



INVITED REVIEW

Clinical xenotransplantation seems close: Ethical issues persist

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Abstract

Scientific barriers that have prevented successful xenotransplantation are being breached, yet many ethical issues remain. Some are broad issues that accompany the adoption of novel and expensive technologies, and some are unique to xenotransplantation. Major ethical questions include areas such as: viral transmission; zoonoses and lifetime surveillance; interfering with nature; efficacy, access, and expense; treatment of animals; regulation and oversight.

KEYWORDS

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The current system of organ donation and allocation saves thousands of lives a year. The availability of organs for transplantation has been grossly inadequate, resulting in thousands of deaths of waitlisted patients annually. Xenotransplantation, the transfer of organs between species, could provide enough organs to reduce or even eliminate waitlists, and potentially expand the range of eligible patients.

Norman Shumway famously commented that xenotransplantation is the future of transplantation, and always will be.¹ Experimental xenotransplantation started more than 120 years ago² but clinical xenotransplantation has not had long-term success due to immune rejection, even in the presence of immunosuppressive therapies.

Recent concerns arose after the discovery that retroviruses, such as porcine endogenous retroviruses (PERVs), can be embedded in the genomes of potential organ sources and could cause zoonotic infections. Pigs seem the most suitable source of organs for humans for many reasons, including appropriate anatomy and size, large litter sizes, and short gestation periods, allowing a copious organ supply. Recent advances in genetic manipulation have resulted in the ability to decrease the human immune response to porcine tissues and to deactivate PERVs. As a result, at least two recent attempts at pig-to-human xenotransplantation have been initially successful. A porcine kidney was transplanted into a human who had been declared brain dead in order to observe organ function



and acute rejection in the short-term setting,³ and a porcine heart was transplanted into a patient with end-stage heart failure who was not a candidate for conventional therapies, in order to assess medium-term function and immunology.⁴

Scientific barriers that have prevented successful xenotransplantation are being breached, yet many ethical issues remain. Some are broad issues that accompany the adoption of novel and expensive technologies, and some are unique to xenotransplantation. We will focus on several major ethical questions: viral transmission; zoonoses and lifetime surveillance; interfering with nature; efficacy, access, and expense; treatment of animals; regulation and oversight.

1 | VIRAL TRANSMISSION

The potential for transmitting viral disease from the donor animal to the human host and the potential for zoonotic transmission to other people is a major concern, even if the risk is believed to be low. The devastation caused by the SARS-CoV-2 pandemic has elevated apprehension about zoonotic transmission because of the direct damage from the zoonotic pathogen, and the enormous collateral damage from mistaken and ineffectual governmental actions, and the rampant spread of misinformation through social media. Many types of infectious agents may be transmitted when pig organs are implanted in humans; of particular concern, however, are the porcine endogenous retroviruses (PERVs) that reside within the porcine genome. Their presence in the genome negates the efficacy of screening and isolation of donors, which are used for other pathogens.

Of the three main types of these retroviruses, PERV-A, PERV-B, and PERV-C, only the first two have been found to infect human cells *in vitro*. The recombinant PERV-A/C can also infect human cells.⁵ While these infections have been observed *in vitro*, they have not been seen *in vivo* in either primate models or in humans who have received tissues from pigs.⁶ Consequently, animals that are not infected with PERV-C and have low rates of PERV-A and PERV-B expression should be chosen for xenotransplantation.⁵ Recently, animals have been treated with CRISPR-Cas9 to deactivate these endogenous viruses, theoretically minimizing the chance of human infection.⁷ About 8% of the human genome is composed of sequences of retroviral origin.⁵ In theory, recombination between residual PERV fragments and human endogenous retroviral (HERV) sequences could produce a new pathogen with unpredictable capabilities.

While *in vivo* data has not shown transmission, most porcine-derived living tissues have been implanted in

humans with no or minimal immunosuppression, and many such attempts have used pancreatic islet cells, which are encapsulated, preventing them from releasing PERV.⁸ The risk of infection may be reduced with the use of retroviral medications or vaccination,⁹ but relevant data are limited. Limited data exist on the viability of xenografted tissue after transplantation, which might affect the likelihood of retroviral infection.¹⁰ Though the available data indicate that transmission is unlikely, PERV transmission in a recipient could still occur at a low rate and eventually lead to retroviral infection.

