzing the social perception of incorporating an animal organ into the human body is the cultural aspect, because there are important cultural differences in the way this type of procedure is dealt with.

Difference Between Knowledge and Acceptance Towards Xenotransplantation

Finally, a major problem when talking about public perception is the tendency to attribute rejection or uncertainty about these concepts to a knowledge deficit that could or should be addressed by higher education. A well-recognized assumption in public policy and health care debates is known as the ‘knowledge deficit model’ of public understanding of science. This is a problematic assumption because it fails to recognize that differences in opinion may represent genuine differences in values. Indeed, there are considerable data suggesting that, while knowledge and education may predict the strength of attitudes towards scientific issues, attitude positivity is poorly correlated with knowledge [11].

This aspect should be kept in mind because there is a tendency to consider attitudes and knowledge as similar. However, attitudes may be related more to sociocultural values than to knowledge, although this statement is not supported by all authors [12].

The Attitude and Social Perception Towards Xenotransplantation

General Evaluation of Studies Assessing Attitude and Social Perception

Although there is the impression that there is extensive knowledge about the attitude and social perception towards xenotransplantation, in reality there is only partial understanding. A useful tool to clarify this situation—although it has its limitations and criticisms—is meta-analysis. We have already highlighted the one performed by Mitchell et al. [8]. The authors stated, 'The question then becomes, how reliable is any meta-analysis about patient views that include only three studies?', when raising doubts about meta-analysis. This question highlights the reality that exists: there appears to be a lot of information and articles, but there is actually little real, quality information.

Hence, for several years research groups such as ours (the International Donor Collaborative Project [PCID]) have tried to carry out homogeneous, quality and comparable studies [10]. However, this is proving to be an almost impossible task because each group continues to use different tools that are not comparable. In addition, each new research group or person who performs this type of study generates a new tool.

It is essential that psychosocial research groups are aware of the importance of standardizing studies with validated questionnaires that measure what they really have to measure, to ensure that studies are comparable and useful. The existing heterogeneity should make us reflect on the psychosocial research that is being carried out.

Social Perception Towards Xenotransplantation

To first approximate the attitude and social perceptions, it is interesting to analyze the data of the meta-analysis carried out by Mitchell et al. [9], which includes the publications on the subject up to the year 2019. Most of the studies are at the patient level [9, 40, 41] and not at the population level. This aspect is important to take into account, because in patients, survival and being pragmatic usually take precedence over other ethical or emotional aspects [13], although the preference is still to be transplanted with a human organ [38]. Regarding the limitations of these studies, the authors indicated that, of the 41 assessed studies on patient perception, only three provided sufficient data for analysis.

On the other hand, the other large group for which there is information on the attitude and social perception towards xenotransplantation is centered on university students and health center personnel [8, 14–16].

Reviewing the bibliography as a whole, there are about 200 publications that have dealt with the subject in some of its aspects and in different population groups, both the general population, health care workers, patients, etc. As indicated above,

most of these studies present results from very localized geographical areas, and with very diverse methodologies that prevent the generalization of the results [14–32, 39, 41].

As a general rule, if the results are similar to those obtained with human organs, the favorable attitude towards xenotransplantation is around 50%, although is varies widely from 10% to 90% depending on the population considered [14–31].

Given the difference in the methodologies and questionnaires, it is difficult to perform comparative analyses among the studies.

Factors Associated with Attitude Towards Xenotransplantation

Some of the published studies have examined factors associated with the attitude towards xenotransplantation [8, 14–31, 39]. The factors most frequently associated with a favorable attitude towards xenotransplantation are:

1. Personal experience with organ transplantation;
2. Favorable attitude at the family and partner level towards transplantation and xenotransplantation;
3. Geographic area of residence;
4. Knowledge that their religion is in favor of organ transplantation;
5. Favorable attitude towards human organ donation;
6. Considering the possibility of needing a transplant in the future;
7. Education level; and
8. Age of the respondent.

Most of these factors are related to human organ donation and transplantation. Therefore, the general promotion of organ donation and transplantation is considered a good way to promote xenotransplantation [14–16].

On the other hand, there are specific fears generated by xenotransplantation, among which the following stand out [14–16]:

1. Fear that a porcine xenograft may alter one's own image;
2. Fear of animal infections transmitted to humans (xenozoonosis); and
3. Fear of personality changes that could be produced by the xenotransplantation.

Studies of the International Collaborative Donor Project

Our research group, the PCID [10], has standardized and validated a survey that considers the three above-mentioned components (cognitive, affective and willingness), and we have applied it to different groups [10]. This endeavor has allowed us to determine the social perception of different social groups towards

xenotransplantation and to compare the results among groups. Based on our survey, we have formed a real idea of the differences among social and professional groups (Table 19.1). On the contrary, every time different research groups conduct studies and try to compare the results, we do not know whether the differences are real or due to methodological, cultural or social changes and differences.

Being able to compare is what makes psychosocial studies useful. As can be seen in Table 19.1, which presents some of the data obtained by the PCID, the attitude towards xenotransplantation was more negative in our center with a preclinical xenotransplantation program than among the general population [14, 32]. This finding has conditioned several informative cycles directed towards different groups of workers in our center, prioritizing them over the general population. If a worker in a center that performs xenotransplantation (even if he/she is not a non-health care worker) is not in favor of xenotransplantation, a climate of distrust will be generated, because just by working in our center with a preclinical program, he/she generates an opinion at the population level. Thus, at the population level, distrust is generated: 'if a person who works there is not in favor, there must be a reason'. In this sense, comparable and validated studies have allowed us to make decisions, specifically changing the information policy on xenotransplantation, from the population to our own center. This approach has also allowed us to select the population groups less sensitized to xenotransplantation, as can be seen in Table 19.1. However, in most cases the reality is that reflected by Mitchell et al. [8]: studies have used different methods and thus we cannot know whether the differences are real or a consequence of the different methodologies.

Table 19.1 Attitude towards organ xenotransplantation in case of presenting good clinical results

Study group	Attitude in favor
Population groups	
Spanish population [32]	74%
British population residing in Spain [33]	69%
German populaton residing in Spain [34]	61%
Eastern European population residing in Spain [24]	43%
Latin American population residing in Spain [35]	40%
Latin American population residing in Florida (USA) [36]	10%
Sanitary groups	
Staff of a Spanish hospital with a preclinical xenotransplantation program [14]	67%
Primary health care staff. Spanish multicenter study [37]	79%
Hospital Center staff. Multicenter study in Spanish-speaking countries [15]	61%
Patients on the waiting list	
Patients on the waiting list for renal transplantation [13]	76%
Patients on the waiting list for liver transplantation [13]	67%
University students	
Medicine students. Spanish multicenter study [16]	81%
Nursing students. Spanish multicenter study [30]	74%

Importance of the Health Profession in Raising Awareness of Xenotransplantation in the Population

Currently, xenotransplantation is overcoming barriers that until a few years ago many thought could not be overcome. Indeed, the field of xenotransplantation is advancing. However, the population has little information on the subject, has many doubts and fears, and often receives confusing information. To achieve maximum social support, xenotransplantation must be seen as something acceptable and beneficial. Therefore, one of the basic elements to achieve a reliable social perception is to obtain clear, real and credible information.

Since the establishment of the Hippocratic School, one of the duties of physicians is the 'promotion of health and preventive care'. One example is the provision of adequate information to the public about organ donation and transplantation as well as new therapies under development such as xenotransplantation. Public awareness of xenotransplantation should be based on adequate and correct information provided by health care professionals. It should be remembered that lack of information or a sense of uncertainty and doubt reduces public confidence.

References

1. Loewendorf A, Csete M. Concise review: immunologic lessons from solid organ transplantation for stem cell-based therapies. Stem Cells Transl Med. 2013;2:136–42. https://doi.org/10.5966/sctm.2012-0125.
2. Cross-Najafi AA, Lopez K, Isidan A, Park Y, Zhang W, Li P, Yilmaz S, Akbulut S, Ekser B. Current barriers to clinical liver xenotransplantation. Front Immunol. 2022;13:827535. https://doi.org/10.3389/fimmu.2022.827535.
3. Shah AM, Han JJ. First successful porcine to human heart transplantation performed in the United States. Artif Organs. 2022; https://doi.org/10.1111/aor.14203. Epub ahead of print.
4. Hernández R. Escalas para medir las actitudes. In: Hernández-Sampieri R, Mendoza C, editors. Metodología de la investigación. Las rutas cuantitativa, cualitativa y mixta. 3rd ed. México: Editorial McGraw-Hill; 2018. p. 255–6.
5. Vargas LM. On the concept of perception [sobre el concepto de percepción] article in Spanish. Alteridades. 1994;4:47–53.
6. Blakeslee R. In: Thomas R, Blakeslee R, Hahn LE, editors. El factor de la actitud Prolongue su vida cambiando su manera de pensar. México: Editorial Trillas; 2000. p. 10–48.
7. Larsson A, Oxman AD, Carling C, Herrin J. Medical messages in the media—barriers and solutions to improving medical journalism. Health Expect. 2003;6:323–31.
8. Mitchell C, Lipps A, Padilla L, Werkheiser Z, Cooper DKC, Paris W. Meta-analysis of public perception toward xenotransplantation. Xenotransplantation. 2020;27:e12583. https://doi.org/10.1111/xen.12583.
9. Ríos A, López Navas A, de Francisco C, Sánchez A, Hernandez AM, Ramírez P, Parrilla P. Psychometric characteristics of the attitude questionnaire toward the donation of organs for transplant (PCID-DTO-RIOS). Transplant Proc. 2018;50:345–9.
10. Ríos ZA. Proyecto collaborativo internacional donante (international colaborative donor project). Cir Esp. 2018;96:69–75.
11. Allum N, Sturgis P, Tabourazi D, Brunton-Smith I. Science knowledge and attitudes across cultures: a meta-analysis. Public Underst Sci. 2008;17:35–54.

12. Skowronski G, Ramnani A, Walton-Sonda D, Forlini C, O'Leary MJ, O'Reilly L, Sheahan L, Stewart C, Kerridge I. A scoping review of the perceptions of death in the context of organ donation and transplantation. BMC Med Ethics. 2021;22:167. https://doi.org/10.1186/s12910-021-00734-z.
13. Martinez-Alarcon L, Rios A, Pons JA, et al. Attitudinal study of organ xenotransplantation in patients on the kidney and liver transplant waiting list in a country with a high rate of deceased donation. Xenotransplantation. 2011;18:168–75. https://doi.org/10.1111/j.1399-3089.2011.00673.x.
14. Ríos A, Conesa C, Ramírez P, et al. Hospital personnel faced with organ xenotransplantation: an attitudinal survey in a hospital with a pre-clinical liver xenotransplantation program. Xenotransplantation. 2006;13:447–54.
15. Ríos A, Martínez-Alarcón L, López-Navas A, et al. Level of acceptance of solid organ xenotransplantation among personnel in Spanish, Mexican and Cuban hospitals. Xenotransplantation. 2014;21:84–90.
16. Ríos A, López-Navas A, López-López A, et al. The level of acceptance of Spanish medical students of the transplantation of solid organs from animals: a stratified and multicenter study. Xenotransplantation. 2015;22:476–86.
17. Chlitt HJ, Brunkhorst R, Haverich A, Raab R. Attitude of patients toward transplantation of xenogeneic organs. Langenbeck's Arch Surg. 1999;384:384–91.
18. Deschamps JY, Roux FA, Gouin E, Sai P. Reluctance of French patients with type 1 diabetes to undergo pig pancreatic islet xenotransplantation. Xenotransplantation. 2005;12:175–80.
19. Long T, Wray J, Myers L, Banner N. Attitudes of potential candidates for heart and heart-lung transplantation to xenotransplantation. Prog Transplant. 2002;12:280–8.
20. Rios A, Conesa C, Ramirez P, et al. Attitude toward xenotransplantation among residents. Transplant Proc. 2006;37:4111–6.
21. Persson OM, Persson NH, Ranstam J, Hermeren G. Xenotransplantation public perceptions: rather cells than organs. Xenotransplantation. 2003;10:72–9.
22. Mikla M, Rios A, Lopez-Navas A, et al. Looking for new alternatives: what nursing students of Lodz's medical University in Poland think about the use of organs coming from animals. Transplant Proc. 2016;48:2476–8.
23. Rubaltelli E, Burra P, Sartorato V, et al. Strengthening acceptance for xenotransplantation: the case of attraction effect. Xenotransplantation. 2008;15(3):159–63. https://doi.org/10.1111/j.1399-3089.2008.00474.x.
24. Rios A, Martinez-Alcaron L, Sanchez J, et al. Population study about the attitude toward organ xenotransplantation in the population from Eastern Europe resident in Southeast Spain. Int J Artif Organs. 2010;33:30–9.
25. Martinez-Alarcon L, Rios A, Pons JA, et al. Attitudes toward islet cell and tissue xenotransplantation among kidney and liver patients no the transplant waiting list. Transplant Proc. 2010;42:3098–101. https://doi.org/10.1016/j.transproceed.2010.05.071.
26. Rios A, Febrero B, Lopez-Navas A, et al. Xenotransplantation of cells for diabetes: is there a good acceptance rate among Spanish adolescents? Transplant Proc. 2011;43:55–7. https://doi.org/10.1016/j.transproceed.2010.11.007.
27. Mikla M, Rios A, Lopez-Avas A, et al. Attitude of nursing students at the University of Lublin Poland toward xenotransplantation. Transplant Proc. 2015;47:2583–6.
28. Gungormus Z, Gungormus M. Effects of religious beliefs in selecting graft materials used in oral and maxillofacial surgery. J Oral Maxillofac Surg. 2017;75(11):2347–53. Found at. https://doi.org/10.1016/i.joms.0217.07.160.
29. Amin L, Hashim H, Mahadi Z, Che Ngah A, Ismail K. Determinants of stakeholders' attitudes to xenotransplantation. Xenotransplantation. 2018;25(6):e12430. https://doi.org/10.1111/xen.12430.
30. Martinez-Alarcon L, Rios A, Santaines-Borreda E, et al. Student nurses at Spanish universities and their attitude toward xenotransplantation. Xenotransplantation. 2019;26:e12507. https://doi.org/10.1111/xen.12507.

31. Rubaltelli E, Burra P, Canova D, et al. People's attitude toward xenotransplantation: affective reactions and the influence of the evaluation context. Xenotransplantation. 2009;16:129–34.
32. Ríos A, Conesa C, Ramírez P, Rodríguez MM, Parrilla P. Public attitude toward xenotransplantation: opinion survey. Transplant Proc. 2004;36:2901–5.
33. Ríos A, Ramírez P, Martínez L, et al. British citizens in a regional community of South-Eastern Spain with a pre-clinical organ xenotransplantation program. A study of attitude toward xenotransplantation. Xenotransplantation. 2007;14:255–64.
34. Ríos A, Martínez L, Sánchez J, et al. German residents in South-Eastern Spain: a study of attitudes toward organ xenotransplantation. Organs Tissues Cells. 2009;12:107–14.
35. Ríos A, López-Navas A, Martínez-Alarcón L, et al. A study of the attitude of Latin American residents in Spain toward organ xenotransplantation. Xenotransplantation. 2014;21:149–61.
36. Ríos A, López-Navas A, Martínez L, et al. Acceptance of organ xenotransplantation among Latin American immigrants resident in the United States. Xenotransplantation. 2016;23:269–78.
37. Conesa C, Ríos A, Ramírez P, et al. Attitude of primary care professionals in Spain towards xenotransplantation. Transplant Proc. 2006;38:853–7.
38. Rubaltelli E, Burra P, Canova D, Germani G, Tomat S, Ancona E, Cozzi E, Rumiati R. People's attitude toward xenotransplantation: affective reactions and the influence of the evaluation context. Xenotransplantation. 2009;16:129–34. https://doi.org/10.1111/j.1399-3089.2009.00523.x.
39. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28:e12684. https://doi.org/10.1111/xen.12684. Epub 2021 Mar 7.
40. Padilla LA, Hurst DJ, Jang K, Rosales JR, Sorabella RA, Cleveland DC, Dabal RJ, Cooper DK, Carlo WF, Paris W. Racial differences in attitudes to clinical pig organ xenotransplantation. Xenotransplantation. 2021;28:e12656. https://doi.org/10.1111/xen.12656. Epub 2020 Oct 25.
41. Padilla LA, Rhodes L, Sorabella RA, Hurst DJ, Cleveland DC, Dabal RJ, Cooper DK, Paris W, Carlo WF. Attitudes toward xenotransplantation: a survey of parents and pediatric cardiac providers. Pediatr Transplant. 2021;25:e13851. https://doi.org/10.1111/petr.13851. Epub 2020 Oct 6.
42. Ríos A. Commentary on the manuscript: "Meta-analysis of public perception towards xenotransplantation". Xenotransplantation. 2020;27:e12588. https://doi.org/10.1111/xen.12588. Epub 2020 Mar 14.
43. Paris W, Jang K, Bargainer R, Colsch L, Nour B, Prus A, Cooper DKC. Psychosocial challenges of xenotransplantation: the need for a multi-: disciplinary; religion; and cultural dialogue. (letter to the editor/commentary). Xenotransplantation. 2016;23(5):335–7.

