PERSPECTIVE

Ethical considerations in xenotransplantation of thoracic organs – a call for a debate on value based decisions

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Xenotransplant covers a broad ethical territory and there are several ethical questions that have arisen in parallel with the technological advances that have allowed the first porcine transplants to occur. This brief communication highlights ethical considerations regarding heart and lung xenotransplantation, with an emphasis on unresolved value-based concerns in the field. The aim of this text is therefore to encourage the readers to consider the vast potential of this emerging technique to do good, but also the risk of doing harm, and to participate in a discussion. The list of questions presented here is not exhaustive but hopefully represents some of the questions that appear to be most pressing as the field advances. The focus is on the value-based, or ethical questions, not the questions related to the practical medical procedures.

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Solid organ transplant is established as a lifesaving treatment for terminal heart or lung diseases. More than 4000 lung transplants and a similar number of heart transplants are performed annually worldwide.1,2 However, the availability of organ donors remains limited. In the United States, about 800 patients died in 2021 waiting for a heart or lung transplant (https://unos.org/data/transplant-trends/).

Pigs have been selected for study in the provision of organs that may be used for human transplant, both because of anatomical similarities, rapid reproduction time, and the pre-existing experience in raising pigs for human consumption. In January 2022, the first porcine heart was transplanted into a human recipient who lived for 8 weeks after the procedure.3–5 The second porcine heart transplant occurred in September 2023; the recipient lived nearly 6 weeks.

That these 2 transplants occurred is a medical and scientific feat. Xenotransplant (XTx) covers a broad ethical territory and there are several ethical questions that have arisen in parallel with the technological advances. This brief communication highlights ethical considerations regarding heart and lung xenotransplantation, with an emphasis on unresolved value-based concerns in the field.

Aim of this document

While there is no doubt that the successful development of XTx has the potential to save many human lives, there are...
many pending questions. In a statement on XTx, the American Medical Association (AMA) emphasizes that it is the responsibility of medical professionals who pursue the development of xenotransplantation to “encourage education and public discussion of xenotransplantation in light of the unique risks such procedures pose to individual patients and the public.”

(https://code-medical-ethics.ama-assn.org/ethics-opinions/xenotransplantation)

In agreement with this, we believe that it is the responsibility of the International Society for Heart and Lung Transplantation (ISHLT) to promote awareness of the possibilities, limitations and concerns regarding XTx of hearts or lungs among the members of the ISHLT. The aim of this text is therefore to encourage the readers to consider the vast potential of this emerging technique to do good, but also the risk of doing harm, and to participate in a discussion within the ISHLT, in other societies engaged in XTx, and elsewhere. To initiate this discussion, the ISHLT Board of Directors charged the ISHLT Ethics Committee to create a document outlining questions that need to be discussed regarding XTx. The list of questions presented here is not exhaustive but hopefully represents some of the questions that appear to be most pressing as the field advances. We deliberately and exclusively focus on the value-based, or ethical questions, not the questions related to the practical medical procedures, which more appropriately should be addressed in methodological review articles and as research questions in future studies.

**Ethical questions for xenotransplant of thoracic organs**

**Experimental design**

For decades, human subject experimentation has been governed by a set of rules and declarations designed to protect subjects who may be vulnerable and unaware of their risks. The ethical practice of such research requires that there be a reasonable standard of informed consent, with risks and benefits understood by the involved parties. It also holds that subjects involved in medical research have the right to withdraw at any time and for any purpose. The following questions emerge regarding the experimental development of XTx to humans:

- Should XTx to humans be developed and successfully tested for kidneys before it is introduced for thoracic organs?
  - This question addresses how low the risk of having to reverse the transplant (i.e. by removing the organ due to any unforeseen complications) must be before animal to human transplantation of thoracic organs can be considered. While a transplanted kidney may be removed and the recipient kept alive by dialysis, no such durable alternative is available after heart or lung transplantation. Therefore, the question that needs to be discussed is how low the expected risk of having to reverse a XTx needs to be before it is reasonable to conduct animal to human transplants of heart or lungs.
- Should the clinical application of XTx wait until there are more data from XTx grafts into humans who, after neurologic death have donated their bodies for transplantation research?
  - Short term studies have been conducted with pig-to-human renal transplants in recently brain-dead humans. In 1, the contribution of the pig kidney to renal clearance was not performed so that the function of the xenograft could not be determined. A second study in which the human brain-dead recipients underwent nephrectomies prior to the XTx, despite urine production there was no improvement in creatinine clearance. A single case was reported with improved creatinine clearance in the same model.
- What is the appropriate trial design for XTx, and what regulatory oversight should be employed?
  - To date, animal to human heart XTx has been approved under emergency use authorization (“compassionate” use) regulations in the United States. Should future research in XTx receive similar exceptional consideration or should standard clinical trial ethical and regulatory considerations apply? One requirement for “compassionate use” is that enrollment in a clinical trial is not possible. Should it be considered crucial for further advancement of animal to human XTx that clinical trial protocols are developed? Establishment of clinical trials would allow for the following: standardization of protocols to minimize variability and increase the ability to generate generalizable knowledge. What regulatory oversight, whether national or international should be employed?
- How does the concept of “informed consent” apply to human XTx?
  - Coerciveness: While consent may be problematic in any study offering a possible lifesaving treatment to someone who would otherwise die, it is worth asking whether this risk of coerciveness is different in XTx.
  - Who must consent: While lifelong observation may be necessary (and recommended) for allotransplantation, the risk of withdrawing from a clinical trial of standard allotransplantation is carried by the subject. Unique for XTx might be the potential need for surveillance of close contacts or even society in the broader sense due to the risk of disease transmission (see below). Does this challenge the standard of allowing research subjects the right to withdraw from trial participation? Does this extended risk require an extended need for consent? Do close contacts, including the transplant health care team, need to be asked for consent as part of a study protocol, given the potential risks to them? Although not typically required in the context of transplantation and human transmissible infections—for example, donors with hepatitis B or C—should the bar be
higher in XTx for considering the study population to extend beyond the transplant candidate?

- Should surrogate consent be allowed for XTx? For many procedures or interventions, surrogate consent is widely accepted based either on substituted judgment or best medical interest. Additional complexities arise in XTx, particularly in pediatric XTx, where ethical considerations regarding 2 parent consent, patient assent, and waiver of assent become relevant.11

- Who should be responsible for recruiting subjects and obtaining informed consent for XTx studies?

  - The research consent process should minimize potential conflicts of interest, including personal or financial stakes in recruiting subjects into a clinical trial and the trial outcomes. Uniquely in transplantation, potential subjects may feel pressure to participate if approached by members of their clinical care team, particularly those with whom they have a long-standing relationship. This rule applies for all medical studies on human subjects, and it should be discussed whether XTx is different.

- What are the conditions for considering clinical alternatives and assuming clinical equipoise in thoracic XTx experiments or trials?

  - Discussion of trial design has included use of the language from typical Phase 1 or Phase 2 studies to minimize the potential for therapeutic misconception.
  - As durable mechanical support for advanced heart failure has a 5-year survival that nears 60%,12 and as this technology improves and is miniaturized, the expected benefit of a heart XTx to a particular recipient needs to be considered and compared to its alternatives when designing future experiments and studies. It must be discussed what is the acceptable risk-standard that should be considered when weighing even short-term survival with temporary devices compared with the recent XTx outcomes.

- What would be the conditions to assume clinical equipoise in pediatric cases of XTx? Since both the access to allotransplantation and the possibility of alternative treatments (such as mechanical support) are far more limited in pediatric cases than adult, a separate discussion of clinical equipoise in thoracic XTx for children is necessary.13,14

- To what extent should XTx clinical trials aim for equal opportunities and diversity for participation?

**Immunological and pharmacological considerations in XTx**

Cells in porcine organs do not carry human leukocyte antigen (HLA)-antigens. On the other hand, porcine cells carry surface antigens that cause immune reactions in a human host, such as the glycan antigens. Also, the lack of inhibitory NK-cell ligands in porcine cells could invoke human NK-cell mediated responses. Therefore, the pigs need to be genetically modified to be suitable for human organ transplantation. The CRISPR/Cas9 technique has enabled such modification, and several for-profit companies are currently developing pigs with genetic modifications for the purpose of XTx.15 Nevertheless, it seems that the different immunological situation in a XTx setting may require a post-operative immunosuppressive regimen that differs from conventional post-transplant immunosuppression.16