The need for PERV inactivation is debated. Some note that if PERV inactivation is the most effective way to prevent transmission of the retrovirus to humans,¹⁰ then non-PERV inactivated tissues should not be used. Others note that, in addition to the lack of *in vivo* infection seen clinically, no PERV infection of human or non-human primate cells has been identified *in vivo*, despite over 10 000 years of domestication and intimate contact between pigs and human beings.¹¹

The risk of retroviral transmission cannot be reduced to zero, and the SARS-COV-2 pandemic has reminded us that the consequences of transmission can be disastrous. No level of acceptable risk has been determined, and it is not clear how such a determination should be made. The potential for zoonotic infection may be very small, but should a pandemic result, the mortality, morbidity, and economic consequences would be borne worldwide. The SARS-CoV-2 pandemic has shown that smaller and poorer countries are likely to be hit hardest in terms of death and economic decline, and are not well-equipped to administer vaccines or other therapies. Thus, if a pandemic were to occur as a result of xenotransplantation, the countries least likely to reap the benefit may be the hardest hit from any resulting infection. At a minimum, this argues in favor of international standards for determining when risks are sufficiently low for clinical xenotransplantation to begin.

2 | ZOONOSSES AND LIFETIME SURVEILLANCE

2.1 | The recipient

The risk of zoonoses raises important ethical questions for transplant centers and recipients. Monitoring recipients for zoonotic infection will be mandatory. The infection could occur at any time in the near or distant future, so monitoring will be necessary indefinitely. In recent clinical trials of porcine pancreatic islet cells implantation, the recipients were subject to lifetime surveillance.¹² Logistically, patients become harder to track with the



passage of time. Loss of follow-up surveillance would constitute a danger to public health. A more difficult problem would arise if a transplant recipient wishes to withdraw from the trial and the on-going monitoring. One of the fundamental tenets of medical research is that participation is voluntary and the subject can withdraw at any time. Yet, because of the public health implications of zoonotic disease, recipients may be required to waive their right to withdraw from infectious disease surveillance, even if they retain the right to withdraw from other forms of participation in the study.¹³

2.2 | Public health

The risk of transmitting the zoonotic disease to others raises a variety of ethical questions. For example, will the recipient be required to disclose their transplant status to family members, romantic partners, or co-workers who could be exposed? If a recipient acquires a contagious zoonotic infection, how long would quarantine be necessary: for life? Would close contacts need monitoring as well? In the pancreatic islet studies, contact tracing was performed and close contacts were monitored when infection in the patient was suspected.¹² Blood samples were taken from the contacts and then stored for later analysis if host infection was demonstrated. Some community resistance to contact tracing was seen during the SARS-CoV-2 pandemic. Can patients be compelled to provide a list of contacts, and can the contacts be compelled to be monitored or provide blood samples, given that they did not volunteer for the study?

Sample storage will present major logistical problems. The U.S. Food and Drug Administration recommends that samples acquired during xenotransplantation studies be kept for 50 years, which will require substantial funding and extensive storage facilities.¹⁴ In the pancreatic islet trials, a total of 38 patients and their contacts generated over 30 000 samples in about 10 years.¹² Large volumes of samples must be retained over an extended period of time wherever a xenotransplantation trial is performed. The safety of patients and society at large requires a plan for prolonged data and sample retention in all jurisdictions where xenotransplantation is performed, even if trial sponsors cease operations.

2.3 | Legal limits on compulsion

Xenotransplantation is unique because no other medical treatment puts so many others at risk. In 1905, the U.S. Supreme Court ruled in *Jacobsen v. Massachusetts* that the state could compel vaccination of smallpox to

protect public health.¹⁵ In the Kaci Hickox case, however, the courts ruled that the state could not mandate quarantine for potential Ebola exposure.¹⁶ Recently, the U.S. Supreme Court blocked a mandate requiring masks or vaccination to protect against SARS-COV-2 for employees of large businesses, citing the lack of authority of federal agencies.¹⁷ In many states, local or state rules requiring the use of masks have been struck down by federal or state courts on grounds that personal freedom outweighs public health interests except in the most extreme circumstances. In a pluralistic society that places a high value on personal freedom, placing substantial restrictions on transplanted individuals or their contacts will be difficult. It is likely that restrictions will be legally challenged and that resolution could take too long to avert or contain a pandemic in its early stages.