Public and Patient Opinions on Xenotransplantation and Cell Therapy

20

Kathryn S. Maxwell and Luz Padilla

Abbreviations

CHSS	Congenital Heart Surgeons Society
PHTS	Pediatric Heart Transplant Society
T1DM	type 1 diabetes mellitus
WHO	World Health Organization
XTx	xenotransplantation

Introduction

Several events from regulatory bodies like the World Health Organization (WHO) and other agencies have precipitated the need to assess perceptions of xenotransplantation (XTx) from stakeholders such as patients, providers, and the general public [1, 2]. In 2008, the WHO produced the Changsha Communiqué, a document relaying conclusions from the global consultation to establish regulatory requirements regarding future clinical trials for XTx [1]. The U.S. Department of Health and Human Services similarly issued guidance in 2016 concerning the source animal, product, preclinical, and clinical issues of XTx [2]. Instances such as pandemics and the tragic case of Baby Fae also raise questions about infectious disease

K. S. Maxwell (✉)
Department of Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: ksmaxwell@uabmc.edu

L. Padilla
Departments of Epidemiology and Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: lpadilla@uabmc.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_20

transmission risks and ethics and have the potential to influence attitudes across the world.

Baby Fae was the first infant subject of XTx and received a baboon heart in 1984 only to pass away within a month of receiving the xenograft [3]. Public assessment efforts have been made in the past with limited success, like Australia's Public Consultation in 2002 and 2004 [4]. Unfortunately, this effort to assess XTx attitudes was flawed in both design and process because it preemptively suggested that the desired outcome was to be "allowed to proceed." Furthermore, it failed to meaningfully engage and involve the public resulting in a complete moratorium of clinical trials from animal to human organ transplantation until 2009 [4]. In addition, Canada conducted an assessment in view of a proposed knowledge deficit model, where citizens were theorized to be more accepting of new ideas and technologies when given an opportunity to learn more about them. On the contrary, this assessment found that people had more favorable attitudes when they were unaware of XTx, and were more fearful and reluctant after further education [5]. This chapter will provide a broad overview of what is known about attitudes and perceptions of patients, providers and the general public of solid organ and cell XTx.

Solid Organ Acceptance

Hospital Staff

The literature on attitudes toward XTx is limited. However, Rios et al. in Spain have published some of the initial key papers on this topic. Rios et al. investigated hospital personnel attitudes to solid organ XTx in a hospital conducting pig to baboon liver XTx. Compared to a control group representing the general population, hospital employees had a less favorable attitude toward animal to human XTx (67% vs 74%; $p = 0.0378$) [6]. Factors related to favorable attitudes included younger age, male sex, physicians, attitudes of religion toward XTx, and partner's attitude to XTx. Attitudes are also more favorable among those who may need a transplant in the future and those in favor of cadaveric donation and living kidney and liver donation.

Stakeholders

Amin et al. (2008) in Malaysia surveyed stakeholders to determine relevant factors in the framework of attitudes toward XTx [7]. These stakeholders included scientists, producers, policy makers, NGOs, media, religious scholars, university students, and the general public. This publication describes a complex theoretical framework of concepts intertwined in attitudes such as engagement, attitude to nature, religiosity, perceived risks, perceived benefits, and perceived moral concerns. The results showed moderately positive attitudes toward XTx, with the most important factors being perceived benefits and perceived moral concern. Within the

layers and intricacies of the stakeholders' views, they were overall cautious toward XTx.

Meta-Analysis

Mitchell et al. conducted a meta-analysis that examined the existing literature from 1985 to 2019 related to public perception of XTx [8]. Of more than 200 publications identified, only 51 studies were included. Although 80% (41/51) of the included studies surveyed patients, only three included sufficient patient data for inclusion in the final meta-analysis. The remaining minority of studies in this meta-analysis pertained to students, healthcare workers and other stakeholders, revealing the dearth of information in the existing literature about broader public views and perceptions of XTx. The most important factors in supporting XTx were having a personal experience with a transplant, having perceived benefit of XTx, or a partner with a favorable attitude toward XTx, geographic area of a country where each participant lived, favorable attitude of an individual's religion towards XTx, favorable attitude towards cadaveric donation, and whether or not the participant was a current organ donor (Table 20.1). Conversely, the metanalysis also found the odds ratio comparison for variables that indicate less support or no support for XTx. Concerns included that a porcine xenograft would alter self-image, the expense of the procedure in relation to income, and perceived medical risk. In one particular study of nursing students, another factor of influence inversely related to support of XTx was education. The most important takeaways of this meta-analysis are that, until recently, the literature did not have as robust an understanding of patient and public attitudes toward XTx as previously assumed, and according to policy guidelines from the WHO and the International XTx Association, there may be insufficient information to initiate clinical trials.

Students

Padilla et al. conducted a cross-sectional study in 2017 among nursing students at one university in the Midwest U.S., piloting an electronic, anonymous, Likert scale

Table 20.1 Factors identified in meta-analysis associated with increased support for XTx

Factors	Odds ratio	Significance
Personal experience with transplantation	16.8	$p < 0.00$
Perceived benefit of the procedure	9.8	$p < 0.00$
Partners' positive attitude toward medical treatment	5.6	$p < 0.00$
Positive attitude toward deceased human organ donation	2.6	$p < 0.00$
Higher education level	2.4	$p < 0.00$
Engagement with biotechnology	2.1	$p < 0.00$

survey of XTx attitudes and beliefs [9]. Of the survey respondents, 90% were female, 80% were Caucasian, and 88% identified as Christian. This study found that knowledge of genetic modification of pig organ donors was very poor at 7%. Overall, a high number of respondents had positive attitudes toward human organ transplantation and the regression analysis showed that the willingness to accept a human organ, the medical risk factors, and psychosocial sequelae, were significantly associated with consideration of a pig organ. The biggest influencing factor for the acceptance of a pig organ was the psychosocial concern of potential negative self-image after receiving a xenograft.

Kidney Patients and Providers

The same group (Padilla et al.) refined the survey instrument piloted with the nursing students and conducted a subsequent study among kidney transplant patients (post-transplant and waitlist) and providers who care for kidney transplant patients [10]. The study was conducted in a large academic hospital in the Southern U.S. where kidney and heart pig to baboon XTx experiments are taking place. The majority of providers (80%) and patients (69%) had positive responses to XTx if the risks and results were likely to be similar to allotransplantation. However if these results were not comparable to allotransplantation, their acceptance dropped 30% for providers and 42% for patients. When considering XTx as a bridge to allotransplantation, the acceptance was higher among patients (41%) than providers (30%). This finding may suggest that patients are more open to alternatives that offer a change to the morbidity and mortality associated with their current treatments than their providers. The benefits for patients receiving a bridge xenograft would include no longer having to undergo dialysis, a potential decrease in wait-list mortality and perhaps a higher quality of life. Opposition to XTx as a bridge was associated with a reduced acceptance of XTx overall in this study. The majority of both patients and providers did not think the genetic modification of the pig influenced their acceptance. In light of the COVID-19 pandemic, only 13% of providers thought that there were zoonotic or public health risks associated with XTx, compared with 56% that were not concerned. Low public health concern is a promising finding for XTx as the risk of transmitting infectious diseases continues to be an initial drawback in discussions of XTx. There was a small proportion in both groups with psychosocial concerns about personality changes, interactions with others, and being less human, consistent with past studies. Overall, the logistic regression model found that the odds of patients accepting XTx were greater if there were no religious concerns and if they also were likely to use XTx as a bridge. Kidney providers rated the influence of religious beliefs in medical decisions (45% vs. 15%) and genetic engineering (43% vs. 25%) as being more important than patients ($p < 0.05$). Provider bias, or the presence of stereotypes that may affect the way in which providers frame information about XTx to their patients, can ultimately affect a patient's clinical decisions and uptake of the treatment under consideration. Furthermore, the existence of implicit provider biases has been associated with worse outcomes for patients [11].

To summarize, this study demonstrated that acceptance is high when there are no perceived religious barriers and because of that, it may be necessary to develop interventions that target implicit biases and address barriers regarding religious beliefs in order to increase acceptance towards XTx.

Public Perceptions

Concurrently, Hurst et al. recorded responses and perspectives from members of the public via five focus groups in 2019 [12]. Participants were surprised by the use of pigs as an organ source organism since they are generally considered to be dirty animals. Interestingly, they viewed the genetic engineering of the pigs positively and were reassured to know ordinary farm pigs and food source pigs would not be used for XTx. There was a high awareness of donor organ shortages and concerns of pig organ allocation vs. human organ allocation. Healthy people were more reluctant to accept a pig organ transplant compared to those who were sick, given that XTx outcomes were comparable to allotransplantation outcomes. There were no objections on religious or spiritual grounds, with a general consensus that a human life takes precedence over animal life, and that the animals should be treated humanely regardless. Other minor concerns included reservations about isolation measures for preventing potential infectious disease, the effect having a pig organ could have on a recipient's perceived humanity, and jokes and bullying particularly in the case of pediatric patients.

Congenital Heart Surgeons, Cardiologists, Nurses and Parents of Children with Congenital Heart Disease

To explore acceptance of cardiac XTx, Padilla et al. engaged the congenital heart disease (CHD) community, surveying members of the Congenital Heart Surgeons Society (CHSS) and Pediatric Heart Transplant Society (PHTS) [13]. It is possible that children with CHD may benefit from cardiac XTx more than adults with heart failure. This Likert survey was designed similarly to previous surveys assessing attitudes toward XTx. The acceptance of XTx was high in both of the provider groups if the risks and results were similar to allotransplantation. However if the results of XTx were not as comparable, acceptance dropped significantly. Forty-one percent of surgeons said that they would consider XTx as a bridge compared to only 17% of cardiologists. Over 80% of respondents in both groups agreed that if their patients were given a pig heart and it proved to work well, they would not recommend the patient undergo a second surgery to replace it with a human heart. If provider acceptance is only contingent on positive outcomes, this is a promising finding for overall acceptance and attitudes. The use of XTx as a primary treatment option for newborns with hypoplastic left heart syndrome received intermediate support from both groups of providers even if it offered no waitlist time.

The same survey (with some edited questions) of physicians nationwide who care for children with CHD was implemented to nurses and to parents of children with CHD [14]. Potential acceptance of XTx was high overall (75.3%) given that the outcomes were similar to allotransplantation and highest among physicians (86%) compared to nurses (71%) and parents (64%; $p < 0.001$). Despite being lower than the physicians, nurses' and parents' acceptance was still relatively high. Healthcare providers with moral and/or ethical hesitations to XTx were less likely to accept it compared to those who did not perceive any moral or ethical concerns (OR 0.04; CI 0.01–0.21). However, parents were more concerned with psychosocial aspects of XTx, such as how it would affect other peoples' interactions and perceptions of their child. Higher parental psychosocial concerns were associated with lower acceptance (OR 0.17; CI 0.03–0.80). In the overall cohort, respondents who reported religion as an influencing factor in medical decision making were less likely to accept XTx (OR 0.48; CI 0.24–0.97).

Racial Differences in Attitudes Among Parents

Only one study has assessed racial differences in attitudes to XTx [15]. Padilla et al. conducted this survey in 2019 adapting the previous Likert-scale instrument for distribution at outpatient clinics to parents of children with CHD and patients with kidney disease. Although Black kidney patients' acceptance of XTx was high (70%), it was lower than White kidney patients (91%; $p = 0.003$). White kidney patients were also more likely to accept XTx if the results were equivalent to allotransplantation (OR 4.14; CI 4.51–11.41) and less likely to be concerned with psychosocial changes when compared to Black kidney patients. White kidney patients were less likely to believe that receiving a pig organ would change their personality and change their interaction with others when compared to Black kidney patients. Over 15% of Black kidney patients had concerns of changes in personality and social interaction following XTx, compared to less than 6% of their White kidney patient counterparts ($p < 0.01$). There were no racial differences in attitudes to XTx among parents with children with CHD.

Cell Xenotransplantation Acceptance

As solid organ XTx presents a potential solution for organ shortages, cell XTx is exciting in its own right for, among other things, a new therapy for type 1 diabetes mellitus (T1DM) has been developed using porcine islet cells. This next section will provide an overview of the literature surrounding acceptance of cell XTx specifically. Like solid organ XTx, not many studies have explored cell XTx and, from the literature that does exist, overall acceptance for cells does not differ widely from organ acceptance.

The aforementioned attitudes towards cell XTx treatment of T1DM were assessed by Kögel et al. [16]. They conducted a focus group with T1DM patients to find out their concerns and barriers to acceptance. Concerns included disease transmission risks, immunosuppression risks, and the potential for no decrease in the disease burden. The use of pigs was not problematic to the patients, but given the complexity of the IFC process, particularly in XTx, it was suggested personal consultations be offered during the consent process. The most important factor tied to acceptance for cell therapy in T1DM is to become independent of insulin or to decrease the disease burden for T1DM.

It is interesting that patients are sometimes more open to novel procedures than their healthy counterparts and providers [13], which is telling about the burden of disease for heart failure, kidney failure, T1DM, etc. Susanne Lundin observed that patients have a desire to be healthy and are willing to test an "unnatural technique" if that is what it takes to be healthy even if it involves psychological distress. One patient even expressed feeling like cell xenotransplantation would allow them a chance at living a normal life, and that being healthy and living a normal life was their highest wish [17].

Martínez-Alarcón et al. surveyed kidney and liver patients on the transplant waitlist about islet cell and tissue XTx [18]. In a group of 373 respondents, there was higher acceptance among those with formal education, those with children, and those who were married.

Abalovich et al. conducted a survey in Argentina of staff in a hospital that had performed cell XTx and compared attitudes with staff members of another hospital that had not conducted XTx [19]. The focus of the survey was concerning islet cell and kidney XTx. Acceptance was higher among the staff where the procedure had taken place compared to the staff acceptance at the other hospital. This suggests that acceptance could increase further as XTx becomes more familiar and common.

Xiao et al. explored attitudes toward cell XTx for cardiac repair [20]. They found that the respondents were more favorable to cell XTx than to whole organ XTx. The primary concern was immunorejection and immunosuppression following engraftment, a topic somewhat unique to this article.

Ríos et al. surveyed acceptance of cell XTx for treatment of diabetes among 3633 Spanish adolescents [21]. They found a high level of acceptance of animal cells among those who also accepted deceased organ donation and XTx of solid organs and animal tissues.

Abalovich et al. focused on acceptance of pig islet cells in a Latin American diabetic population [22]. Interestingly, this study took place during the H1N1 outbreak and acceptance was not affected by the outbreak. They found 79% acceptance in the setting of dependent and non-insulin dependent individuals. Also 57% indicated acceptance even with the potential transmission of viral infections could not be assured, decreasing the barrier of possible zoonotic risk. Both of these findings are of current relevance and interest due to the COVID-19 pandemic.