- What is the potential for financial conflicts of interests with the commercialization of these technologies, and how might that be mitigated in the choice of potential recipients?
- How does the substantial financial investment in the development and production of suitable donor animals affect the selection of candidates, both in the initial experiments and in potential future organ allocation?
- How could a for-profit production of organs for transplant alter the selection of transplant candidates?
- How is the immunological situation different in XTx for pediatric recipients?11,17

**Infectious considerations in XTx**

Pigs inherently carry several porcine endogenous retroviruses (PERV) embedded in their DNA. Under certain circumstances, PERVs have been shown to have the ability to infect human cells with potential for replication and oncogenesis.18 Furthermore, porcine cytomegalovirus (also known as porcine herpesvirus) can also be present in the xenograft organ as was seen with the first porcine-human XTx.19 The extent to which the use of porcine organs in human recipients may lead to zoonosis is unknown.

In addition to the directly transmitted, it is conceivable that porcine organs transplanted to humans may be susceptible to porcine virus-mediated disease after the transplant. The known cross-reactivity of influenza viruses between pigs and humans may be of particular interest if lungs are transplanted as this has the potential for inciting a human immune response. To date, the anatomical and physiological structure of porcine lungs does not allow considering their use for lung xenotransplantation in humans. But the rapidly evolving capacities of genetically modifying animals may lead to a pig lung that is functionally adapted to human physiology, and it is relevant to discuss XTx also in the context of influenza virus risk.20,21

Increased risks around the natural evolutionary processes of respiratory viruses (especially the influenza group viruses that naturally spread between birds, pigs, and humans) may dramatically affect the exposure of human beings to unknown zoonoses. The immunosuppressed state of the recipient may augment the nature of such infections. Importantly, in addition to the risk of donor to recipient transmission of disease, as seen in any transplant, there is a risk of transmission from the recipient to close contacts, or even to others, potentially affecting public health. Unlike the risk of opportunistic infection seen in any immunosuppressed organ transplant recipient, the animal-borne infections and those potentially acquired by the human recipient through the animal organ may conceivably
also be passed on to other humans, possibly in a mutated state. Thus, the infectious disease surveillance of the recipient after the transplant would be motivated not only by the best interest of the recipient, but also by the interest of the recipient’s contacts and in the interest of the global society; and lifelong follow-up has been recommended by the US Public Health Service (§4.1.1.1) (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5015a1.htm) and by a working group commissioned by the World Health Organization in 2008.

Thus far, no transmission of viruses or other zoonoses to third parties has been detected in the experimental models of pig-to-human transplant. In the first patient who received a porcine heart, however, porcine cytomegalovirus (pCMV) was observed in the donor heart at time of autopsy. This had not been detected prior to the transplant, but whether it contributed to the death of the recipient is presently still unclear.

• What principles should guide us regarding the risk of animal-to-human transmission of porcine retroviruses or other infectious agents?
• Who carries the burden to prove that the individual and societal risk is sufficiently low before porcine organs are transplanted into humans who are expected to live in the community after the transplant?
• Do different risk thresholds apply for other zoonoses where the risk to close contacts and society is less clear?
  ○ Although infectious risk to close contacts and to the global society may never be absolutely ruled out in XTx, a discussion about what should be the acceptable limit for such a risk is warranted.
• Are the risk of infections different in pediatric XTx?

Other considerations in xTx

Candidate selection

The availability and the cost of organs for transplant would be very different from the current situation where organs from human donors are utilized, procured, and allocated under the administration and oversight of national and international organizations. It is currently not clear how the cost of producing the organs for XTx should be covered or how animal organs should be allocated compared to conventional human hearts or lungs, or mechanical circulatory devices.

• Who would be a suitable candidate for XTx of thoracic organs in clinical practice?
  ○ While candidate selection criteria for conventional transplantation of thoracic organs have been developed over several decades, adjusting to the scientific progress and societal expectations, it may be that these traditional criteria (i.e. estimations of need and survival benefit based on prognostic factors, and appraisals of social justice) would not entirely apply to XTx. For example, do factors that increase the risk of failure after a regular transplantation (such as high age, substance use, or poor adherence) represent an opportunity or a contraindication for XTx?
  ○ What specific considerations must be made when considering XTx in the pediatric population? As discussed, both the conditions for consent, the clinical options and equipoise, and the immunological and infectious risk may be different in the pediatric population, and within it (e.g., neonates and peripubescent adolescents). Also, it is conceivable that the emotional context in pediatric cases creates a different balance in the considerations of value-based decisions regarding XTx.
  ○ Is it a disservice to the development of XTx if only candidates with poor prospects of success after regular transplantation are selected for XTx? Such a selection may conceivably lead to poor results and thus unduly delay the development of XTx.
  ○ Is it problematic to offer a patient XTx if other, more established, and less uncertain methods are available? Specifically, a very rigorous definition is required of the subgroup of advanced heart failure patients who are ineligible for either human transplantation or uni- or biventricular assist devices and who would then be considered for XTx. The discussion of a suitable candidate may change with the development of this technology and if XTx becomes more widely available.
  ○ The absence of HLA antigens on porcine cells may render such organs particularly advantageous for human transplant candidates where significant pre-transplant immunization may limit access to timely organ transplant using a human organ.
  ○ Could XTx be a viable option as a bridge to allo-transplantation, particularly in pediatric cases. How would this effect organ allocation strategies in the future?