2.4 | Non-adherence

The recent porcine heart recipient, David Bennett, was offered this option because he was not a candidate for allotransplantation, partly due to prior nonadherence to medical recommendations.¹⁸ What if a xenotransplant recipient refuses to comply with treatments intended to decrease the chance of zoonotic infection? The SARS-COV-2 pandemic has revealed widespread distrust of scientific information and, when the narrative is established by social media, conspiracy theories spread, and misinformation and disinformation produce turmoil. A patient's preexisting tendency for nonadherence could be exacerbated by exposure to misinformation, potentially increasing the likelihood of spreading zoonotic infection. Nonadherence, whether foreseen or developing later, has the potential to harm many more people than just the recipient. If the prevention of zoonotic infection requires adherence to medical therapy, then a history of medical nonadherence should be a relative contraindication to xenotransplantation.

3 | INTERFERING WITH NATURE

3.1 | The natural order

Some have criticized xenotransplantation on grounds that it represents "playing God", or interfering with the natural order of things.¹⁹ Mixing of tissues from different organisms into a single being creates a new form of life that did not exist in nature. This is unlike the use of bioprosthetic valves in that the lack of cellular viability of the implanted product negates the concept of a chimera, or a being composed of cells that



are genetically different. No such criticism has been directed at allotransplantation, however, although it produces the same result: a chimera or hybrid of the living tissues of two different beings, albeit of the same species. Although this is not a cross-species chimera, it is a hybridization outside of the “natural order”.

3.2 | Gene editing

Xenotransplantation requires genetic manipulation to decrease the risks of rejection and infection. The pig used in the recent xenotransplantation had 10 genetic interventions: 3 knockouts to eliminate hyperacute rejection, 1 knockout to eliminate continued growth of the implanted heart, and insertion of 6 human genes to reduce immunological rejection.⁴ All known life is based on the nucleic acid-based genetic code. Manipulation of this code is tantamount to manipulation of life itself, which some consider to be a dangerous and perhaps unethical undertaking.²⁰ Genetic manipulation to eliminate diseases in humans or to modify the genetic material of crops has been subject to similar criticism, but human beings have been manipulating the genetics of life in less sophisticated ways for millennia through the selective breeding of crops and animals, which has not been challenged on ethical grounds. Contemporary tools for gene editing provide a more targeted approach, but the goals of the manipulation are the same, whether the intent is to create normal physiology by altering defective genes or to enhance form or function by altering normally-functioning genes.²¹

The altered porcine genome used in xenotransplantation could theoretically be achieved by random mutation and selective breeding over long periods, so the knockout process could be viewed as creating natural variations at a faster rate. A more subtle variation is the addition of human genes to porcine cells to make them more human-like, thus avoiding rejection. Adding human genes to the porcine genome would not occur in nature, and thus raises its own ethical issues. Is a pig organ recipient a chimera, a new organism that is of human creation and thus morally suspect, or is xenotransplantation merely a medical advance? The answer to this depends on one's view of the limits on what humans should be permitted to do to preserve health.

3.3 | Religious considerations

A related question about xenotransplantation is its acceptance among various religions. For example, Judaism and Islam view meat from a pig as unclean; nevertheless, scholars from many of the world's major religions,

including Judaism and Islam, have accepted xenotransplantation as compatible with religious law.²²

3.4 | Emotional burden

A person whose survival depends on an animal heart might suffer emotional distress, or at least carry the burden of being abnormal in some way. Such problems have emerged in recipients of transplanted hands and faces, and patients living with a left ventricular assist device (LVAD) or artificial heart. It seems likely that some porcine xenotransplant recipients will manifest similar problems. Recipients of an animal organ might suffer social isolation or hostility, on grounds of being a health risk to others,²³ as happened in the early days of HIV/AIDS, and anti-Asian sentiments during the SARS-COV-2 pandemic. The resilience of the recipient will be an important determinant of the presence and severity of emotional burden.