Conclusion

Acceptance is high for both organ and cell XTx, though higher for cell XTx. This acceptance appears to be dependent on the success of the treatment in improving the patient's well-being and quality of life after the xenograft as compared to current allograft outcomes. It is also contingent on mitigation of risks surrounding infectious disease transmission and the psychosocial aspects of receiving a xenograft. However, the existing body of literature on attitudes and acceptance is limited. As noted with the meta-analysis [8], there is only a small number of studies so far, which prohibits comparative analysis due to the lack of standardization for the survey instruments. Furthermore, how the COVID-19 pandemic is shaping zoonotic risk aptitude is completely unknown. Many of the studies highlighted in this chapter have been published by the same group, Padilla et al., because (1) a limited number of studies in the area as mentioned in the meta-analysis findings above; (2) a similar survey was used across various populations and stakeholders which is helpful to make comparisons across groups and findings. While there is no minimum or maximum number of studies necessary before clinical trials of XTx procedures can occur, more studies are needed in this field, particularly in the communities that may be exposed to the clinical trials, as these clinical trials may happen soon [23]. In addition, a validated and standardized tool designed for use in a variety of contexts and populations would be helpful in gaining more insight into attitudes and acceptance as this treatment option approaches clinical viability and commonality. A standardized approach would be useful in creating opportunities for comparative analysis. The concerns of animal rights organizations and psychosocial and religious concerns may need to be addressed further in the community, perhaps through education.

References

1. The Changsha Communiqué. First WHO global consultation on regulatory requirements for xenotransplantation clinical trials: Changsha, China, 19–21 November 2008. Xenotransplantation. 2009;16(2):61–3. https://doi.org/10.1111/j.1399-3089.2009.00520.x
2. US Department of Health and Human Services. Source animal, product, preclinical, and clinical issues concerning the use of Xenotransplantation products in humans: guidance for industry. 2016. https://www.fda.gov/media/102126/download. Accessed 7 Jan 2022.
3. Bailey LL, Nehlsen-Cannarella SL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA. 1985;254(23):3321–9. https://doi.org/10.1001/jama.1985.03360230053022.
4. Cook. What constitutes adequate public consultation?: xenotransplantation proceeds in Australia. J Bioethical Inq. 2011;8(1):67–70. https://doi.org/10.1007/s11673-010-9269-8.
5. Cremona M, editor. New technologies and EU law. Oxford, New York: Oxford University Press; 2017. p. 9–37.
6. Ríos A, Conesa C, Ramírez P, et al. Hospital personnel faced with organ xenotransplantation: an attitudinal survey in a hospital with a pre-clinical liver xenotransplantation program. Xenotransplantation. 2006;13(5):447–54. https://doi.org/10.1111/j.1399-3089.2006.00334.x.
7. Amin L, Hashim H, Mahadi Z, Che Ngah A, Ismail K. Determinants of stakeholders' attitudes to xenotransplantation. Xenotransplantation. 2018;25(6):e12430. https://doi.org/10.1111/xen.12430.

8. Mitchell C, Lipps A, Padilla L, Werkheiser Z, Cooper DKC, Paris W. Meta-analysis of public perception toward xenotransplantation. Xenotransplantation. 2020;27(4):e12583. https://doi.org/10.1111/xen.12583.
9. Padilla LA, Hurst DJ, Jang K, Bargainer R, Cooper DKC, Paris W. Acceptance of xenotransplantation among nursing students. J Evid Based Soc Work. 2021. https://doi.org/10.1080/26408066.2021.1938775.
10. Padilla LA, Hurst DJ, Lopez R, Kumar V, Cooper DKC, Paris W. Attitudes to clinical pig kidney xenotransplantation among medical providers and patients. Kidney360. 2020;1(7):657–62. https://doi.org/10.34067/KID.0002082020.
11. Huibregtse BM, Boardman JD. Provider bias as a function of patient genotype: polygenic score analysis among diabetics from the Health and Retirement Study. Obes Sci Pract. 2018;4(5):448–54. https://doi.org/10.1002/osp4.293.
12. Hurst DJ, Padilla LA, Cooper DKC, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28:e12684. https://doi.org/10.1111/xen.12684.
13. Padilla L, Sorabella RA, Carlo WF, Dabal RJ, Rhodes L, Cleveland DC, Cooper DK, Paris W. Attitudes to cardiac xenotransplantation by pediatric heart surgeons and physicians. World J Pediatr Congenit Heart Surg. 2020;11(4):426–30. https://doi.org/10.1177/2150135120916744.
14. Padilla LA, Rhodes L, Sorabella R, Hurst DJ, Cleveland D, Dabal RJ, Cooper DK, Paris W, Carlo WF. Attitudes toward xenotransplantation: a survey of parents and pediatric cardiac providers. Pediatr Transplant. 2020;00:e13851. https://doi.org/10.1111/petr.13851.
15. Padilla LA, Hurst DJ, Jang K, Rosales JR, Sorabella RA, Cleveland DC, Dabal RJ, Cooper DKC, Carlo WF, Paris W. Racial differences in attitudes to clinical pig organ Xenotransplantation. Xenotransplantation. 2021;28:e12656. https://doi.org/10.1111/xen.12656.
16. Kögel J, Thiersch S, Ludwig B, Seissler J, Marckmann G. What does it take to consent to islet cell xenotransplantation?: insights from an interview study with type 1 diabetes patients and review of the literature. BMC Med Ethics. 2021;22(1):37. Published 2021 Apr 1. https://doi.org/10.1186/s12910-021-00607-5.
17. Lundin S. Creating identity with biotechnology: the xenotransplanted body as the norm. Public Underst Sci. 2002;11:333–45. https://doi.org/10.1088/0963-6625/11/4/302.
18. Martínez-Alarcón L, Ríos A, Pons JA, et al. Attitudes toward islet cell and tissue xenotransplantation among kidney and liver patients on the transplant waiting list. Transplant Proc. 2010;42(8):3098–101. https://doi.org/10.1016/j.transproceed.2010.05.071.
19. Abalovich A, Matsumoto S, Wechsler CJ, et al. Level of acceptance of islet cell and kidney xenotransplants by personnel of hospitals with and without experience in clinical xenotransplantation. Xenotransplantation 2017;24(4). https://doi.org/10.1111/xen.12315.
20. Xiao YF, Min JY, Morgan JP. Immunosuppression and xenotransplantation of cells for cardiac repair. Ann Thorac Surg. 2004;77(2):737–44. https://doi.org/10.1016/j.athoracsur.2003.08.036.
21. Ríos A, Febrero B, López-Navas A, et al. Xenotransplantation of cells for diabetes: is there a good acceptance rate among Spanish adolescents? Transplant Proc. 2011;43(1):55–7. https://doi.org/10.1016/j.transproceed.2010.11.007.
22. Abalovich A, Wechsler C, Lara S, Bervottini M. Pig islet xenotransplantation acceptance in a Latin-American diabetic population. Xenotransplantation. 2010;17(4):263–6. https://doi.org/10.1111/j.1399-3089.2010.00598.x.
23. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;22:1037–53. https://doi.org/10.1111/ajt.16930.

Potential Applicability of Cardiac Xenotransplantation in Pediatrics: Just Around the Corner

21

Waldemar F. Carlo and David C. Cleveland

Introduction

With scientific advances in xenotransplantation detailed in this book, the time has arrived for consideration of clinical application. The field of pediatric heart failure and transplantation offers great potential as an early adopter of xenotransplantation. Infant heart transplantation in particular offers lessons from one of the earliest and most controversial xenotransplants performed. In 1985, Leonard Bailey and his team in Loma Linda transplanted a baboon heart into Baby Fae, a newborn with hypoplastic left heart syndrome (HLHS), who would go on to survive 20 days [1]. With autopsy studies revealing only "traces of cellular rejection," the authors suggested the cardiac xenograft injury may have resulted from antibody or complement mediated rejection potentially secondary to blood type incompatibility. While clinical advances with cardiac xenotransplantation ceased, the team at Loma Linda became pioneers in infant allotransplantation for HLHS, demonstrating excellent long-term outcomes [2].

In this article, we review why children, and in particular infants, may have immunologic advantage for accepting a xenograft, which patients may be most appropriate recipients, and the potential next steps in this patient cohort.

W. F. Carlo (✉)
Department of Pediatrics, University of Alabama Birmingham, Birmingham, AL, USA
e-mail: wfcarlo@peds.uab.edu; wfcarlo@uabmc.edu

D. C. Cleveland
Department of Cardiovascular Surgery, University of Alabama Birmingham, Birmingham, AL, USA
e-mail: dcleveland@uabmc.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_21

Infants and Neonates

Infant allotransplant grafts as a group demonstrate some of the best outcomes in solid organ transplant recipients. The neonatal (< 1 month old) experience from Loma Linda reports a median graft survival greater than 25 years [2] which exceeds that of adult solid organ transplants [3] as well as pediatric outcomes in heart (15 years) [4], kidney [5], liver [6], and lung [4] transplantation. Recent national data likewise reports a median survival of 22 years for infants (<1 year old) receiving a heart transplant [7]. When accounting for patients with peri-operative and early mortality, long-term outcomes conditional on 1-year survival exceed the statistics reported above and indeed may still be non-calculable [8].

The age-related advantages in heart allotransplantation may form the basis of optimism for similar advantages in infant xenotransplantation. If xenotransplantation works, it may work best in infants. There are general advantages of the infant immune system that are reviewed in greater depth elsewhere [9–11]. Newborns have deficiencies in both the adaptive and innate immune system. Complement components and regulatory proteins are decreased. The adaptive immune system may favor tolerogenesis with increased regulatory T cells, a higher balance of anti- versus pro-inflammatory components, and decreased or ineffective cytotoxic T cells and B cells. Furthermore, thymectomy, which occurs with heart transplant surgery, results in profound depletion of T cell numbers and diversity.

A specific and well-known example of the advantage of the infant immune system is exemplified by blood group incompatible allotransplantation. Infants lack polysaccharide antibodies such as anti-blood group antibodies early in life, as these develop later in the first year. Reasoning that no humoral response against blood group antigens would occur, Lori West pioneered intentional ABO incompatible (ABOi) allotransplantation in the 1990s as a response to high waitlist mortality in infants of blood group O [12]. These children subsequently did not develop antibodies to donor blood type antigens suggesting an acquired donor-specific B-cell tolerance [13]. Long term, infants with an ABOi allograft have clinical outcomes that are at least equivalent to those of ABO compatible transplanted infants [14]. Success in blood group incompatible allotransplantation in infants may have important implications for xenotransplantation.

Candidates for Xenotransplantation

The characteristics of the infant immune system noted above support the contention that xenotransplantation has the best chance of meaningful success in infants. Specific infant candidates need to be identified. These infants would have high risk of short-term mortality with lack of reliable options for bridging to an allotransplant. In this scenario, clinical xenotransplantation would seem justified as an alternative strategy for hemodynamic support.

Severe cardiac failure in the infant may represent such a scenario. Older children can be supported quite successfully with mechanical circulatory support (MCS) including ventricular assist devices (VADs). However, MCS outcomes with VADs or extracorporeal membranous oxygenation (ECMO) in infants have historically been very poor. For example, Almond et al. reported that 64% of infants under 5 kg died within 2 months of receiving a Berlin Heart VAD [15]. Another study with this same device reported 89% mortality after stage I palliation for single ventricle congenital heart disease [16], a subgroup of patients in whom ECMO support (when done for hemodynamic purposes as opposed to hypoxemia) has similarly poor outcomes [17]. While outcomes with MCS in single ventricle infants might improve with experience and selective use [18], infants with single ventricle heart disease after stage I palliation continue to have the poorest outcomes (60% mortality at 2 months) with VAD support in a recent PediMACS registry report [19]. Need for biventricular assist device support also is associated with poor outcomes in infants [20].

To compound the problem of poor survival after MCS use in infants, this age group also faces long wait times for allotransplantation. Infants in general have the highest waitlist mortality among heart candidates [21]. Infants on the waitlist are likely a less critically ill cohort than the entire cohort of those receiving MCS (covered in the prior paragraph). This notwithstanding, waitlisted infants less than 5 kg with congenital heart disease and MCS have a 50% 2-month mortality rate [22]. Among infants in general, the current schema for waitlisting and allotransplantation yields less than 50% 1 year survival among those in any of the following categories: smallest size (< 2.5 kg), ECMO, CHD + small size, and CHD + ventilator [23]. These outcomes suggest that infants with severe cardiac failure, especially those needing MCS, those with failed stage I single ventricle palliation, and those with the most illness severity, may be the most appropriate candidates for consideration of alternative therapies to bridge to allotransplantation.

Much of the conversation regarding xenotransplantation and infants has focused on HLHS because of the large potential population of these infants, the historical experience with primary allotransplantation, and guarded long term outcomes. However, outcomes on the waitlist are actually worse for infants with non-HLHS congenital heart disease [24]. Significant atrioventricular valve regurgitation and ventricular dysfunction may be particularly disadvantageous in the setting of single ventricle heart disease. Pulmonary atresia with intact ventricular septum (PA/IVS) and right ventricular dependent coronary circulation is a particularly high risk anatomy. ECMO support in this circulation can lead to coronary ischemia secondary to right ventricular decompression. The discussion should extend beyond congenital heart disease as well. Infants with restrictive or hypertrophic cardiomyopathy demonstrate significant mortality after listing, perhaps in part due to poor MCS support options in this group [25]. Infants with intractable arrhythmia may also be inadequately supported with current MCS options.

Children of All Ages

While infants may face the best chances for success in xenotransplantation, there are situations common to heart transplant candidates in general in which this therapy can be considered.

VADs can be used as destination therapy in patients with end-stage heart failure who are not candidates for cardiac transplantation [26]. Improving outcomes with such devices results in meaningful gains in quality of life and life expectancy for select patients. Unfortunately, smaller children who may be considered for destination therapy remain ineligible for adult VADs due to size constraints. As such, children who are deemed not candidates for allotransplantation and who cannot receive an outpatient-compatible VAD may be considered possible candidates for xenotransplantation as destination therapy. Specific, albeit rare, situations for children with end stage heart failure could include high risk social candidacy (medication nonadherence for example, lack of adequate social support infrastructure), coexisting terminal condition, and extreme allosensitization.

Highly sensitized patients warrant consideration beyond destination therapy. First, we would expect highly sensitized patients to not have preformed antibodies against the pig graft and preliminary evidence exists supporting this [27]. Second, xenotransplantation could increase the chance of finding a matching allograft simply by extending a patient's survival on the waitlist. Furthermore, some evidence exists that highly sensitized patients may experience a decline in anti-HLA antibody strength during the first several months post-allotransplant [28].

Finally, early allograft failure could be another scenario in which xenotransplantation could be considered as VADs may not be suitable in the immunosuppressed state, mortality is high [8], and clinicians may be hesitant to retransplant for fear of recurrence.

Possible Consequences of Xenotransplantation

While xenotransplantation may be technically doable and immunosuppressive regimens may permit longer term success, there can also be unintended consequences. Waitlist times remain long, especially for infants and young children [29]. Successful bridging of more patients with a xenograft would only extend those times for all candidates in that size range. If the intent is to bridge to transplant, there is no current criteria for high priority listing in the current Organ Procurement and Transplantation Network policy (https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf). These patients would be disadvantaged compared to VAD recipients if they would not qualify for status 1A (high priority) listing. We would suggest that the initial patient with a bridging xenograft be granted status 1A by exception while hospitalized.

Another possible unintended consequence of xenotransplantation would be development of allosensitization which could jeopardize candidacy for subsequent

allotransplantation. While there is no evidence that this will be a problem, we are initiating a protocol to help confirm the feasibility of this. We intend to bridge juvenile baboons with a genetically engineered pig heart for 3 months followed by allotransplantation from a same species donor.

