# *Existing Ethical Tensions in Xenotransplantation*

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**Abstract**

The genetic modification of pigs as a source of transplantable organs is one of several possible solutions to the chronic organ shortage. This paper describes existing ethical tensions in xenotransplantation (XTx) that argue against pursuing it. Recommendations for lifelong infectious disease surveillance and notification of close contacts of recipients are in tension with the rights of human research subjects. Parental/guardian consent for pediatric xenograft recipients is in tension with a child's right to an open future. Individual consent to transplant is in tension with public health threats that include zoonotic diseases. XTx amplifies concerns about justice in organ transplantation and could exacerbate existing inequities. The prevention of infectious disease in source animals is in tension with the best practices of animal care and animal welfare, requiring isolation, ethologically inappropriate housing, and invasive reproductive procedures that would severely impact the well-being of intelligent, social creatures like pigs.

Key words:

Xenotransplantation, Zoonotic disease, COVID-19, Research ethics, Animal well-being

## Background and History of Xenotransplantation

The shortage of organs for transplantation has been a chronic problem for decades, spanning the entire history of successful transplants. The need for organs is in part the outcome of the success of transplant surgery and immunosuppression. Numerous strategies and solutions have been implemented to increase the supply of lifesaving organs. The adoption of neurological criteria for legal death made it possible to procure healthy, viable organs and tissues from humans with cardiac activity. Donation after circulatory death (DCD) in donors with severe brain injuries has modestly increased the donor pool, as has the use of so-called "high-risk" or "expanded criteria" donors (e.g. older donors, and donors with comorbidities including viral infections like Hepatitis C and HIV). Some countries have adopted presumed consent or opt-out organ donation policies, which increase donation as compared to policies that require opt-in/explicit consent for donation[1]. Kidneys and liver lobes can be donated by living donors. Technological advances in intensive care, including cardiopulmonary bypass and extracorporeal membrane oxygenation can extend life in some patients while they await organs, and hemodialysis can extend life in those with renal failure.

As early as the 1960s, attempts at xenotransplantation (XTx)–transplanting organs from one species into another–have been unsuccessfully attempted in humans. In 1963, James Hardy transplanted a chimpanzee heart into a human, noting the difficulty (in the time before brain death had been recognized) of obtaining a heart from a human donor. Notably, the patient's dire condition would have made him ineligible for a transplant by today's standards, but, Hardy explained, "although survival was not achieved, the situation was one in which the patient had no chance, except for the slim possibility that the transplant could be made to support the circulatory requirements and rejection could be prevented"[2]. The patient died within two hours of surgery. In 1977, Christiaan Barnard, who performed the first successful human-to-human heart transplant

in 1967, reported on his attempts to transplant baboon and chimpanzee hearts, respectively, into two adult human recipients[3]. Both recipients died within days. Baby Fae, a premature infant girl with hypoplastic left heart syndrome, received a heart from an adolescent female baboon in a California hospital in 1984. Baby Fae died 20 days later of progressive necrosis[4]. In 1964, Thomas Starzl et al reported on six patients transplanted with baboon kidneys. The patients survived between 19 and 98 days, with renal failure and lethal infections precipitated by the need for high-dose immunosuppression to prevent rejection. Four died with the baboon kidneys still in place, and the remaining two died after the baboon kidneys were removed and human kidneys from "volunteer convict donors" were engrafted[5]. In 1992, Starzl transplanted a baboon liver into a human recipient who survived for 70 days[6].

Xenografts of solid organs in living human recipients have not been attempted since, but researchers recently reported success in using a brain dead human subject to test the viability of a pig kidney xenograft[7]. The possibility of using brain dead humans not only as organ donors, but as experimental organ recipients, raises interesting and novel ethical concerns. Research using the dead is not governed by the same regulations that apply to research with living human subjects, and brain dead individuals fall into a moral and regulatory grey area[8]. The use of a brain dead subject for XTx research would, presumably, prevent their being a deceased organ donor. Ironically, this worsens the organ shortage by removing an actual donor from the pool, in order to pursue an aspirational but highly speculative solution. Because each organ donor can contribute numerous organs and tissues, potentially many possible recipients are also affected, and those effects can be expected to multiply if such experimentation continues. XTx experimentation with brain dead subjects, then, is problematic for both human welfare and, as discussed below, for animal welfare.