4 | EFFICACY, ACCESS, AND EXPENSE—SHORT AND LONG TERM

Three requirements for the future success of xenotransplantation are good clinical outcomes, willing patients, and adequate funding, each of which has implications for the short and long term.

4.1 | THE SHORT TERM

The level of success will be understood gradually with experience, but it has important implications for the enrollment of patients and funding. Before xenotransplantation becomes accepted as safe and effective, subjects will be needed to volunteer for initial research, which will be variably successful. The companies developing the modified organs will continue to have large expenses in addition to the years of prior investment. If the technology is to become approved for widespread use, a critical mass of patients and substantial funding will be necessary.

The short-term costs of each xenotransplantation will be large. The companies that provide the animals and associated technologies must meet their costs and make a profit in order to remain viable, and the required experiments are very expensive. Revivicor is one of the companies active in the development of organs for xenotransplantation, and its early application for FDA approval was rejected. The FDA wanted all organs to come from a clinical-grade research facility and for experiments to be performed in baboons before human trials began.¹⁸



When a potential recipient was identified, the company, at the clinician's request and with the approval of the FDA, agreed to human implantation; one of the surgeons cited the cost of \$500 000 per experimental baboon as one of the reasons to move forward with human implantation.¹⁸

The two main current clinical treatments for end-stage heart failure are heart transplantation and LVAD support. Transplantation is the gold standard treatment for end-stage heart disease. LVADs can be used either as a bridge to transplantation or as an alternative to transplantation. LVAD therapies now produce clinically acceptable results. On the contrary, non-human primate heart xenotransplantation experiments have demonstrated limited graft durability and survival.²⁴ In light of all this information, patients might well be reluctant to undergo an experimental procedure that has been unsuccessful in the past, even if the techniques have been improved and problematic issues resolved. It seems likely that they would choose xenotransplantation only if other options were not available to them. For example, the recently xenotransplanted patient was determined not a candidate for human heart transplantation.⁴ He was also not a candidate for LVAD therapy due to arrhythmias. His plight is emblematic of that of many whose choices are severely limited by social or economic factors, which are likely to play a role in determining who will step forward for high-risk xenotransplantation research.

Medical nonadherence is associated with lower socioeconomic status, as those who cannot afford prescriptions or to see a physician on a regular basis are often deemed non-adherent even though external factors play an important role in their ability to seek care and comply with medical recommendations.^{25–27} Non-adherence is also seen more often in people who distrust the medical establishment, such as the Black community, in which the effects of the Tuskegee syphilis experiments still linger.²⁸ Access to appropriate medical care is influenced by insurance status. Non-insurance or under-insurance may lead to inadequate or delayed health care that can cause more serious illness. The patients who are asked to volunteer for unproven procedures may more often belong to disadvantaged and vulnerable groups whose members might not be candidates for conventional therapies because of advanced illness, yet the broadest applicability of the results of xenotransplantation studies requires that the volunteer subjects accurately represent the intended treatment group.

4.2 | The long term

Long-term issues related to the clinical practice of xenotransplantation focus on the expense and equitable

access. This therapy will be expensive. All transplantation is associated with immunosuppression costs, but additional expensive novel immunotherapy may be required for xenotransplantation.²⁹ Competition among the companies involved in creating these organs might keep the costs in check, but this seems not to have happened with many medical therapies. For example, when two U.S. companies produced LVADs, the costs of the devices remained high despite the competition. The price of medical devices is often set independently of the cost of development and manufacturing of the device. This relationship is complicated by the fact that the consumer of a xenotransplant (the patient) is not the payer (insurance company), a prominent feature of the entire health care system of this country. If xenotransplantation is substantially more expensive than allotransplantation, it seems likely that access will be limited to those with private insurance or the capability to pay out of pocket. If the results of xenotransplantation rival those of allotransplantation, then there is likely to be the disparity in organ access, favoring those with better financial resources. This could result in a two-tiered system, in which wealthier individuals have greater access to life-saving therapies and can avoid a prolonged time on the waitlist. This could have the unintended effect of increasing waitlist time for those who cannot afford an organ if the availability of organs for xenotransplantation decreases the perceived need to donate human organs and results in fewer human organ donors. Similar concerns that surrounded allotransplantation in the past have proven poorly founded; while access is not perfectly equitable, it is less unbalanced than some believed likely.²⁵