Next Steps

Recent steps forward in clinical xenotransplantation have been reported. At The University of Maryland Medical Center, researchers received compassionate use authorization from the Food and Drug Administration to perform a porcine xenotransplant in a 57-year old man with end stage cardiac disease (Mohiuddin MM, Griffith BG, 2022, unpublished). At the University of Alabama at Birmingham, researchers working under an institutional review board approved protocol transplanted a porcine kidney into a brain dead human [30]. Hyperacute rejection did not occur. These incremental advances in clinical xenotransplantation may serve as possible investigative templates for researchers who can apply these models in infants with heart failure. Further considerations would include defining: (a) the specific genetically engineered pig that is of appropriate size and is rapidly available, (b) a clinically acceptable regimen of induction and maintenance immunosuppression, (c) a protocol to monitor xenograft function using echocardiography (endomyocardial biopsy is a challenge in a small infant) and serum biomarkers, and (d) insurance coverage for clinical care after xenotransplantation. We believe that xenotransplantation has evolved to the point where laboratory researchers and clinicians should accelerate collaborative efforts to ensure appropriate entry of this therapy for infants and children of advanced heart failure.

References

1. Bailey LL, Nehlsen-Cannarella SL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA. 1985;254:3321–9.
2. John MM, Razzouk AJ, Chinnock RE, et al. Primary transplantation for congenital heart disease in the neonatal period: long-term outcomes. Ann Thorac Surg. 2019;108:1857–64.
3. Rana A, Godfrey EL. Outcomes in solid-organ transplantation: success and stagnation. Tex Heart Inst J. 2019;46:75–6.
4. Chambers DC, Perch M, Zuckermann A, et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult lung transplantation report - 2021; focus on recipient characteristics. J Heart Lung Transplant. 2021;40:1060–72.
5. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 annual data report: kidney. Am J Transplant. 2017;17(Suppl. 1):21–116.
6. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 annual data report: liver. Am J Transplant. 2018;18(Suppl. 1):172–253.
7. Rossano JW, Cherikh WS, Chambers DC, et al. The registry of the International Society for Heart and Lung Transplantation: twentieth pediatric heart transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant. 2017;36:1060–9.

8. Dipchand AI, Rossano JW, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: eighteenth official pediatric heart transplantation report--2015; focus theme: early graft failure. J Heart Lung Transplant. 2015;34:1233–43.
9. Bikhet M, Morsi M, Hara H, et al. The immune system in infants: relevance to xenotransplantation. Pediatr Transplant. 2020;24:e13795.
10. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015;282:20143085.
11. Platt JL, Cascalho M, West L. Lessons from cardiac transplantation in infancy. Pediatr Transplant. 2009;13:814–9.
12. West LJ, Pollock-Barziv SM, Dipchand AI, et al. ABO-incompatible heart transplantation in infants. N Engl J Med. 2001;344:793–800.
13. Fan X, Ang A, Pollock-Barziv SM, et al. Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. Nat Med. 2004;10:1227–33.
14. Urschel S, Ballweg JA, Cantor RS, et al. Clinical outcomes of children receiving ABO-incompatible versus ABO-compatible heart transplantation: a multicentre cohort study. Lancet Child Adolesc Health. 2021;5:341–9.
15. Almond CS, Morales DL, Blackstone EH, et al. Berlin heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation. 2013;127:1702–11.
16. Weinstein S, Bello R, Pizarro C, et al. The use of the Berlin heart EXCOR in patients with functional single ventricle. J Thorac Cardiovasc Surg. 2014;147:697–704. discussion -5
17. Allan CK, Thiagarajan RR, del Nido PJ, Roth SJ, Almodovar MC, Laussen PC. Indication for initiation of mechanical circulatory support impacts survival of infants with shunted single-ventricle circulation supported with extracorporeal membrane oxygenation. J Thorac Cardiovasc Surg. 2007;133:660–7.
18. Philip J, Powers E, Machado D, et al. Pulsatile ventricular assist device as a bridge to transplant for the early high-risk single-ventricle physiology. J Thorac Cardiovasc Surg. 2021;162:405–13 e4.
19. Peng DM, Koehl DA, Cantor RS, et al. Outcomes of children with congenital heart disease implanted with ventricular assist devices: an analysis of the pediatric interagency registry for mechanical circulatory support (Pedimacs). J Heart Lung Transplant. 2019;38:420–30.
20. Zafar F, Jefferies JL, Tjossem CJ, et al. Biventricular Berlin heart EXCOR pediatric use across the United States. Ann Thorac Surg. 2015;99:1328–34.
21. Colvin M, Smith JM, Ahn Y, et al. OPTN/SRTR 2020 annual data report: heart. Am J Transplant. 2022;22(Suppl. 2):350–437.
22. Conway J, Cantor R, Koehl D, et al. Survival after heart transplant listing for infants on mechanical circulatory support. J Am Heart Assoc. 2020;9:e011890.
23. Rizwan R, Zafar F, Chin C, Tweddell J, Bryant R 3rd, Morales D. Listing low-weight or ill infants for heart transplantation: is it prudent? Ann Thorac Surg. 2018;106:1189–96.
24. Guleserian KJ, Schechtman KB, Zheng J, et al. Outcomes after listing for primary transplantation for infants with unoperated-on non-hypoplastic left heart syndrome congenital heart disease: a multi-institutional study. J Heart Lung Transplant. 2011;30:1023–32.
25. Dipchand AI, Naftel DC, Feingold B, et al. Outcomes of children with cardiomyopathy listed for transplant: a multi-institutional study. J Heart Lung Transplant. 2009;28:1312–21.
26. Fukunaga N, Rao V. Left ventricular assist device as destination therapy for end stage heart failure: the right time for the right patients. Curr Opin Cardiol. 2018;33:196–201.
27. Li Q, Hara H, Banks CA, et al. Anti-pig antibody in infants: can a genetically engineered pig heart bridge to allotransplantation? Ann Thorac Surg. 2020;109:1268–73.
28. Patel JK, Coutance G, Loupy A, et al. Complement inhibition for prevention of antibody-mediated rejection in immunologically high-risk heart allograft recipients. Am J Transplant. 2021;21:2479–88.
29. Williams RJ, Lu M, Sleeper LA, et al. Pediatric heart transplant waiting times in the United States since the 2016 allocation policy change. Am J Transplant. 2022;22:833–42.
30. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;22:1037–53.

The Implications of Living as a Xenograft Recipient

22

Samantha Floyd and Wayne D. Paris

Abbreviations

IXA	International Xenotransplant Association
UAB	University of Alabama at Birmingham
WHO	World Health Organization
XTx	Xenotransplantation

Introduction

The progress of xenotransplantation (XTx) research along with the recent porcine kidney surgeries on brain dead individuals in Alabama, New York, and heart surgery on an alive individual in Maryland portends that clinical trials may be imminent [1–4]. We no longer should think about the possibility of pig-to-human organ trials, but rather anticipate them as probable in the near future [5]. The question is, are programs as prepared to address patient and family psychosocial issues as surgeons are to implant the organ? To answer that question, this chapter will explore XTx in relation to allotransplantation, report the attitudes and beliefs of patients, medical staff, and the public from a university program in preparation for clinical trials, and provide a research outline to identify and report their identified psychosocial concerns relevant to adult kidney patient and pediatric family care going forward.

S. Floyd
Pediatric Cardiology, Heart Transplant & Mechanical Device Social Worker, Children's Hospital of Alabama, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: Samantha.Floyd@childrensal.org

W. D. Paris (✉)
School of Social Work, Abilene Christian University, Abilene, TX, USA
e-mail: wayne.paris@acu.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_22

Relation to Allotransplantation

One of the most important potential benefits of XTx is that it removes the uncertainty of whether or not a donor organ will become available [5]. If XTx clinical trials were to be successful, donor availability will no longer be centered on having to choose candidates based on maximizing the use of a scarce societal resource. An unlimited supply of donor organs would afford an immediate opportunity to thousands of individuals who otherwise would die from organ failure, absent a donor organ assuming XTx offered similar results to allotransplantation. This would mean a reduction in medical complications from extended patient wait-list times, and the stress related to the uncertainty of organ availability [6]. However, it is important to note that an unlimited supply of donor organs does not alleviate or negate the importance of psychosocial problems that any form of organ transplantation may present to the recipient.

Medical compliance is a concern, regardless of the source of the donor. The literature has identified medical compliance as the only 'shared' area of importance to both allotransplantation and XTx [7]. The ability and willingness to submit for lifelong monitoring, based on the current state of knowledge and suggested protocols for those undergoing XTx clinical trials is critical given the potential infection risks the recipient may present to family, friends, and the broader community [8]. This raises the question about the choice made by the University of Maryland Medical Center group in the first heart XTx in choosing a candidate rejected for allotransplantation at multiple transplant programs for his history of noncompliance with medical recommendations [1]. Selecting a candidate for XTx with a history of noncompliance was a monumental decision. If the patient had survived and left the hospital, then this would have brought into question the extent to which any future noncompliance could have jeopardized his ongoing medical treatment, and limited the information expected to be gained from clinical trials. Further, it raises the question for consideration the role of non-compliance in limiting the number of potential pig organs a patient might receive? The far-reaching question of their candidate selection influence on public opinion about XTx as a clinical option has yet to be fully determined.

Additional areas of 'possible' psychosocial problems for XTx recipients and their families identified in earlier literature were: religious concerns; individual perception of 'humanness'; animal rights concerns; stress of public opinion; and public health concerns [7, 9]. The limitation with these early studies between allotransplantation and XTx is that they were based on the moral and ethical questions that the early XTx literature addressed [7, 9]. One initial review of psychosocial factors between allotransplantation and XTx found, 'the reality is that the views and beliefs of potential xenotransplant recipients and families have not been widely explored to the extent necessary for widespread introduction of clinical trials' [7]. Consistently the World Health Organization (WHO) and International Xenotransplant Association (IXA) have held that 'it is important to evaluate and determine whether the existing knowledge is sufficient to recruit patients, with the reasonable expectation that the public is in full agreement to do so' [10 , p. 278]. Views need to document the

involvement from relevant local voices, rather than general public studies from groups unlikely to be involved in clinical trials.

Reports that are more recent would suggest that the information about public agreement to support XTx clinical trials continues to be lacking. Although the vast majority of public studies to date show the public's general acceptance of XTx, a 2019 meta-analysis of the public perception literature from 1985–2019 found that '… the bulk of what we really know about attitudes toward XTx comes from students, stakeholders, and hospital staff' [11 , p. 2]. Only three patient studies contained adequate information that allowed for comparative analysis of their results. The authors summarized the problem this way, '… more directed research is necessary from individual programs to achieve sufficient understanding of the attitudes of patients and the broader public, and the level of risk that is acceptable …' [p. 6]. In other words, only through center and locality specific information will the appropriate level of local involvement expected by WHO and IXA be achieved, as well as the guidance necessary to assess and appropriately anticipate local psychosocial needs. Unfortunately, there is no set standard of what exactly 'appropriate level' means; however, to date UAB has been the only center to follow through with a multi-dimensional program of qualitative and quantitative studies in an attempt to further clarify the level of understanding and involvement that may be necessary.

Patient, Staff, and Public Attitudes Towards Potential Clinical Trials

In an attempt to meet WHO and IXA expectations for the assessment of local opinions, a series of quantitative surveys and focus groups were conducted at the University of Alabama at Birmingham (UAB) in 2018–2019. The specific purpose of these studies was to explore and report staff, patient, and public attitudes towards the possibility of clinical trials of pig-to-human adult kidney and pediatric heart transplantation [12–16].

Overall quantitative survey data analysis found that medical personnel were significantly more agreeable to XTx, than were patients ($p < 0.05$) (see Table 22.1), and a majority supportive of the procedure (80% + vs 60%+, respectively. Kidney healthcare providers rated religious concerns as significantly more important than their adult patients ($p < 0.05$). Across adult patient and pediatric parent groups, religious concerns, moral and ethical questions were predictive of willingness to accept a XTx. In pediatric parents, apprehension about how others would interact with their child were they to receive a xenograft was of additional predictive value of willingness to accept a pig organ.

The influence of psychosocial concerns were dissimilar depending on the comparison. A very low rate of kidney medical providers and patients expressed any psychosocial concerns (<15%), while pediatric cardiac parents were significantly more likely to have them ($p < 0.01$). Only pediatric parents and cardiac care providers had a high rate of concern about the genetic modifications (approximately 50%) required in a pig xenograft.

Table 22.1 Quantitative comparison of patient, staff, and public attitudes towards XTx from the UAB program/population in preparation for clinical trials

Groups studied	n=	Findings	References
Kidney patients and medical providers	40 medical staff 163 patients	– 80% staff/69% patients approve of XTx. – Kidney staff rated religious beliefs and genetic engineering as sig (p,0.05) more important than patients in making medical decisions. – < 15% of both groups had any concerns about potential personality changes, how others would interact with them, being less human, or had moral or ethical concerns. – Logistic regression found: (a) that the odds of patients accepting XTx were 25 times greater if they had no religious concerns; and (b) but acceptance were less likely if they were not willing to use as a bridge to allotransplantation.	[12]
Pediatric parents and cardiac care providers	134 physicians 62 nurses 101 parents	– Differential rates of XTx acceptance: 86% physicians; 71% nurses; 64% parents. – Approximately 50% of all respondents believed that genetic modification would influence their decision to accept. – Psychosocial concerns were few among all groups, but parents had a sig ($p < 0.01$) higher proportion who had concerns about personality changes, interaction with others, as well as being undecided. – Regression analysis found that those less likely to accept XTx were: (a) religious influence on medical decisions and those who would not use as a bridge to allotransplantation; (b) providers who reported moral or ethical concern; and, (c) parents who expressed concern with how other people may interact with their child.	[13]
Kidney patients and parents of pediatric heart patients	148 kidney patients 97 parents of children with congenital heart disease	– White kidney patients were sig ($p < 0.03$) more agreeable to XTx than black patients (91 vs 70%, respectively). – Regression analysis found that: (a) when white kidney patients were compared to black patients they were 4 times more likely to accept XTx if results were similar to allotransplantation, and less likely to be concerned with any potential psychosocial problems; and (b) black parents were more concerned that XTx would change their child's personality and social interaction.	[14]

The comparison of pediatric parent and kidney patients found a major concern from Black recipients. Significantly ($p < 0.03$) more White kidney patients would consider a XTx than Black patients (91% vs 70%, respectively). Regression analysis found that White patients were four times more likely to accept XTx if the results were 'similar' to human organ transplantation and less likely to have any

psychosocial concerns regarding the procedure. Black parents were more concerned than White parents that XTx would change their child's personality and social interaction with friends and family.

Qualitative public perception and attitudes from the representative community focus groups are found in Table 22.2 [15, 16]. There was wide agreement among all community participants that XTx was an acceptable use of a pig organ. However, there were identified concerns about their use for medical purposes, rather than human food consumption. Also, animal ethics, organ allocation logistics, concerns about quality of life, and acceptance by certain theological traditions were raised as potential concerns.

An in-depth analysis of the theological focus group found a somewhat more concise picture of potential concerns. The themes identified personal feelings about the proposed procedure, specific religious/theological issues, social concerns, and the pig as an animal. It was virtually unanimous from the local sample of Birmingham's clergy that there were no specific religious barriers to acceptance of a pig xenograft, although they did have a tendency to talk about 'other religions' potential concerns while identifying few, if any of their own. However, they did struggle to reconcile their conflicting feelings about the use of the pig as a food source (which they all supported) and its use for transplantation. They also discussed animal stewardship in light of Judeo-Christian scripture. As expected, they discussed what could be personal ramifications for the recipient, society, and future generations that could result from XTx.