Current research efforts have focused on using organs from genetically modified pigs instead of nonhuman primates (NHPs). Although chimpanzees are the closest phylogenetic and evolutionary relatives to humans, their status as endangered species, regulatory restrictions and prohibitions on their use in research, and moral qualms about killing them have removed chimpanzees from consideration as sources of organs. The biological similarity between other NHPs and humans increases the risk of zoonotic infections, which has dampened enthusiasm for using them as sources of organs. In the United States, the Food and Drug Administration (FDA) has effectively banned the use of NHPs for xenotransplantation, characterizing the risk of zoonotic infection to be unacceptably high. Numerous retroviruses are known to infect NHPs and are often found in high rates in captive NHP colonies. Most NHPs harbor Simian Foamy Viruses, and studies have shown that these viruses can persistently infect humans occupationally exposed to the animals. According to the FDA,

> Evidence suggests that transmission of certain infectious agents from nonhuman primates to humans can have serious public health consequences… current scientific data indicates that human subjects, including individual xenotransplant recipients, their close contacts, and the public at large, would be exposed to significant infectious disease risk by the use of nonhuman primate xenografts[9].

Despite their virtual exclusion as potential sources of organs, NHPs continue to be used in pig-to-primate XTx experiments.

80 million years of evolutionary divergence from humans notwithstanding, pigs are favored because they have organs approximately the same size as human organs, they are easily and quickly bred, and they are already killed in vast numbers for meat. Pigs thus seemingly represent an "unlimited supply" of organs[10], if the hurdles can be overcome. But as Claus

Hammer notes, the hurdles are quite high: “Xenogeneic transplantation into human recipients seems to be just around the corner, but the corner is a tricky one: we need to ‘outwit’ the 180 million years of evolution”[11].

Two major medical hurdles to using pig-grown organs are the transmission of zoonotic disease[12], and hyperacute rejection, which has bedeviled XTx from the start. Hyperacute rejection occurs when a recipient’s immune system reacts violently to foreign cells and rejects a transplant within minutes or hours. It is a significant and deadly risk, one that increases when, like humans and pigs, species are discordant (that is, not closely related)[13]. Zoonosis occurs when a disease-causing organism spills over or jumps from one species to another. Examples include Rabies virus, Ebolavirus, and SARS-CoV-2. Genetically modified pigs are the proposed solution to both problems. Genetically modified and cloned pigs free of specific viruses have been developed, as have knockout pigs who lack the gene to produce alpha-gal, a sugar in pig cells that is attacked by human and NHP immune systems, causing hyperacute rejection. The use of human stem cells to prompt genetically modified pigs to grow human-compatible organs is another experimental target. The genetic modification of pigs exemplifies what Bernard Rollin calls “technological sanders,” measures that alter animals to “force square pegs into round holes… with animal welfare severed from profit and efficiency”[14]. In the case of XTx, the sanding is to fit pig organs into human bodies without causing catastrophic rejection and infection. While some have proposed XTx as a bridge to allotransplant, buying time for the recipient until a human organ is available, the zoonotic risk could remain even if xenografts are only temporary.

This paper will focus on several ethical tensions inherent in XTx, in particular those related to zoonosis, the rights of human subjects in research, and the well-being of genetically modified nonhuman animals (hereafter called "animals") used for organ and tissue grafts.