If the results of xenotransplantation are reasonable but not as good as those of allotransplantation, then these organs might be offered to patients further down the waitlist where there is a higher risk of mortality while waiting (in terms of kidney transplantation) or a very long expected waiting time at a low priority status (in the case of heart transplantation). If this should happen, few issues with access or vulnerability are likely, but waitlist problems could be exacerbated if xenotransplant recipients survive and remain on the waitlist for a human organ. While prolonging life is a worthy goal, we might see the unintended consequence of a longer waitlist and the need to continue the search for alternative sources of human organs.

5 | TREATMENT OF ANIMALS

A sentient being, that is, one with the ability to feel emotions is generally viewed as having a higher moral standing than a non-sentient being. Just how moral standing relates to degrees of sentience or self-awareness has been



vigorously debated.³⁰ Pigs are sentient beings, yet have a lower degree of consciousness and self-awareness than humans—it seems unlikely that a pig can contemplate its mortality. While some would argue that one sentient being should not be sacrificed for the sake of another, animals are killed on a regular basis for food production. In general, while taking the life of a species with a lower degree of sentience could be considered wrong, saving a human life is usually seen to justify it, especially when no better alternatives exist. All beings have an intrinsic value, which is not the same as their value to humans.³¹ When animals are used for xenotransplantation, we should respect their intrinsic value.

Speciesism can be viewed as the belief that the human species ranks above all others, or as the belief that some animal species are more valuable than others despite similar interests. Many humans are uneasy when considering using the organs of non-human primates for xenotransplantation, but are less so with non-primate species, perhaps related to capacities that human and non-human primates share. Speciesism might lead one to believe that four-legged animals are better suited for xenotransplantation than non-human primates because they lack characteristics that humans value. Beyond philosophical or theoretical considerations, however, practical reasons to prefer pig organs over those from non-human primates are many. Pigs are not an endangered species, and the numbers necessary to supply the needs for human organs would be vanishingly small compared to the total number of pigs raised and killed annually for food: in 2019, 1.3 billion worldwide and 118 million in the U.S.³²

General considerations govern the treatment of animals for human use. As few animals as necessary for a particular purpose should be killed.³¹ Creating animals with modified genetics is a complex process with a relatively high rate of failure, resulting in fewer than 1% of modified embryos surviving to generate a pig.⁷ This high failure rate seems out of line with the goal of minimizing the extinction of animal lives to serve the human population. The animals used for xenotransplantation are largely created by private companies, so substantial intellectual property issues are involved, requiring other companies to create their own set of genetic modifications, sacrificing even more animals.³¹ Additionally, downstream effects might occur due to inadvertent manipulations or unintended interactions between various parts of the altered genome, in some way harming the animal. Cloning or inbreeding of modified pigs could have damaging effects on the offspring.³¹

To minimize the transmission of infections to humans, animals will need to be housed in a strictly controlled environment, unlike animals bred for human consumption. Their care is chronic, with frequent testing, often in

isolation,³³ which may negatively affect their well-being.²³ Their housing will more resemble a research laboratory than a farm; the inability to roam freely and behave normally could be emotionally harmful.

6 | REGULATION AND OVERSIGHT

Potential harm from xenotransplantation zoonoses could affect the family, friends, and other contacts of the porcine organ recipient, and could also extend well beyond the boundaries of regional and national jurisdictions in case of a pandemic. International regulation is highly desirable for several reasons, such as the inadequacy of regulation at a lower level and the possibility that a patchwork of regulations could exacerbate some dangers of xenotransplantation.