Table 22.2 Focus group comparison of patient, staff, and public attitudes towards XTx from the UAB patient and broader community groups in preparation for clinical trials

Focus groups (n=)	Findings	References
Religious leaders (n = 10) Organ procurement staff (n = 5) Patients/parents of patients (n = 9) Business leaders (n = 3)	– Wide agreement among participants that XTx is an exciting and acceptable option as an organ alternative. – Concerns were expressed re: Issues of animal ethics; stigma regarding how pigs are viewed in society; organ allocation logistics; quality of life after XTx and how XTx would be accepted by certain theological traditions.	[15]
Religious leader in depth analysis (n = 10)	– Four major themes identified: Baseline personal feelings about XTx; religious/theological issues; social issues; and, comments in regard to the pig as an animal. – Overall, were receptive to the idea of XTx and expressed no religious barriers to accepting a pig xenograft, yet struggled to reconcile conflicting feelings surrounding pig consumption, animal stewardship in light of Judeo-Christian scripture, and what XTx may entail for the recipient, society, and future generations.	[16]

Psychosocial Implications for the Prospective Patient and Family

A majority of the those surveyed in the UAB study supported (minimum of 60%+; ranged from a high of 80% + to a low of 60% depending on the group surveyed) the possibility of XTx as a clinical option. When coupled with a similar level of support from the focus group participants, it is possible that there may be adequate acceptance of and support for XTx to implement clinical trials. However, not everyone was willing to consider a pig organ, and attitudes and concerns varied significantly between different ethnicities and patient groups. This suggests that when compared to their adult kidney and pediatric cardiac allotransplant patients, clinical trials will present medical and ancillary staff with unique assessment and treatment challenges. The question being, is the current level of information about public, patient, and staff views about XTx as reported by UAB sufficient to help meet the WHO, IXA, and FDA expectations and provide meaningful guidance to meet those unique needs? To help answer that question, a single-system research design might be one useful approach to consider (see the section "Suggested Clinical Trial Research Design").

One major area of potential concern is with the level of individual religious concerns and their potential influence on willingness to consider XTx. Analysis of both kidney patients and pediatric parents has found those with higher number of religious concerns, and moral and ethical questions were predictive of an unwillingness to consider a XTx. This would suggest that both the kidney and pediatric heart programs might want to consider collaborating with the individual patient's clergy and keep them actively involved through the entire assessment and post-surgical clinical trial process.

Though rare within allotransplantation, this may theoretically result in having an otherwise good medical candidate refuse to be considered. A decision, though unusual within allotransplantation (except in rare instances such as Jehovah's Witnesses and blood transfusions which has its own concessions and varies in methodology in the adult population versus the pediatric population) may have a significant impact for both the patient and immediate family. For example, what would be the impact for the patient who chose to proceed with XTx, but family and friends did not agree that it was theologically appropriate. Given the documented importance of social support in the success for allotransplantation, any factor that may reduce family support could have a very negative impact on the initial patient's outcomes. In addition to the transplant psychosocial team members, having the patient's clergy involved from early in the assessment process, and their potential to help mediate with the larger family, could prove very helpful to both track and deal with the associated problems.

There was a very low rate of kidney medical providers and patients who expressed any psychosocial concerns (<15%). This does not mean that they do not have them or that they may develop them later. Given the complex nature of what is involved with the personal acceptance of a foreign organ (especially from an animal) would still necessitate the transplant team continue to monitor the patient about their personal feelings and social interactions. For a more in-depth analysis of this point, please refer to Chap. 19 on psychological aspects.

Only pediatric parent and cardiac care providers had a high rate of concern about required organ genetic modifications (approximately 50%). Although not a significant factor in their willingness to consider XTx, one should be concerned about how this may influence a decision when the option is no longer a hypothetical one.

Overall, the UAB research findings discussed were relatively consistent from a quantitative and qualitative perspective. The willingness to consider (i.e., accept) XTx were robust enough to support the initiation of clinical trials for both adult kidney and pediatric heart candidates. However, as indicated, each group studied did present with unique concerns and views that would suggest the need for a more in-depth exploration and analysis of psychosocial issues through the clinical trials themselves. One cannot ignore the level of identified concerns for each clinical trial group. Another area of concern is that each of the studies were hypothetical in nature, and did not represent an actual opportunity for the patient, pediatric parent, or medical staff. This would suggest the importance to include a very intensive assessment and monitoring of adult patients and pediatric parents be included as part of clinical trial implementation.

Suggested Clinical Trial Research Design

Given the small number of patients included within clinical trials, a single-system research design would be a reasonable approach to consider. The importance of such an approach is that its use allows staff to focus on individual patient problems and issues [17]. This will be especially important during XTx clinical trials in helping to identify initial patient and family concerns and track them over time. The goal being to identify specific outcome measures that best reflect changes in the patient's psychosocial situation, and then track progress or regression over time. In simple terms, this would mean starting with the individual patient concerns and track how they may evolve over set periods of time. Unlike other forms of research the purpose is not to identify causality, per se, but rather to simply identify the relevant patient factors that the individual patient and their family may experience. Nugent's (2010) model for evaluating single-system or more commonly referred to as an individual patient research design would be one guide to consider [18]. The findings may not provide generalizable population level information, but rather would generate information helpful to the individual team in patient monitoring and refinement of psychosocial assessment and intervention strategies as clinical trials proceed.

Summary

What conclusions can be made about living as a XTx recipient? First, that there are measurable differences of attitudes, beliefs, and influences within individual groups. These differences need to be further identified and explored. Second, the hypothetical nature of the studies conducted provide only an estimate of potential areas of concern for the transplant team more will rise when/if clinical trials occur and some

preparation is warranted. Third, to meet the needs of patients and families will require the inclusion of a psychosocial research agenda—an agenda that is multidisciplinary in nature with agreed upon protocols and definitions.

References

1. Shah AM, Han JJ. First successful porcine to human heart transplantation performed in the United States. Artif Organs. 2022;46(4):543–5. https://doi.org/10.1111/aor.14203. Epub ahead of print
2. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;22(4):1037–53. https://doi.org/10.1111/ajt.16930.
3. Montgomery RA, Stern JM, Lonze BE, et al. Results of two cases of pig-to-human kidney xenotransplantation. N Engl J Med. 2022;386(20):1889–98. https://doi.org/10.1056/NEJMoa2120238.
4. Griffith BP, Goerlich CE, Singh AK, et al. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med. 2022;387(1):35–44. https://doi.org/10.1056/NEJMoa2201422.
5. Cooper DKC, Hara H, Iwase H, et al. Pig kidney xenotransplantation: progress toward clinical trials. Clin Transpl. 2021;35:e14139. https://doi.org/10.1111/ctr.14139.
6. Cooper DKC, Hara H, Iwase H, et al. Justification of specific genetic modifications in pigs for clinical organ xenotransplantation. Xenotransplantation. 2019;26:e12516. https://doi.org/10.1111/xen.12516.
7. Paris W, Jang K, Bargainer R, et al. Psychosocial challenges of xenotransplantation: the need for a multi-disciplinary; religion; and cultural dialogue. (commentary). Xenotransplantation. 2016;23(5):335–7.
8. Patience C, Takeuchi Y, Weiss RA. Infection of human cells by an endogenous retrovirus of pigs. Nat Med. 1997;3:282–6. https://doi.org/10.1038/nm0397-282.
9. Paris W, Seidler J, Fitzgerald K, et al. Jewish, Muslim, and Christian theological views of xenotransplantation. Xenotransplantation. 2018;25(3):e12400. https://doi.org/10.1111/xen.12400.
10. Paris W, Mitchell C, Werkheiser Z, et al. Public perspectives towards clinical trials of organ xenotransplantation. In: Cooper DKC, Byrne G, editors. Pathways to clinical xenotransplantation. New York: Springer; 2020.
11. Mitchell C, Lipps A, Padilla L, et al. Patient, physician, and nursing opinions about xenotransplantation: a meta-analysis. Xenotransplantation. 2020;27(4):e12583. https://doi.org/10.1111/xen.12583.
12. Padilla L, Hurst D, Lopez R, et al. Attitudes to clinical pig kidney xenotransplantation among medical providers and patients. Kidney360. 2020;1(7):657–62. https://doi.org/10.34067/KID.0002082020.
13. Padilla L, Rhodes L, Sorabella RA, et al. Attitudes toward xenotransplantation: a survey of parents and pediatric care providers. Pediatr Transplant. 2021;25(2):e13851. https://doi.org/10.1111/petr.13851.
14. Padilla L, Hurst DJ, Jang K, et al. Racial differences in attitudes to xenotransplantation. Xenotransplantation. 2021;28(2):e12656. https://doi.org/10.1111/xen.12656.
15. Hurst D, Padilla L, Cooper DKC, Paris W. Attitudes toward xenotransplant clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684. https://doi.org/10.1111/xen.12684.
16. Hurst D, Padilla L, Cooper DKC, et al. The attitudes of religious group leaders towards xenotransplantation: a focus group study. Xenotransplantation. 2022;29(5):e12777. https://doi.org/10.1111/xen.12777.
17. Kazi MAF. Realist evaluation in practice. London: Sage Publications; 2003.
18. Nugent WR. Analyzing single system design data. New York: Oxford University Press; 2010.

Clinical and Ethical Implications of Adult Cardiac Xenotransplantation

23

A. Cozette Killian, W. Hampton Gray, and Robert A. Sorabella

Introduction

Over the next decade, 800,000 patients are projected to develop advanced heart failure (HF) which is associated with 25–50% 1-year mortality [1, 2]. Cardiac allotransplantation is the ideal treatment for advanced HF, as recipients are afforded 1-year survival nearing 90% with improved quality of life [3, 4]. However, the current supply of this lifesaving therapy falls far short of the demand. Approximately 5000 patients are waitlisted for transplant each year and less than 3900 cardiac transplants are performed annually in the United States [5, 6]. As such, alternative therapies to cardiac allotransplantation are needed.

Mechanical circulatory support (MCS) offers additional therapeutic options with durable left ventricular assist devices (LVADs) most commonly being utilized for bridge-to-transplantation, bridge-to-transplant candidacy, and destination therapies. Given that 1-year LVAD survival is greater than 80%, use of this therapy has doubled in the last decade with more than 3000 implants performed in 2019 [7].

A. C. Killian · W. H. Gray
Department of Surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: akale@uabmc.edu; whgray@uabmc.edu

R. A. Sorabella (✉)
Department of Surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

Section of Pediatric Cardiac Surgery, University of Alabama at Birmingham, Heersink School of Medicine, Birmingham, AL, USA
e-mail: rsorabella@uabmc.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_23

However, high risk complications, high costs, and contraindications among specific patient populations limit widespread use of this therapy [8–10].

Alternatively, the utility of xenotransplantation has remained controversial for decades as some leaders in cardiac transplantation believed that xenotransplantation was, and would always remain, a therapy of the future [11]. The primary barrier to xenotransplantation has been the cross-species immunologic incompatibilities associated with porcine-specific carbohydrate antigens such as galactose-α1–3-galactose, SDa, and N-glycolylneuraminic acid [12]. However, advancements in gene-editing via CRISPR-Cas9 have allowed not only for the knockout of the enzymes that produce these immunogenic antigens, but also the alteration of genes associated with complement (hDAF, hCD46), coagulation (hTBM, hvWF, hTFPI, hEPCR), inflammation (hCD47, hHLA-E) and cell death (hHO1) [12, 13]. Differing combinations of these genetic modifications in donor pigs continue to be investigated through collaborations between academia and industry, and have resulted in successful porcine to non-human primate (NHP) xenotransplantation experiments [12, 14].

These preclinical advancements led to the first porcine-to-human orthotopic cardiac transplant performed at the University of Maryland School of Medicine (UMSOM) on January 7th, 2022 [15, 16]. The recipient was a 57-year-old male with advanced HF who was ineligible for cardiac allotransplantation or MCS due to non-compliance [16, 17]. The recipient received the xenotransplant for compassionate use and passed away 60 days post-transplant [17, 18]. While many view this as a watershed moment in the decades-long quest to develop xenotransplantation into a solution for the persistent organ shortage, a number of questions and uncertainties remain.

In this chapter we discuss where cardiac xenotransplantation may fit into the landscape of care for adults with advanced HF. We first review the current alternative therapies to cardiac allotransplantation, and subsequently discuss the potential added utility of cardiac xenotransplantation and which adult populations may be best suited for this treatment. Finally, we explore the possible ethical implications of cardiac xenotransplantation that must be considered prior to widespread clinical use.

Alternative Therapies to Cardiac Transplantation

Given the high mortality rate associated with advanced HF and the limited supply of cardiac transplantation that necessitates a waitlist, therapies have been developed to bridge patients in need of hemodynamic support until a donor organ becomes available [8, 9]. Moreover, as a limited public health resource, careful stewardship of cardiac transplants necessitates clinical and psychosocial contraindications to transplantation [19]. For patients with advanced HF ineligible for transplant, LVADs have been increasingly used as destination therapy as well [8, 9]. The initiation and duration of MCS therapy has been guided by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profiles for patients on optimized

medical therapy, which range from Profile 1 indicating critical cardiogenic shock to Profile 7 indicating advanced New York Heart Association Class III [20]. While the use of MCS has increased substantially the last few decades, associated complications and contraindications may limit its use to 25–50% of patients with an indication for advanced HF therapy [9]. We will briefly review temporary (t-MCS) and durable MCS (d-MCS) therapies for advanced HF as well as the limitations to their widespread use.

Temporary

Temporary MCS therapies are used to provide hemodynamic support within timeframes of hours to weeks following an acute decompensation [8, 20]. These therapies are employed primarily among patients with INTERMACS Profiles 1–2 and can be used as a bridge to recovery, bridge to d-MCS therapy (discussed below), or bridge to urgent transplant [8, 20]. The most commonly used t-MCS devices include the intraaortic balloon pump (IABP), percutaneous and paracorporeal ventricular assist devices, and veno-arterial extracorporeal membrane oxygenation (ECMO) [8].

The use of t-MCS devices has increased following the new donor heart allocation system in 2018 which gives priority to patients sustained on t-MCS therapy [6, 21], though the evidence of clinical benefit from these devices has been mixed [22]. Evaluation of patients who received t-MCS for bridge to d-MCS compared to Profile 1 patients who did not receive t-MCS demonstrated similar rates of postoperative right HF, renal failure, and death following d-MCS placement [23]. Moreover, IABP use has been shown to improve waitlist survival, though comparison of t-MCS for bridge to transplant vs. primary transplantation demonstrated no post-transplant survival benefit [21, 24]. Ultimately, t-MCS therapies may benefit patients awaiting more sustainable treatment, but are unlikely to provide benefit long-term.

Durable

Durable MCS therapies are used among INTERMACS Profile 3 patients requiring intervention within weeks to months [20]. The most common d-MCS device used for bridge to transplant is the LVAD, though for patients with biventricular disease, biventricular VADs (BiVAD) or the total artificial heart (TAH) are available options [25]. Importantly, the success of LVADs has expanded their use as destination therapy and consideration of LVAD use in patients of lesser acuity continues to be explored [26].

Over the last four decades 1-year survival among candidates listed for heart transplantation increased from 34% prior to 1990 to 68% after 2011 [27]. While changes in allocation policy helped facilitate this improvement in waitlist survival, the creation and subsequent evolution of VADs during this time must be acknowledged [27]. The REMATCH trial compared the early pulsatile LVAD to optimal medical therapy and demonstrated LVAD use was associated with lower

all-cause mortality [28]. Among LVAD patients, 1-year survival was 52% compared to 25% among patients who received optimal medical therapy [28]. Compared to pulsatile devices, continuous flow devices were found to improve 2-year stroke free-survival and demonstrated reduced device failure in the HEARTMATE II trial [29]. Moreover, continuous flow LVADs used as bridge to transplant demonstrated not only effective support, improved functional status and quality of life [30], but also improved waitlist survival compared to propensity-matched cohorts [31].

The MOMENTUM 3 trial later compared two continuous flow devices, Heartmate III vs. Heartmate II, among patients undergoing bridge to transplantation or destination therapy [32]. While the centrifugal flow pump (Heartmate III) demonstrated superior results compared to the axial-flow pump (Heartmate II), 1-year survival free from disabling stroke or reoperation for device malfunction was greater than 73% among the Heartmate II cohort and greater than 84% among the Heartmate III cohort [32]. Given this increased survival with LVAD use, the role of d-MCS among ambulatory, non-inotrope dependent INTERMACS profiles has been explored [26]. Results from the ROADMAP study suggest patients ineligible for transplantation with INTERMACS Profile 4 may benefit from LVAD therapy with improved survival, function, and quality of life [33].