**Zoonosis and Risks to Individual Organ Recipients**

Retroviruses are among the most concerning infectious organisms for zoonotic transmission. In pigs, human-similar viruses include porcine cytomegalovirus, porcine lymphotropic herpesvirus, and porcine adenovirus[15]. Porcine Endogenous Retroviruses (PERVs) are present in the entire pig genome, and in every cell of pigs, and have been the target of research to genetically modify pigs using CRISPR/Cas9 to inactivate PERVs, with the ultimate aim of making pig organs safe for XTx[16]. The risks of PERVs to organ recipients remains equivocal, as do the risks of transmitting other infectious diseases, with available data based on in vitro cell cultures and pig-to-primate xenografts. Human cells in vitro are susceptible to PERV infection. NHPs do not have active PERV receptors, and Joachim Denner *et al* have argued that experiments with animals provide no conclusive evidence about the risks of PERV infection, and "there are no alternative approaches to test this in an experimental setting: essentially clinical trials are needed," to answer the question of transmissibility to a human graft recipient[17].

In its "Guidance to Industry," the FDA notes several possible routes to infection in xenograft recipients:

> Xenotransplantation may facilitate inter-species spread of infectious agents from animals to the human host through several mechanisms: a) surgery disrupts the normal anatomical barriers to infection such as skin, membranes, etc.; b) transplant recipients are usually iatrogenically immunosuppressed to facilitate

graft survival; and c) patients' underlying disease(s), such as AIDS or diabetes, may compromise their immune response to infectious agents. Consequently, the recipient of a xenotransplant is potentially at risk for infection with infectious agents already known to be transmissible from animals to humans as well as with infectious agents which may become transmissible only through xenotransplantation and which may not be readily identified with current diagnostic tools. Infected xenograft recipients could then potentially transmit these infectious agents to their contacts and subsequently to the public at large. In this regard, infectious agents which result in persistent latent infections which may remain dormant for long periods before causing clinically identifiable disease are of particular concern[18].

Potential recipients, assuming they have decisional capacity, can and do consent to the risks of allotransplantation. The known risks include those associated with surgery, anesthesia, a lifetime regimen of immunosuppressive drugs, acute or chronic graft versus host disease and rejection, and the relatively small risk of infectious disease. These can be weighed against the known risk of death for individuals who do not receive a needed transplant. The same risks exist and are magnified with XTx. To date, all known human recipients of animal organs have died relatively quickly from rejection and/or infection. The risks to organ recipients of currently unknown and unidentified zoonotic pathogens are impossible to quantify or foresee, which decidedly limits the extent to which consent to XTx can be truly informed.

*The Rights of Human Research Subjects*

XTx remains experimental. Any potential recipients of xenografts would therefore be considered research subjects, and both their consent and their safety would be governed by human subjects research regulations and guidance. XTx poses unique and perhaps unprecedented challenges related to voluntary consent and the research subject's right to withdraw from research at will. Several advisory organizations that have considered the risks of zoonosis have concluded that it will be necessary for XTx organ recipients to submit to extended, potentially lifelong surveillance for zoonotic infectious diseases.

The United Kingdom's Nuffield Council on Bioethics report on XTx notes that

> Regular physical examinations with archiving of serum and, where appropriate, tissue samples should continue throughout the lifetime of the recipient. Serum samples taken from health care workers caring for the xenograft recipients should also be archived. The recipient should be required to report any serious unexplained illness. Close contacts, that is, family members, household members, sexual contacts and others with whom bodily fluids may be shared, should also be encouraged to report unexplained illnesses. Recipients should be asked to agree to an autopsy on their death… In addition, xenograft recipients should be asked to take routine precautions to minimise the transmission of any infectious disease. They should not donate blood, tissue or organs. They should be counselled on methods of minimising the transmission of diseases, for example, by sexual contact.
>
> Patients consenting to xenotransplantation should be informed that post-operative monitoring for infectious organisms is an integral part of the procedure, and that their consent to the operation includes consent to this monitoring [19].

In the position paper of the Ethics Committee of the International Xenotransplantation Association (IXA), the committee notes the significant tension between the rights of research subjects and the rights of others, including society as a whole:

> Normally, the burden of risk is borne largely by the research subject. In the case of XTx, however, the burden of risk is also carried by close contacts and medical caregivers and by society, which may reasonably insist that the research subject agrees to life-long monitoring, avoids blood donation, informs close contacts about the xenotransplant and its potential risk of infection, and follows patterns of behavior with his or her close contacts that will minimize infectious risks[20].