Local regulation is inadequate as it seems unlikely that local IRBs and institutional animal regulators will have the level of expertise needed to address exceedingly complex issues. National regulation can lead to a patchwork of solutions with varying degrees of rigor. For example, at least 29 xenotransplant treatments were available in 12 different countries by 2010; 9 of the 12 countries had no regulations addressing xenotransplantation.³⁴ Xenotransplantation oversight lacks clarity, as many jurisdictions have not determined the legal framework to regulate human-animal chimeras or animals with multiple genetic changes.³⁵ In the U.S., regulation falls under the Food and Drug Administration,³⁶ but different branches regulate different aspects; for example, one branch manages genetic modifications of the animal and another regulates the use of the resulting organs as medical treatments.

Efforts to regulate xenotransplantation have occurred at the international level over the years. The World Health Organization and the International Xenotransplantation Association have developed guidelines that rely on the member states to enforce.^{37–39} Without uniform regulations and enforcement, however, the potential for problematic tracking and abuse persists.

A lack of uniformity in regulations increases the possibility of xenotransplant tourism as patients travel to other countries seeking less expensive or more immediate treatment. Transplant tourism has been a reality for many years and takes advantage of local populations for financial gain by those at high levels, to the detriment of the less well-off who make the sacrifices necessary to provide the services to foreigners, such as organ donors. Xenotourism could thrive in countries with lax regulations using organs from pigs with less robust genetic manipulation and husbandry, thereby increasing the risk of zoonotic infections.²² These concerns are amplified by



recent events, for example, where an individual engaged in illicit genetic manipulation to make children resistant to acquiring HIV, even though the procedure was against the laws of the host country.⁴⁰

The several companies that are planning to produce organs for xenotransplantation create their own genetic modifications to the donor organs. Revivicor has produced hearts with 10 genetic modifications, while eGenesis and Qihan Biotech have worked together to develop pigs with deactivated PERVs. NZeno has developed pigs with kidneys that will not grow after implantation.^{18,41,42} The degree of PERV inactivation in each of the models is unclear, as are other mitigation strategies. Each companies' approaches to gene editing contain proprietary information, so details may not be readily available for an independent analysis of risk. These factors emphasize the need for rigorous oversight for the protection of the patients, donor animals, and society.

7 | CONCLUSIONS

Xenotransplantation is ethically complex—while there is the great potential to save many human lives, there is the potential for great harm as well. Infections from the donor organ could affect not only the recipient but also the community at large. Should an infection occur and prove contagious, this could have a worldwide impact. International regulation will be difficult to achieve but important nonetheless, as many relevant issues have international implications. Xenotourism has the potential to exacerbate inequities in care and to increase the risk of disease transmission as a result of xenotransplantation.

The development of xenotransplantation will be expensive and require volunteers in early experiments. The burden of research should be borne by those likely to benefit from the technology so that vulnerable populations are not misused. Monitoring for zoonotic infection may impact the freedom of the patient to withdraw from monitoring, and may also require monitoring or isolation from non-participants in the trial.

Issues that affect the animals bred for xenotransplantation are also important. The process of genetic manipulation is complex and is associated with a large loss of animal life. Caring for these animals will require strict isolation to minimize the risk of infection. Animals in isolation are likely to feel some level of distress as a result; these animals should receive care that respects their value as living creatures at least as much as their value to humans.

The ethics of xenotransplantation should not be viewed in isolation. The zoonotic risks, surveillance, access, expense, animal burden, and regulatory requirements of

xenotransplantation should be viewed in the context of other options that may help to satisfy the unmet need for transplant organs. For example, controlled donation after circulatory death (cDCD) has the potential to solve some of the current organ shortages. While some forms of cDCD cardiac donation raise ethical issues,⁴³ other forms such as DPP (direct procurement and preservation) can produce excellent results when ex vivo perfusion of the organ is used, while avoiding many ethical concerns.⁴⁴ Donation following cDCD-DPP has the potential to reduce recipient waitlists and may expand eligibility. The risks, expenses, and other liabilities of xenotransplantation may not be justified until the magnitude of the increase in human organ availability through widespread adoption of recently developed approaches to cDCD is known.

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