Limitations to Widespread Use

While LVADs are a viable treatment option for patients awaiting allotransplantation as bridging therapy, as well as patients who are ineligible for transplantation as destination therapy, contraindications that limit LVAD use should be acknowledged. Absolute contraindications to d-MCS therapy as outlined by the American Heart Association include irreversible hepatic, renal, or neurological disease, medical non-adherence, or severe psychosocial challenges [34]. Additional considerations should include ability to tolerate long-term anticoagulation, risk of right HF, presence of aneurysmal aortic disease or dissection, restrictive cardiomyopathy, or presence of certain congenital cardiac abnormalities not amenable to LVAD placement [8]. There are a few relative contraindications that are patient dependent, and these risks should be weighed against its potential benefit [34].

The most common complications associated with LVAD use in the first year following implantation include bleeding, infection, cardiac arrythmia, respiratory failure, and stroke [35]. Bleeding is associated with long-term anticoagulation use as well as coagulopathies, arteriovenous malformations in mucosal surfaces, and angiodysplasia secondary to the blood-device interaction [8]. As such, more than 20% of patients experience a gastrointestinal bleed within the first year after LVAD implantation [7]. LVAD-associated infections due to external drivelines occur in more than 40% of patients, while fewer than 13% of patients suffer a stroke within the first year of LVAD placement [7]. Early causes of death include multisystem organ failure, right HF, and stroke, while stroke remains the leading cause of late death among LVAD patients followed by multisystem organ failure and infection [7,

9, 35]. Other complications of lesser frequency with the newest LVADs include pump thrombosis and device failure [8, 35].

Potential Utility of Adult Cardiac Xenotranpslantation

Any cardiac xenograft created for xenotransplantation use in the United States will be treated as an investigational new drug, regulated by the Federal Drug Administration (FDA), and subjected to clinical trials prior to approved use. During clinical trials, the xenograft must demonstrate safety, efficacy and clinical benefit within the context of the currently available treatments [36]. However, the UHeart from United Therapeutics' 10 gene-edited pig received a FDA emergency use authorization for compassionate use in a 57-year-old male recipient ineligible for heart transplantation or MCS who was sustained on ECMO for 46 days prior to xenotransplantation [17, 37–40]. While the patient's early post-operative xenograft function was normal, the patient was recannulated for ECMO on post-transplant day 49 due to biventricular wall thickening and abnormal global longitudinal strain [17]. Withdrawal of life support was performed on day 60 after irreversible injury to the xenograft secondary to atypical xenograft rejection was noted [17]. The UMSOM group has been lauded for this groundbreaking transplant, though much more remains to be learned from their experience [40]. Nonetheless, given the demonstrated feasibility of cardiac xenotransplantation, clinical trials for the UHeart may be around the corner. In this section, the potential clinical utility of cardiac xenotransplantation is explored within the current landscape of advanced HF therapies. We first discuss the theorized efficacy and possible safety concerns of xenotransplantation, and then delineate potential candidates for whom cardiac xenotransplantation may prove advantageous.

Efficacy and Safety of Cardiac Xenotransplantation

Xenotransplantation may be a potential solution to the organ shortage given that pigs could offer a readily available supply of donor organs. Swine produce large litters and mature rapidly [41, 42]. However, organ availability is arguably only of consequence if the efficacy of cardiac xenotransplantation is proven. The International Society for Heart and Lung Transplantation previously advised a 3-month post-transplant survival of 60% among pre-clinical pig-to-NHP xenotransplantation experiments prior to any pig-to-human experimentation [15, 42]. While NHP orthotopic cardiac xenograft recipient survival has been extended to 264 days [14], outcomes remain inferior to heart transplant or LVAD 1-year survival rates of approximately 90% and 80%, respectively [3, 15, 32, 43]. While the only experience of pig-to-human cardiac xenotransplantation demonstrated survival for only 60 days [17], it is hypothesized that xenografts may eventually be more efficacious in humans than NHPs given that the gene edits were designed to make porcine donors more human-like rather than NHP-like [12, 18]. Thus, with further study and

experience to optimize cardiac xenotransplantation, it may be possible to attain survival rates comparable to existing therapies. At least initially, however, it appears unlikely xenotransplantation can replace heart allotransplantation or MCS [43]. Some have proposed that cardiac xenotransplantation may be used as an adjunct therapy either as bridge to transplantation or destination therapy among patients who are not eligible for allotransplantation or MCS [44]. This application may have merit in certain populations as discussed by Chan et al. and reviewed below [44], given that xenotransplant survival would only need to be greater than optimal medical therapy which is associated with 25% 1-year survival among populations ineligible for allotransplantation [28].

There are a number of potential risks associated with xenotransplantation that must be taken into account when evaluating the safety and efficacy of a new therapy [15]. First, xenotransplant recipients will still require immunosuppression and may require an altered regimen inclusive of novel medications. Notably, the UMSOM xenotransplant recipient received a novel humanized anti-CD40 monoclonal antibody in an effort to replicate prior cardiac xenotransplantation studies among NHPs [17, 45]. Given that current immunosuppressive medications are fraught with side effects, the safety profile and determination of appropriate dosing for this medication among humans, and any other new drugs for xenotransplantation will be required.

Second, perioperative cardiac xenograft dysfunction (PCXD), or xenograft failure within 24–48 hours of transplantation due to ischemia reperfusion injury, initially resulted in high rates of perioperative mortality among NHPs [15, 46]. When continuous cold perfusion of xenografts with XVIVO Heart Solution was performed prior to transplantation, the incidence of PCXD in NHPs was decreased to 20% [46]. Notably, this improved PCXD incidence remains double the rate of primary graft dysfunction for allotransplantation [46]. The XVIVO Heart Solution, which includes adrenaline, cortisol, and cocaine, was used during the UMSOM xenotransplant [17, 45]. The recipient remained on ECMO until postoperative day 4, though he did not require inotropic support and left ventricular ejection fraction of the xenograft was greater than 55% [17]. Nonetheless, the incidence of PCXD among human recipients and its impact on clinical outcomes will require further study.

Finally, the true risk of zoonosis associated with xenotransplantation is unknown. While neither PERV nor other porcine associated pathogens were documented among recipients of islet cell xenotransplantation, porcine cytomegalovirus (pCMV) was detected in the UMSOM xenotransplant recipient [15, 17, 47]. The recipient was treated for pCMV but the overall impact of the infection and it's possible contribution to the xenograft rejection is unknown [17]. Given concern for zoonoses, long-term surveillance has been suggested by a number of regulatory agencies including the FDA, World Health Organization, International Xenotransplantation Society [48]. As such, just as medical non-adherence is an absolute contraindication for cardiac allotransplant or LVAD therapy, it should remain an absolute contraindication to xenotransplantation as well. Notably, the UMSOM recipient was not a suitable candidate for cardiac allotransplantation due to noncompliance [17, 49]. If the safety of xenotransplantation is not ensured, it may undermine any clinical utility it offers.

Potential Cardiac Xenotransplantation Candidates

Cardiac xenotransplantation may be a viable option as a bridge to transplant among adult patients eligible for cardiac transplantation but not MCS therapy, or as destination therapy among those ineligible for cardiac transplantation or MCS therapy, who are suitable surgical candidates [44]. Cardiac allotransplantation should remain the gold standard, with LVADs being a primary alternative therapy given the strong evidence demonstrating improved survival, functional status, and quality of life with these therapies among advanced HF patients [3, 4, 32]. Based on the presently available data, cardiac xenotransplantation may be best utilized to fill the clinical gaps where LVADs are not suitable.

ISHLT Guidelines cannot recommend LVADs for patients with restrictive cardiomyopathy (RCM) [19]. While restrictive cardiomyopathy is the least common etiology of heart failure, the number of patients with restrictive cardiomyopathy listed for heart transplantation more than doubled between 1990 and 2010 suggesting the prevalence of this cardiomyopathy may continue to increase [19, 50]. Xenotransplantation may be an option to either bridge patients who are eligible for allotransplantation or provide destination therapy for those who are not.

Some adults with congenital heart disease (ACHD) who progress to advanced HF are bridged to transplantation with LVAD and demonstrate similar survival to adults without CHD [51]. However, these patients account for only 3% of the ACHD population as single ventricle physiology or complex anatomy may not be amenable to LVAD placement [44, 52]. While BiVADs or TAHs offer other options, ACHD who required these MCS devices were more commonly INTERMACS Profile 1, and have demonstrated lower survival compared to ACHD who received LVAD [51]. Given the growing population of ACHD with HF, development of a viable alternative such as xenotransplantation is of increasing importance [52]. It should also be noted that among children with CHD in need of cardiac transplantation, outcomes associated with MCS differ from those among adults and thus, the utility of cardiac xenotransplantation in pediatric populations requires a separate discussion as the topic of another chapter [53].

Right heart failure is a known complication of LVAD use. For this reason, patients at risk for right heart failure or biventricular disease may benefit from xenotransplantation. Current MCS alternatives to LVAD for these patients include BiVADs and TAHs which have demonstrated 1-year survival rates of 56% and 59%, respectively [35]. While these survival rates are still superior to that of xenotransplantation in NHP models [15], xenotransplant may be preferred among patients at higher risk for MCS associated complications such as bleeding or infection [44].

Moreover, patients who are unable to tolerate long-term anticoagulation required for LVAD treatment may be candidates for xenotransplantation [44]. While xenotransplantation has been associated with coagulopathy in NPH models, this may have been immunologically driven [12, 43, 54]. Thus, assuming effective gene editing and immunosuppression, no anticoagulation should be required. Some have argued that newer MCS therapies, such as the Carmat TAH do not require anticoagulation, negating the utility of xenotransplantation in this population [43].

However, patients are only eligible for this device if they are ineligible for LVAD and studies of safety and efficacy for the Carmat TAH are ongoing [55].

Additional patient populations that may benefit from cardiac xenotransplantation include patients requiring retransplantation and highly sensitized patients [15, 44]. Use of xenografts in patient's requiring retransplantation would decrease utilization of the limited human donor organ supply, particularly given that cardiac retransplantation has been associated with significantly lower survival compared to primary transplantation [44, 56]. However, the impact of sensitization from primary allotransplantation on immune reactivity to a xenograft is unknown. Similar questions remain for highly sensitized patients, whether due to prior transplantation or receipt of blood products with LVAD therapy, though the risk of antibody mediated rejection should be weighed against the risk of allotransplant waitlist mortality in this population [15]. Notably, anti-human leukocyte antigen (HLA) antibodies have been shown to cross-react with swine leukocyte antigen (SLA) [57]. Thus, it is plausible that use of xenotransplantation as a bridge may result in sensitization to allografts. Should this be the case, the utility of xenotransplantation may be limited to destination therapy. Ultimately, further study is required to clearly delineate where benefit may be gained.

Ethical Implications of Adult Cardiac Xenotransplantation

The ethical considerations of xenotransplantation can be evaluated using the four principles of beneficence, non-maleficence, autonomy, and justice [58]. Beneficence supports the idea of xenotransplantation because of the need to provide more patients with a lifesaving therapy in the setting of a scarce resource—human donor organs. However, the true benefit for adults with advanced HF is presently limited, as discussed previously, and certainly not without risk, chief of which concerns zoonotic infection. While evidence suggests the risk of this is low [47], any zoonotic transmission places not only the recipient at risk but all of society, which is in opposition with the principle of non-maleficence [58]. The extent to which the public understands the risk of xenotransplant associated zoonoses is unclear, though concern was raised in focus group evaluations of public attitudes toward xenotransplantation [59]. Moreover, explorations of public perceptions of xenotransplantation have not been performed since the COVID-19 pandemic, which demonstrated the devastating potential of societal exposure to a new virus. COVID-19 highlighted systemic challenges that stunted our ability to respond quickly and effectively to a new virus [43], and emphasized the high value placed on autonomy by patients in the United States. It should be noted, however, that xenograft recipients must be willing to relinquish some autonomy to adhere to regulatory requirements such as long-term surveillance, biobanking, and registry creation [15, 48]. Numerous other ethical implications for xenotransplantation including religious concerns, cost, and animal welfare are discussed in further detail as the subject of another chapter, though in this section we explore the ethical considerations specific to adult cardiac xenotransplantation through the lens of justice.

Should xenotransplantation be introduced into the landscape of advanced HF care options, care must be taken to prevent the exacerbation of existing disparities. Persistent racial disparities in HF have been well described as African American/Black (AAB) populations disproportionately develop HF and suffer higher rates of both HF-related hospitalizations and deaths compared to white counterparts [60, 61]. Of the patients added to the heart transplant waitlist in 2021, however, only 25% were AAB compared to 56% who were white, which actually demonstrates a small but notable improvement in trends over the last decade [5, 6]. Moreover, lower proportions of AAB patients receive LVADs or heart transplants [6, 60, 61]. Of patients receiving LVAD support between 2015 and 2019, 27% were AAB while 63% were white [7]. Similarly, only 24% of heart transplant recipients in 2021 were AAB, compared to 58% who were white [62]. However, access to these advanced HF therapies is contingent on referral. While referral data specific to advanced HF therapy are lacking, evaluation of referral practices for abdominal organ transplantation have demonstrated AAB patients are referred at lower rates than white patients [63, 64]. These data suggest racial disparities in referral for advanced HF therapy may exist, which would inherently limit access to xenotransplantation as well.

Moreover, unintended disparate treatment among patients who are referred may exacerbate inequities in advanced HF care. As discussed in the prior section, current evidence suggests the efficacy of cardiac xenotransplantation is likely to be inferior to allotransplantation or LVAD support, and acceptance of a xenotransplant as a bridge in this scenario was reported to be low, though it should be noted this evaluation was performed in consideration of pediatric cardiac xenotransplantation among both parents and pediatric providers [65, 66]. Patients have also questioned whether xenotransplantation may be akin to receiving a "second-tier organ" which may result in race and class divisions [59]. Unfortunately, this may be a valid concern as implicit racial biases have been shown to influence provider recommendations of currently available advanced HF treatment options [67]. In clinical vignettes that varied by race alone—the AAB patient being evaluated for advanced HF therapy was perceived as more sick and less compliant. Transplantation was more likely to be recommended for the white patient while VAD was more likely to be recommended for the AAB patient, with some providers citing the need for organ stewardship [67]. Given that contraindications for advanced HF therapies such as lack of social support or non-adherence are subjective [19, 34], these data suggest biases may also influence to whom providers offer xenotransplantation, whether as a bridge or destination therapy. Similarly, should cardiac xenotransplantation clinical trials begin outside the auspices of an emergency use authorization, patients considered non-compliant may be deemed ineligible for trial participation, which may not only limit early access to this therapy, but also critical data collection among more vulnerable patient populations.

Finally, patients have also discussed concerns regarding social stigma that may be associated with receipt of a pig xenograft [59]. Community members hypothesized it may impact a recipient's social mobility [59], while 11% of parents of children with CHD believed it may impact the way people interact with their child [65]. While very few in number, some parents also believed a xenotransplant would make

their child "less human" [65]. The attitudes and acceptance of xenotransplantation among adult cardiac candidates and other stakeholders in adult cardiac transplantation has yet to be assessed, and should be evaluated within the context of other available therapies such as LVADs. Before xenotransplantation is employed in the clinical setting, it is imperative that providers and regulators listen to the community and the patients whom they serve to not further marginalize vulnerable populations in need of advanced HF care.

Conclusions

The first porcine-to-human orthotopic cardiac transplant performed in January 2022 demonstrated the feasibility of cardiac xenotransplantation. While the recipient survived only 2 months, much can be learned from the experimental transplant, xenograft preservation technique, and immunosuppressive regimen, and clinical trials may be around the corner. Given the substantial survival benefit associated with both cardiac allotransplantation and LVAD support, available data among NHPs and the single human experience suggest xenotransplantation may, at least initially, be associated with inferior outcomes. As such, cardiac xenotransplantation may be best utilized as a bridge to allotransplantation or as destination therapy among populations for whom MCS is not an option. Understanding that the safety and efficacy of cardiac xenotransplantation is likely to improve with further study and greater clinical experience and the therapeutic role for xenotransplantation may evolve. Until comparable outcomes are achieved with xenotransplantation, further qualitative evaluations among all stakeholders are needed to create systems that will ensure public safety and improve equity in access to advanced HF therapies.