The United States Public Health Service, in its guidance document on XTx, also calls for lifelong surveillance of XTx recipients to monitor for "xenogeneic infectious agents"[21].

Requiring lifelong surveillance and submission to monitoring as a condition of research participation and XTx would be in significant tension with the right of research subjects to withdraw from research at any time, for any reason. The right to withdraw from a research study is endorsed worldwide in ethical guidelines governing human subjects research[22-24], and a critical component of obtaining voluntary informed consent is informing the research subject of this right. The United States Common Rule explicitly states that "participation is voluntary… and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled"[25]. Requiring lifelong surveillance effectively denies a research subject their fundamental right to withdraw, and violates international norms and ethical guidance[26].

Zoonosis implicates not only the XTx recipient, but their close contacts as well, with significant social repercussions:

> intimate contacts may be at higher risk of transmission of diseases such as PERVs, necessitating lifelong avoidance of unprotected sex in addition to the need to take special precautions to avoid exposure of persons with any degree of immune compromise (pregnant women, neonates and so on) to the participant's bodily fluids[27].

Jay Fishman describes the need for "Social and sexual contacts of recipients [to] be considered for inclusion in clinical monitoring should signs of infection develop in a recipient"[28]. This raises novel concerns about the rights and consent of these persons, who may not even know the xenograft recipient at the time of transplant. Similarly, it generates concerns about the privacy and confidentiality of xenograft recipients. Guidelines for organ transplant privacy and confidentiality have previously stressed the necessity of consent from the donor, or the surrogate of a deceased donor, when sharing information with a recipient. Sharing recipient information with the donor requires the consent of the recipient. The information shared typically includes "general health status (general condition, not specific medical information), immediately after transplant and 30 days post-transplant"[29]. The risk of zoonotic infection may *require* informing persons well outside the donor/recipient circle, and could include employers, work colleagues, family, friends, and sexual partners, among others, of the xenograft recipient.

*The Rights of Pediatric Xenograft Recipients*

Daniel Hurst *et al* note particular unease about pediatric patients who are unable themselves to consent to xenotransplantation[30]. Their parents or guardians would be required to consent to the unknown lifelong risks of XTx, and would be committing their children to lifelong surveillance that might have substantially limiting effects on their future freedom and opportunity in ways that would violate the child's right to an open future. For example, there might be a need to limit the freedom of XTx recipients to travel internationally (both to ensure adherence to surveillance and to limit the spread of infectious diseases); the stigma associated with XTx and the fear of zoonotic disease might result in significant social impediments; there may be barriers to employment for recipients (e.g. they might be prohibited from working in healthcare, childcare, education, or in jobs that involve close contact with animals, or with particularly vulnerable humans like infants, pregnant persons, and the elderly); recipients may need to avoid pregnancy and childbearing. Any of these limitations could represent significant burdens for recipients, and likely would be impediments to compliance. Moreover, they are unique to XTx. With allotransplantation, recipients are committed to lifelong adherence to immunosuppression to avoid organ rejection and transplant failure. In some sense this could be characterized as limiting their future freedoms, but it does not involve the other potential limitations currently anticipated with XTx. The risk of rejection and organ failure affect the individual and are self-harming, whereas nonadherence with surveillance, intimate contact, and social distancing could potentially harm others, prompting and justifying coercive enforcement.

It is unclear that parents or guardians could ethically consent to imposing these burdens on children, or that such consent should be considered binding. As noted above, adult research participants would be required to waive the right to withdraw from research and surveillance as a condition of receiving a xenograft. Could parents/guardians waive that right for their children?

As Jean-Jacques Rousseau asserted in *On the Social Contract*, the paternalistic rights of parents over their children do not extend into adulthood:

> Even if each person can alienate himself, he cannot alienate his children. They are born men and free. Their liberty belongs to them; and they alone have the right to dispose of it. Before they have reached the age of reason, their father can, in their name, stipulate conditions for their preservation and for their well-being. But he cannot give them irrevocably and unconditionally, for such a gift is contrary to the ends of nature and goes beyond the rights of paternity[31].