Animal welfare and environmental considerations

While current human-to-human transplantation requires thorough evaluations of the ethical propriety of the organ donation process, e.g. observance of the dead donor rule for vital organs such as hearts and double lungs, the conditions for XTx are different. Genetically modified animals would be developed and bred for the purpose of supplying organs, and like animals used for scientific experiments and for food, the ethical considerations related to killing them tend to focus on welfare and the use of humane procedures. There are myriad other issues relate to animal husbandry, breeding practices for pigs and other animals used in XTx which deserve attention but are beyond the scope of this current discussion.

• Is animal welfare appropriately ensured considering the highly artificial conditions that are necessary to produce animals that would be suitable to supply organs for humans?
  ○ While the concept of animal welfare in the context of XTx has some similarities to animal welfare in
agriculture, there are distinct differences in how these animals are bred and reared.

- Are environmental consequences appropriately considered?
  - Controversies about genetically modified organisms and other concerns related to industrial animal farming that have hitherto been within the purview of other disciplines might become relevant to transplant medicine.

**Societal considerations**

Finally, in addition to the biological and administrative or financial considerations there may be emotional, psychological, or religious sensitivities involved in placing animal organs into humans. 27–30

- How will the research on XTx and the eventual introduction of XTx affect perceptions of organ transplantation and the consent rate for organ donation in the general population?
- Will the extensive use of animal organs for organ transplants (to humans) affect the distinction between how we think about the value of the animal or human lives?
- Will the introduction of XTx lead to increased disparities in access to health care?
  - While disparities in access to organ transplantation may be expected to be proportional to the social differences existing in any country, the development of organ allocation and administrative systems has at least involved the entire society, and a certain “trickle down” effect could be expected as a result, creating an expectation of equal access to human donor organs. The introduction of the highly cost intensive XTx, however, may conceivably exacerbate disparities in access to transplant.
- Is it likely that the cost of XTx will decrease as the method is further developed?

**Conclusion**

Significant progress has been made since the first successful human organ transplants were performed about 70 years ago, for the benefit of tens of thousands of people. While appreciating this enormous benefit, it should not be neglected that human organ transplants were performed about 70 years ago, -

With the recent scientific advances in gene technology and clinical experiments of pig-to-human organ transplantation, it may seem that we are at the dawn of a significant change in solid organ transplant medicine. Notwithstanding these extraordinary achievements, many questions remain unanswered. While thorough and methodical research will further answer the scientific questions, many of the value-based questions should be examined in a continuing dialogue between all stakeholders. This text outlines some such questions.

**Encouragement to debate**

This paper is intended to promote discussion locally, at transplant centers and elsewhere, and within the ISHLT and other societies. On behalf of the ISHLT Board of Directors, we encourage ISHLT members and other readers to participate in the discussion about the value based questions raised by the development of XTx.

**Disclosure statement**

The authors are members of the ISHLT Ethics Committee. Tom Egan receives honoraria for work on National Institutes of Health study sections and is a member of the Editorial Board of the ISHLT, and a member of the Thoracic Organ Committee for the American Society of Thoracic Surgeons. Savitri Fedson receives honoraria from the American Board of Internal Medicine for work with the Advanced Heart Failure/Transplantation board exam committee. Are Holm is a current member of the Board of Scandiatransplant. Manreet Kanwar reports speaking fees from Abiomed; she is on advisory boards for Abbott, Abiomed and CorWave Andrew Courtwright, Kelly Bryce, and Jay Lavee report no additional relationships.

**References**