References

1. Thorvaldsen T, Lund LH. Focusing on referral rather than selection for advanced heart failure therapies. Card Fail Rev. 2019;5(1):24–6.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606–19.
3. Khush KK, Potena L, Cherikh WS, Chambers DC, Harhay MO, Hayes D Jr, et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: 37th adult heart transplantation report-2020; focus on deceased donor characteristics. J Heart Lung Transplant. 2020;39(10):1003–15.
4. Politi P, Piccinelli M, Fusar-Poli P, Klersy C, Campana C, Goggi C, et al. Ten years of "extended" life: quality of life among heart transplantation survivors. Transplantation. 2004;78(2):257–63.
5. National Data [Internet]. 2022 [cited 04/03/22; 08/20/22]. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#.
6. Colvin M, Smith JM, Ahn Y, Skeans MA, Messick E, Bradbrook K, et al. Special Issue: OPTN SRTR 2020 annual data report - heart. Am J Transplant. 2022; 22(S2): 350–437.
7. Molina EJ, Shah P, Kiernan MS, Cornwell WK 3rd, Copeland H, Takeda K, et al. The Society of Thoracic Surgeons INTERMACS 2020 annual report. Ann Thorac Surg. 2021;111(3):778–92.

8. Vieira JL, Ventura HO, Mehra MR. Mechanical circulatory support devices in advanced heart failure: 2020 and beyond. Prog Cardiovasc Dis. 2020, 63;(5):630–9.
9. Miller L, Birks E, Guglin M, Lamba H, Frazier OH. Use of ventricular assist devices and heart transplantation for advanced heart failure. Circ Res. 2019;124(11):1658–78.
10. Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. Circ Heart Fail. 2014;7(3):470–8.
11. Cooper DK. A brief history of cross-species organ transplantation. Proc (Bayl Univ Med Cent). 2012;25(1):49–57.
12. Singh AK, Goerlich CE, Shah AM, Zhang T, Tatarov I, Ayares D, et al. Cardiac xenotransplantation: Progress in preclinical models and prospects for clinical translation. Transpl Int. 2022;35:10171.
13. Porrett PM, Orandi BJ, Kumar V, Houp J, Anderson D, Cozette Killian A, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;22(4):1037–53.
14. Goerlich CE, Griffith B, Hanna P, Hong SN, Ayares D, Singh AK, et al. The growth of xenotransplanted hearts can be reduced with growth hormone receptor knockout pig donors. J Thorac Cardiovasc Surg. 2021;165(2):e69–81.
15. Reichart B, Langin M, Denner J, Schwinzer R, Cowan PJ, Wolf E. Pathways to clinical cardiac xenotransplantation. Transplantation. 2021;105(9):1930–43.
16. Shah AM, Han JJ. First successful porcine to human heart transplantation performed in the United States. Artif Organs. 2022;46(4):543–5.
17. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, et al. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med. 2022;387(1):35–44.
18. Salam E. First person to receive heart transplant from pig dies, says Maryland hospital: The Guardian; 2022. https://www.theguardian.com/us-news/2022/mar/09/first-person-heart-transplant-pig-dies-david-bennett
19. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016;35(1):1–23.
20. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009;28(6):535–41.
21. Huckaby LV, Seese LM, Mathier MA, Hickey GW, Kilic A. Intra-aortic balloon pump bridging to heart transplantation: impact of the 2018 allocation change. Circ Heart Fail. 2020;13(8):e006971.
22. Cogswell R, John R, Estep JD, Duval S, Tedford RJ, Pagani FD, et al. An early investigation of outcomes with the new 2018 donor heart allocation system in the United States. J Heart Lung Transplant. 2020;39(1):1–4.
23. Shah P, Pagani FD, Desai SS, Rongione AJ, Maltais S, Haglund NA, et al. Outcomes of patients receiving temporary circulatory support before durable ventricular assist device. Ann Thorac Surg. 2017;103(1):106–12.
24. Finnan MJ, Bakir NH, Itoh A, Kotkar KD, Pasque MK, Damiano RJ Jr, et al. 30 years of heart transplant: outcomes after mechanical circulatory support from a single center. Ann Thorac Surg. 2022;113(1):41–8.
25. Cook JA, Shah KB, Quader MA, Cooke RH, Kasirajan V, Rao KK, et al. The total artificial heart. J Thorac Dis. 2015;7(12):2172–80.
26. Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical Management in Ambulatory Heart Failure Patients: the roadmap study 2-year results. JACC Heart Fail. 2017;5(7):518–27.
27. Bakhtiyar SS, Godfrey EL, Ahmed S, Lamba H, Morgan J, Loor G, et al. Survival on the heart transplant waiting list. JAMA Cardiol. 2020;5(11):1227–35.
28. Rose EA, Geligns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43.

29. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241–51.
30. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 2007;357:885–96.
31. Trivedi JR, Cheng A, Singh R, Williams ML, Slaughter MS. Survival on the heart transplant waiting list: impact of continuous flow left ventricular assist device as bridge to transplant. Ann Thorac Surg. 2014;98(3):830–4.
32. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC Jr, Yuzefpolskaya M, Salerno C, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. N Engl J Med. 2018;378(15):1386–95.
33. Shah KB, Starling RC, Rogers JG, Horstmanshof DA, Long JW, Kasirajan V, et al. Left ventricular assist devices versus medical management in ambulatory heart failure patients: an analysis of INTERMACS profiles 4 and 5 to 7 from the ROADMAP study. J Heart Lung Transplant. 2018;37(6):706–14.
34. Peura JL, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, et al. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American Heart Association. Circulation. 2012;126(22):2648–67.
35. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant. 2015;34(12):1495–504.
36. Services USDoHaH. Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans: Guidance for Industry.
37. Therapeutics U. https://pipeline.unither.com/product/uheart-xenoheart/description/.
38. Medicine UoMSo. University of Maryland School of Medicine Faculty Scientists and Clinicians Perform Historic Transplant of Porcine Heart into Adult Human with End-Stage Heart Disease 2022. https://www.umms.org/ummc/news/2022/pioneering-transplant-of-porcine-heart-into-adult-human-heart
39. Rabin R. In a first, man receives a heart from a genetically altered pig. The New York Times. 2022.
40. Reardon S. First pig-to-human heart transplant: what can scientists learn? Nature. 2022;601(7893):305–6.
41. Cooper D, Gollackner B, Sachs D. Will the pig solve the transplantation backlog? Annu Rev. Med. 2002;53:133–47.
42. Cooper DK, Keogh AM, Brink J, Corris PA, Klepetko W, Pierson RN, et al. Report of the xenotransplantation advisory Committee of the International Society for heart and lung transplantation: the present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary diseases. J Heart Lung Transplant. 2000;19(12):1125–65.
43. Loebe M, Parker B. Don't pig(!) the wrong heart! J Card Surg. 2021;36(10):3802–4.
44. Chan JL, Miller JG, Singh AK, Horvath KA, Corcoran PC, Mohiuddin MM. Consideration of appropriate clinical applications for cardiac xenotransplantation. Clin Transpl. 2018;32(8):e13330.
45. G. A. Pig-To-Human Heart Transplant: How Scientists Pulled It Off Using Genetic Engineering And Cocaine 2022. https://www.btimesonline.com/articles/153291/20220121/pig-to-human-heart-transplant-how-scientists-pulled-it-off-using-genetic-engineering-and-cocaine.htm
46. Goerlich CE, Griffith B, Singh AK, Abdullah M, Singireddy S, Kolesnik I, et al. Blood cardioplegia induction, perfusion storage and graft dysfunction in cardiac xenotransplantation. Front Immunol. 2021;12:667093.
47. Morozov VA, Wynyard S, Matsumoto S, Abalovich A, Denner J, Elliott R. No PERV transmission during a clinical trial of pig islet cell transplantation. Virus Res. 2017;227:34–40.
48. Goerlich CE, Chan JL, Mohiuddin MM. Regulatory barriers to xenotransplantation. Curr Opin Organ Transplant. 2019;24(5):522–6.

49. Griffith BP. 'I Performed The World's First Pig Heart Transplant' 2022 [updated 1/15/22. https://www.newsweek.com/first-pig-heart-human-transplant-surgeon-1669471
50. DePasquale EC, Nasir K, Jacoby DL. Outcomes of adults with restrictive cardiomyopathy after heart transplantation. J Heart Lung Transplant. 2012;31(12):1269–75.
51. VanderPluym CJ, Cedars A, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, et al. Outcomes following implantation of mechanical circulatory support in adults with congenital heart disease: an analysis of the interagency registry for mechanically assisted circulatory support (INTERMACS). J Heart Lung Transplant. 2018;37(1):89–99.
52. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, et al. Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133(8):802–20.
53. Cleveland D, Adam Banks C, Hara H, Carlo WF, Mauchley DC, DKC C. The case for cardiac xenotransplantation in neonates: is now the time to reconsider xenotransplantation for Hypoplastic left heart syndrome? Pediatr Cardiol. 2019;40(2):437–44.
54. Pierson RN 3rd, Fishman JA, Lewis GD, D'Alessandro DA, Connolly MR, Burdorf L, et al. Progress toward cardiac xenotransplantation. Circulation. 2020;142(14):1389–98.
55. Han JJ. Aeson-the Carmat total artificial heart is approved for enrollment in the United States. Artif Organs. 2021;45(5):445–6.
56. Rizvi SA, Luc JGY, Choi JH, Phan K, Moncho Escriva E, Patel S, et al. Outcomes and survival following heart retransplantation for cardiac allograft failure: a systematic review and meta-analysis. Ann Cardiothorac Surg. 2018;7(1):12–8.
57. Martens GR, Ladowski JM, Estrada J, Wang ZY, Reyes LM, Easlick J, et al. HLA class I-sensitized renal transplant patients have antibody binding to SLA class I epitopes. Transplantation. 2019;103(8):1620–9.
58. Varkey B. Principles of clinical ethics and their application to practice. Med Princ Pract. 2021;30(1):17–28.
59. Hurst DJ, Padilla LA, DKC C, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684.
60. Nayak A, Hicks AJ, Morris AA. Understanding the complexity of heart failure risk and treatment in black patients. Circ Heart Fail. 2020;13(8):e007264.
61. Lewsey SC, Breathett K. Racial and ethnic disparities in heart failure: current state and future directions. Curr Opin Cardiol. 2021;36(3):320–8.
62. Transplants in the U.S. by Recipient Ethnicity [Internet]. [cited 4/16/22]. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#
63. Julapalli VR, Kramer JR, El-Serag HB, American Association for the Study of Liver D. Evaluation for liver transplantation: adherence to AASLD referral guidelines in a large veterans affairs center. Liver Transpl. 2005;11(11):1370–8.
64. Epstein A, Ayanian J, Keogh J, Noonan S, Armistead N, Cleary P, et al. Racial disparities in access to renal transplantation. NEJM. 2000;343:1537–45.
65. Padilla LA, Rhodes L, Sorabella RA, Hurst DJ, Cleveland DC, Dabal RJ, et al. Attitudes toward xenotransplantation: a survey of parents and pediatric cardiac providers. Pediatr Transplant. 2021;25(2):e13851.
66. Padilla LA, Sorabella RA, Carlo WF, Dabal RJ, Rhodes L, Cleveland DC, et al. Attitudes to cardiac xenotransplantation by pediatric heart surgeons and physicians. World J Pediatr Congenit Heart Surg. 2020;11(4):426–30.
67. Breathett K, Yee E, Pool N, Hebdon M, Crist JD, Knapp S, et al. Does race influence decision making for advanced heart failure therapies? J Am Heart Assoc. 2019;8(22):e013592.

Kidney Xenotransplantation

24

Angela Sickels and Luz Padilla

Introduction

Over the course of the last century, kidney transplantation has emerged from an experimental treatment to now being the preferred treatment for qualifying candidates with end stage renal disease (ESRD). Advances in surgical technique, pharmacologic immunosuppression, and techniques of organ preservation (e.g. pump preservation, normothermic perfusion) have greatly advanced the field of transplantation and made it an available option to more candidates than ever. Despite these advances, over 90,000 candidates remain on the waitlist with a median waitlist time of approximately 4 years [1–3]. Even with recent advances in living donor kidney transplantation (LDKT), demand continues to greatly exceed currently available organs.

Transplantation has clear benefits concerning both overall survival and quality of life. The survival for patients undergoing deceased donor kidney transplantation (DDKT) and LDKT was 93.3% and 97.3%, respectively, at 1 year, compared to 81.1% of patients on dialysis. This difference is even further exacerbated at 5 years, with survival of 76.5% for DDKT, 86.1% for LDKT, and 42.9% for dialysis. The myriad of complications affecting nearly every organ system in the body as well as the increased susceptibility to chronic inflammation and infection also compromises quality of life for dialysis patients. Consequently, a significant percentage

A. Sickels
Department of Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: adsickels@uabmc.edu

L. Padilla (✉)
Department of Surgery, The University of Alabama at Birmingham, Birmingham, AL, USA

Department of Epidemiology, The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: lpadilla@uabmc.edu

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_24

choose to withdraw from dialysis, many of whom die within 10 days [4]. Dialysis is also associated with significant financial burden—the yearly cost for hemodialysis (HD) is $88,750 and for peritoneal dialysis (PD) is $75,140 per patient per year [4]. Conversely, the cost after kidney allotransplantation was $34,084 per person per year [4]. With the prevalence of ESRD increasing by over 100,000 people annually, the critical demand for these organs will only continue to increase [3].

Candidate Selection

Substantial progress has been made in the field of xenotransplantation in the last decade. Preclinical trials utilizing genetically modified pig kidneys transplanted into nonhuman primates (NHP) have produced promising results which may provide precedent for human clinical trials in the near future. Xenotransplantation offers a possible solution to the problem of organ shortage as a theoretical unlimited number of organs could be produced [1]. Other possible benefits include: elective availability of organs, the avoidance of the physiological derangements which brain death impels upon the kidney, the donors raised in pathogen free environments will be theoretically free of exogenous infections, and borderline transplant candidates will be more likely to receive an organ as they will not be competing with other candidates for a scarce resource [1, 2]. Currently, the only candidates for whom preemptive transplant is an option are those undergoing LDKT. However, during the evaluation time (average of 10.6 months), 1/3 of patients progress to dialysis anyway. Preemptive kidney transplant has shown superior outcomes in terms of return to baseline functional status—more than 50% of patients returned to work versus 25% who required hemodialysis prior to transplantation [4].

Another advantage of kidney xenotransplantation is that it may act either as destination therapy or as a bridge to allotransplantation. Current evidence suggests that sensitization to pig antigens would not preclude subsequent allotransplantation. This would allow patients to avoid the medical and social consequences associated with dialysis [1, 2, 5]. This is likely to be the case for the first patients and experience will help determine which problems need to be overcome if it is to progress to destination therapy.

The patients most likely to benefit from kidney xenotransplantation are those who are waitlisted but unlikely to receive a DDKT and for whom a living donor is not an option. These include patients in their late 50 s/early 60 s without other significant medical comorbidities. Patients who no longer have reliable vascular access and those with rapid recurrent kidney disease (e.g. FSGS, MPGN type II) should also be considered [2, 4, 6–8]. The average remaining lifespan for patients age 65–69 on dialysis is 4.6 years, compared to 11.4 years after kidney transplantation, indicating that older patients are more likely to benefit [4]. There is some controversy about whether highly allosensitized patients should be considered. Some experts argue that including allosensitized patients would be beneficial as they are more likely to spend prolonged time on the waiting list. Genetic engineering can be used to knockout any swine leukocyte antigen (SLA) II gene against which a patient

may have antibodies [8]. If these patients were to experience rejection, the graft could be excised and dialysis re-initiated. Additionally, these patients would still be candidates for subsequent allotransplantation. Others argue that these patients should not be included in the first clinical trials so as to mitigate the risk of rejection, though highly sensitized patients may be most likely to benefit long-term [2, 4].