Finally, the burdens on XTx recipients would not be lifted if, at some later time, the xenograft was removed and a human organ was transplanted in its stead. One of the concerns with PERVs and other retroviruses is the potential for "latent infections which may remain dormant for long periods before causing clinically identifiable disease"[32], infections for which effective screening is not available, as well as the potential for previously unidentified infectious agents to emerge in immunocompromised hosts through the mechanism of XTx, or when the recipient interacts with some environmental trigger. Thus, waiving the right to withdraw from surveillance must be irrevocable, both for adults and for children.

**Zoonosis and Risks to Public Health**

The origins of SARS-CoV-2, the virus that causes COVID-19, which first emerged in Wuhan, China in late 2019, remain uncertain. The prevailing theory is that it was a zoonotic disease that jumped from a captured wild animal to a human, possibly in a market where live wildlife is sold, subsequently spreading to other humans. The SARS-CoV-2 virus may have originated in the sarbecovirus found in Horseshoe bats, and one hypothesis is that the virus

spilled over into pangolins, who are the bridge species between bats and humans[33]. The result was a global pandemic that has killed millions of people, devastated health systems, and caused social and economic upheaval.

SARS-CoV-2 has been found in captive mink on fur farms (resulting in millions of animals being culled across Europe), in domesticated dogs, cats, and ferrets, in several species of animals held captive in zoos, including chimpanzees, gorillas, otters, tigers, lions, and pumas[34], and in free-living white-tailed deer in the United States[35]. Numerous species have been experimentally infected, including ferrets, Golden Syrian hamsters, rhesus macaques, and Chinese tree shrews[36]. The numerous animals that can be infected with SARS-CoV-2 suggest multiple possible natural animal reservoirs for the virus, making eradication highly unlikely. SARS-CoV-2 is a single zoonotic virus that successfully mutated to become both easily transmitted among humans, and exceedingly deadly. The virus continues to circulate and mutate in unvaccinated human populations, with numerous variants–some more deadly and transmissible than the original alpha variant–identified within the first two years of the global pandemic, resulting in multiple deadly waves of COVID-19.

SARS-Cov-2 led to a rapid pandemic that quickly overtook the world, and the virus is on course to become endemic. HIV-AIDS was a relatively slow pandemic, but one that is also now endemic and found everywhere humans live. It likely originated in a monkey retrovirus. Ebola and Marburg monkey viruses have caused large and deadly disease outbreaks in humans, and Ebolavirus has also devastated endangered mountain gorillas in West Africa[37]. Hendra virus is found in flying foxes (a large bat), horses, and humans, and horse-to-human transmission was seen in Australia in 1994[38]. The closely-related Nipah virus spilled over from pigs to humans and caused an outbreak of viral encephalitis among pig farmers in Malaysia in 1998 and 1999,

resulting in more than 100 human deaths and the culling of more than a million pigs[39]. The source, again, was believed to be bats. Both the Hendra and Nipah viruses can infect multiple species, and cause fatal disease in humans. Longstanding fears about zoonotic influenza viruses and their potential to cause deadly pandemics among both animals used for food and humans in contact with those animals, further demonstrates the known risks of human interactions with agricultural animals. Animals typically used in agriculture, such as the pigs whose organs are currently being eyed for XTx, may pose similar as-yet-unidentified risks.

*Individual Consent and Collective Harms: Xenotransplantation After COVID-19*

The risks of unleashing a new infectious disease on the world changes the stakes of XTx considerably, highlighting an important difference between allotransplantation and xenotransplantation. Arguably, everyone in the world is at risk from an XTx-related infection, not merely the individual xenograft recipient. This makes the matter of consent quite different and more complicated than traditional informed consent for allotransplantation, which involves only two parties: the donor and the recipient.

Robert Sparrow has argued that all those whose lives are at stake have a right to participate in democratic decisions concerning XTx, because "The relevant community is clearly global… the risk of xenozoonosis is not restricted to the citizens of the nation in which experiments are taking place"[40].