Overcoming Barriers of Xenotransplantation

An additional advantage of xenotransplantation is the risk of transplant related infectious diseases may be lower compared to allotransplantation due to source animals being raised in designated pathogen free facilities. Infections typical in allotransplantation (e.g. Hepatitis B, Hepatitis C, human immunodeficiency virus) only infect human cells and therefore would not be of concern for donor to recipient transmission. However, porcine endogenous retroviruses (PERVs) are intrinsic to the pig genome and therefore present within all transplanted tissues. While there is evidence that the sequences encoding PERVs can be eliminated with gene editing technology (e.g. CRISPR/Cas9, virus neutralizing antibodies, miRNA targeting), so far there has been no evidence of transmission in NHP models [8–10]. Undoubtedly, highly sensitive surveillance of PERV transmission will be necessary if xenotransplantation is to progress to clinical trials, which will require reliable assays specific to PERVs to be developed [11]. Whether it is possible to genetically modify organ source pigs to eliminate all PERVs or the ability to provide a pathogen-free pig remains to be determined [10].

Additionally, infection with cytomegalovirus (CMV) in particular, has been shown to contribute to increased morbidity and mortality in addition to higher rates of graft dysfunction and rejection in allograft recipients. In baboon models, the presence of porcine CMV in the donor organs was associated with markedly decreased graft survival [12]. This finding highlights the importance of developing highly sensitive and expedient assays for detecting porcine CMV so as to assure that donor animals are porcine CMV free prior to transplant.

One of the most significant breakthroughs allowing for the advancement of xenotransplantation in recent years is gene editing technology, particularly CRISPR/Cas9. Triple knockout (TKO) pigs, in which the genes for three known carbohydrate xenoantigens against which humans have preformed antibodies are eliminated, have been used in preclinical trials with markedly prolonged survival of xenograft recipients. The deletion of these genes is contributory to preventing hyperacute and acute humoral xenograft rejection (AHXR). Multiple studies have confirmed that simultaneous inactivation of galactose-α1,3-galactose (Gal) and two non-Gal antigens, N-glycolylnueraminic acid (Neu5Gc) and Sda, produced by cytidine monophosphate-N-acetylneuraminic aid hydroxylase (CMAH) and β 1,4 N-acetylgalactosaminyltransferase 2 (β4GalNT2), dramatically decreases the binding of human antibody to pig tissues [9, 10]. Further donor modification is likely required to diminish the effects of AHXR. TKO pigs are now being used as the basis in all preclinical experiments, but additional genetic modifications have not yet been standardized [9].

There are a few areas where further genetic modification will be necessary before progressing to clinical trials. Additionally, multiple experiments with the same genetic modifications will have to be verified.

The expression of human complement regulatory proteins (e.g. CD39, CD46, CD55) has also been associated with prolonged survival in pig to NHP studies [2, 5–7, 13]. Induction of these genes has been shown to prevent complement mediated injury in the xenografts. In addition, NHP models in which one or two human complement regulatory proteins were introduced did not exhibit proteinuria, which was previously identified as a significant barrier to kidney xenotransplantation [8, 14]. Part of the problem with complement deposition is not only graft rejection but also coagulation dysfunction. Complement deposition can result in antibody binding and resultant pig vascular endothelial destruction. This can result in thrombotic microangiopathy (TMA) in the graft and/or systemic consumptive coagulopathy [9]. In one study, TMA was one of the features that indicated impending graft failure [13]. While complement deposition plays a role in coagulation dysfunction, there are other factors which can be the target of genetic modification. These include thrombomodulin (TBM) (strong anticoagulant effect), tissue factor pathway inhibitor (TFPI), and endothelial protein C receptor (EPCR) (has both anticoagulant and anti-inflammatory effects)[9, 15].

Systemic inflammatory responses can also occur in response to the xenograft, which can result in further coagulation disturbances, aggravated immune response, and enhanced resistance to immunosuppressive therapy. In order to diminish this effect, some researchers have experimented with including an IL-6 inhibitor and anti-TNFα agents however, they have not demonstrated efficacy [5, 9]. The induction of anti-inflammatory transgenes (e.g. hemeoxygenase-1 (HO-1) or A20) may suppress the inflammatory response, but whether to sufficient levels remains to be seen [6].

Advancement in genetic engineering technology has made innumerable permutations of modifications available. However, as the number of genetic modifications increase, pigs generally become more ill and it becomes more difficult to make these embryos viable [7]. Therefore, the genetic modifications required for the optimal balance between minimum immunogenicity and maximum donor health have yet to be realized. The current suggestion for the optimally genetically modified pig kidney includes one or two transgenes that would address each of the above barriers to xenotransplantation. The TKO pig constitutes the basis in which known antigenic proteins to humans are deleted. The insertion of hCD46 and hCD55 would protect from complement mediated injury. Insertion of hEPCR would suppress TMA in the graft and suppress consumptive coagulopathy in the recipient. hCD 47 would inhibit the cellular immune response. Finally hHO-1 and hA20 would avoid the systemic inflammatory response [9]. Further studies will be required to determine how this affects the health of the source pig as well as any possible unintended consequences of this combination of genetic manipulations. Ultimately, the genetic modifications will have to be standardized and reproducible in order to present acceptable data to authorities for the initiation of human clinical trials [14, 16].

Immunosuppression

The other major obstacle to overcome if xenotransplantation is to become a clinical reality is determining the appropriate immunosuppression regimen for xenotransplant recipients. The currently available agents used in allotransplantation—antithymocyte globulin (ATG), anti-CD20 monoclonal antibody (mAb) (rituximab), tacrolimus, corticosteroids, mycophenolate mofetil (MMF), and corticosteroids have not seen the same rates of success in xenotransplantation [8]. Many studies have suggested that a co-stimulation blockade with an anti-CD40/anti-CD154 mAb will block the T cell mediated elicited antibody and cellular response [6]. These are usually added to a combination of conventional immunosuppression (e.g. MMF, rapamycin, tacrolimus + steroids). Importantly, there have been no reports of increased drug related complications than with conventional immunosuppression [5]. One study in a NHP model tested conventional immunosuppression regimen against a regimen including an anti-CD40 monoclonal antibody. They found that the group which received the anti-CD40 mAb had significantly longer overall and rejection free survival, no evidence of consumptive coagulopathy, and no development of TMA or arterial vasculitis (which indicated impending graft failure). These results indicate that the co-stimulation blockade of the indirect T cell response is essential to preventing xenograft rejection and failure [13]. Unfortunately, anti-CD40/anti-CD154 mAbs are not yet approved by the US Food and Drug Administration (FDA). An anti-CD40 mAb is currently in phase II clinical trials, but for autoimmune diseases [9]. This may present a delay in bringing kidney xenotransplant to clinical trials if FDA approval is first required.

Efficacy and safety must be proven in preclinical models prior to xenotransplantation being approved for human clinical trials. Two groups have shown survival of >7 m. However, at least six experiments with a pig with consistent genetic modifications and a consistent immunosuppression regimen will have to be demonstrated. The target metric will be >90% survival at 1 year. The greatest safety consideration will be the transmission of PERVs. So far, this has not been observed in preclinical models. There will likely need to be a surveillance system in place so as to reliably screen for these infections and respond promptly. Having public support of xenotransplantation will also require significant investment in public education. Surveys so far would indicate that the public is supportive of xenotransplantation if it offers equivalent outcomes to allotransplantation. Additionally, people are more supportive of using pigs than primates as the source of the organ.

Public Acceptance of Xenotransplantation

While there are ongoing efforts to mitigate racial disparities in transplantation, Black patients continue to comprise a disproportionately high percentage of patients with ESRD, more remain on the waitlist for a longer period of time, and are less likely to receive a transplant. Xenotransplantation has the potential to alleviate some of these disparities. However, while acceptance rates of a genetically modified pig

organ are high amongst Black and White patients (assuming outcomes are equivalent to allograft function), a study reported that Black patients are still less likely to accept a kidney xenotransplant compared to White patients. This may be partially attributable to the longstanding distrust of the medical profession in the Black community given prior historical abuses as well as poor personal experiences interfacing with the healthcare system. Interestingly, this study also found that Black patients were more concerned with potential psychosocial implications (e.g. personality changes) perceived as being associated with receiving a pig kidney. If xenotransplantation is to reach clinical trials, it will be essential to recruit a representative patient population in order to draw generalizable conclusions, possibly help increase trust and ultimately provide the best care possible for patients [17].

Approaching Human Clinical Trials

In terms of approaching human clinical trials, a group from the University of Alabama at Birmingham recently published their findings of the first porcine kidney xenotransplant into a human decedent model. The source animal was the TKO pig with the following additional genetic modifications: insertion of two human complement inhibitor genes, two human anticoagulant genes, two immunomodulatory genes, and the pig growth hormone receptor gene. They used a conventional immunosuppression regimen—the induction regimen included a daily methylprednisolone taper, anti-thymocyte globulin (6 mg/kg), and anti-CD20 antibody. Maintenance immunosuppression included mycophenolate mofetil, prednisone, and tacrolimus. Importantly, using a novel flow crossmatch assay, they observed no hyperacute rejection, and therefore concluded that the genetic manipulations utilized in this experiment were sufficient to prevent hyperacute rejection. Additionally, they found that xenograft integrity was maintained at human arterial pressures. Over the course of 3 days, the right kidney (connected to the bladder) made approximately 700 cc of urine and the left approximately 250 cc. The serum creatinine did not improve, attributed alterations in the renal parenchyma which resulted from the genetic mutations. Additionally, the hyperinflammatory state that is characteristic of brain death was also thought to be contributory, which may represent an overall limitation of this model for predicting response to a xenograft in a living recipient. The histologic findings showed diffuse TMA by post operative day one, but no progression to cortical necrosis or interstitial hemorrhage [18]. This set of experiments represents an exciting start in the progression to living human clinical trials, and next steps will likely include testing newer immunosuppressive agents (e.g. anti-CD40 mAb, anti-CD154 mAb, anti-CD5 mAb) in these models in order to optimize graft function and longevity.

Another group of researchers performed a similar study at New York University, transplanting two pig kidney xenografts into two separate braindead human recipients. Similarly to the study performed at UAB, the source animals were TKO pigs and conventional immunosuppression was used. Recipient 2 had a weakly positive crossmatch on the complement dependent cytotoxicity assay however the

only consequence of this was histological evidence of focal Cd4 staining, without significant functional impact on the graft. Both kidneys began making urine within minutes of reperfusion and creatinine decreased after implantation. Additionally, serial biopsies over the course of the 54-hour study demonstrated no evidence of hyperacute rejection. The authors demonstrate that, with TKO pigs and conventional immunosuppression, hyperacute rejection is unlikely. However, this study is also limited by its short observation period and further research over a longer timeframe to determine the sustainability of these xenografts in human recipients [19].

Conclusion

Kidney xenotransplantation likely represents the next breakthrough in transplant surgery. It may alleviate the previously insurmountable problem of donor organ shortage, allow for pre-emptive transplantation and avoidance of the adverse effects of dialysis, and ultimately contribute to maximized life-years and quality of life for kidney transplant patients. While there is more research to be done in order to optimize the genetic modifications to the source pigs as well as determine the ideal immunosuppressive regimen, the first human clinical trials are likely to be underway in the very near future, making this exciting prospect one step closer to becoming a clinical reality for many ESRD patients.

References

1. Cooper DKC, Hara H, Iwase H, et al. Pig kidney xenotransplantation: progress toward clinical trials. Clin Transpl. 2021;35(1):e14139. https://doi.org/10.1111/ctr.14139.
2. Jagdale A, Kumar V, Anderson DJ, et al. Suggested patient selection criteria for initial clinical trials of pig kidney xenotransplantation in the United States. Transplantation. 2021;105(9):1904–8. https://doi.org/10.1097/tp.0000000000003632.
3. System USRD. 2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. Secondary 2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States 2019 2019. https: //www.usrds.org/annual-data-report/
4. Jagdale A, Cooper DKC, Iwase H, Gaston RS. Chronic dialysis in patients with end-stage renal disease: relevance to kidney xenotransplantation. Xenotransplantation. 2019;26(2):e12471. https://doi.org/10.1111/xen.12471.
5. Cooper DKC, Hara H. "You cannot stay in the laboratory forever"*: taking pig kidney xenotransplantation from the laboratory to the clinic. EBioMedicine. 2021;71:103562. https://doi.org/10.1016/j.ebiom.2021.103562.
6. Cooper DKC, Iwase H, Wang L, et al. Bringing home the bacon: update on the state of kidney xenotransplantation. Blood Purif. 2018;45(1–3):254–9. https://doi.org/10.1159/000485163.
7. Shaw BI, Kirk AD. Kidney xenotransplantation. Steps toward clinical application. Clin J Am Soc Nephrol. 2019;14(4):620–2. https://doi.org/10.2215/cjn.12471018.
8. Cooper DKC, Gaston R, Eckhoff D, et al. Xenotransplantation—the current status and prospects. Br Med Bull. 2017;125(1):5–14. https://doi.org/10.1093/bmb/ldx043.
9. Yu X-H, Deng W-Y, Jiang H-T, Li T, Wang Y. Kidney xenotransplantation: recent progress in preclinical research. Clin Chim Acta. 2021;514:15–23. https://doi.org/10.1016/j.cca.2020.11.028.

10. Cowan PJ, Tector AJ. The resurgence of xenotransplantation. Am J Transplant. 2017;17(10):2531–6. https://doi.org/10.1111/ajt.14311.
11. Goerlich CE, Chan JL, Mohiuddin MM. Regulatory barriers to xenotransplantation. Curr Opin Organ Transplant. 2019;24(5):522–6. https://doi.org/10.1097/mot.0000000000000678.
12. Yamada K, Tasaki M, Sekijima M, et al. Porcine cytomegalovirus infection is associated with early rejection of kidney grafts in a pig to baboon xenotransplantation model. Transplantation. 2014;98(4):411–8. https://doi.org/10.1097/TP.0000000000000232.
13. Yamamoto T, Hara H, Foote J, et al. Life-supporting kidney xenotransplantation from genetically engineered pigs in baboons: a comparison of two immunosuppressive regimens. Transplantation. 2019;103(10):2090–104. https://doi.org/10.1097/tp.0000000000002796.
14. Shah JA, Lanaspa MA, Tanabe T, Watanabe H, Johnson RJ, Yamada K. Remaining physiological barriers in porcine kidney xenotransplantation: potential pathways behind proteinuria as well as factors related to growth discrepancies following pig-to-kidney xenotransplantation. J Immunol Res. 2018;2018:6413012. https://doi.org/10.1155/2018/6413012.
15. Kim H, Hawthorne WJ, Kang HJ, et al. Human thrombomodulin regulates complement activation as well as the coagulation cascade in xeno-immune response. Xenotransplantation. 2015;22(4):260–72. https://doi.org/10.1111/xen.12173.
16. Ekser B, Li P, Cooper DKC. Xenotransplantation: past, present, and future. Curr Opin Organ Transplant. 2017;22(6):513–21. https://doi.org/10.1097/MOT.0000000000000463.
17. Padilla LA, Hurst DJ, Jang K, et al. Racial differences in attitudes to clinical pig organ xenotransplantation. Xenotransplantation. 2021;28(2):e12656. https://doi.org/10.1111/xen.12656.
18. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;22(4):1037–53. https://doi.org/10.1111/ajt.16930.
19. Montgomery RA, Stern JM, Lonze BE, et al. Results of two cases of pig-to-human kidney xenotransplantation. N Engl J Med. 2022;386(20):1889–98. https://doi.org/10.1056/NEJMoa2120238.

Index

D. J. Hurst et al. (eds.), *Xenotransplantation*, https://doi.org/10.1007/978-3-031-29071-8