As the COVID-19 pandemic has demonstrated, lower income nations are as susceptible to infectious diseases as wealthier nations, but have fewer medical resources to combat disease and treat the sick. Given the unequal and inequitable distribution of healthcare, and especially expensive healthcare like organ transplants, much of the world has little to gain from the

development and implementation of XTx, but potentially much to lose. A truly democratic process for soliciting consent from communities worldwide, if such a process were possible, would therefore be unlikely to obtain consent[41]. While zoonotic diseases and pandemics know no geopolitical borders, persons in lower income countries with less access to healthcare resources are in an all-risk/no-benefit position with respect to XTx.

The Nuffield Council rightly notes that the consent of individual recipients alone cannot justify imposing the risks of infectious diseases on the public:

> The ethical question is how to balance the needs of individual transplant recipients, and the potential benefits to them of xenotransplantation, against the uncertainties associated with the possible transmission of a new infectious disease to the general population. Even allowing that xenografts might bring benefits to patients in terms of increased quality and length of life, the potential public health risks nevertheless counsel caution. The consent of individuals to take these risks does not justify their imposition upon the public[42].

*Xenotourism*

Citizens of wealthy nations in need of organ transplants can currently find them through transplant tourism, effectively bypassing lengthy waiting periods at home and taking advantage of a global market in human organs that includes trafficked organs of uncertain and sometimes unsavory provenance[43]. Transplant tourists exploit the developed medical resources and personnel of countries where many citizens often have little to no access to even basic healthcare. There is little reason to think XTx would be easier to control than the trade in human organs, and when the source of organs is animals, the potential for unlimited expansion and

exploitation without ethical oversight is immense. Indeed, it is speculated that XTx, should it become a viable option, may drive xenotourism to countries with laxer rules and enforcement, including the absence of requirements for surveillance and monitoring. Existing international travel and immigration policies, although they sometimes screen for infectious diseases such as tuberculosis and agricultural exposures, do not include restrictions on travel for organ recipients. As the IXA's Ethics Committee cautions,

> At present, no country's immigration authorities routinely ask a question that would reveal that a particular person is a xenograft recipient. The scale of such "casual" xenotourism is likely to be small. However, there is a risk that entrepreneurial xenotransplanters may deliberately set up business in countries with minimal or no regulation and set about attracting foreigners with organ failure to come to be transplanted and then return home. The absence of questioning about XTx upon re-entry, and the absence of a mechanism for bringing such patients into surveillance programs in their home countries almost guarantee that such patients will avoid surveillance when they return home[44].

It is not possible to predict or quantify the risks, but in a worst-case scenario–a global pandemic–the consequences could be devastating, costing millions of lives. Nor is it likely that, given the difficulties of tracing infectious outbreaks to their sources, such a pandemic could be prevented or easily contained once the lid is off the proverbial Pandora's box.

> The most difficult question is what procedures should be followed if it is found that a disease has indeed been transmitted from the animals used to provide organs or tissue to human xenograft recipients? In principle, steps should be taken to prevent transmission of the disease to other people. In practice, this is a very

> difficult issue. For a start, it is very unlikely that, at the outset, the mode of transmission of the disease will be understood. The appropriate response will depend on the mode of transmission and on how infectious the disease is. It would hardly be acceptable to isolate xenograft recipients suffering from an infectious disease, or to ask them to refrain from sexual intercourse or, in the case of a virus transmitted from parent to offspring, from having children. This highlights how difficult it would be to prevent the transmission of an infectious disease originating from xenotransplantation. It is sobering to reflect on the difficulty, despite globally coordinated attempts, of controlling and eliminating infectious diseases such as malaria, hepatitis and AIDS[45].

In the wake of the zoonotic SARS-CoV-2 pandemic, it is difficult to overstate the dire need for more robust precautions, or the importance of reasserting that the burden of proof is on those developing XTx to show that it will not cause serious harm. It is time to reassess XTx in light of the risks for the whole world of a deadly zoonotic disease outbreak, and in light of the requirements of justice in the distribution of the burdens and benefits of XTx.

## The Ethics of Using Animals as Sources of Organs

### *Novel Uses of Animals in Xenotransplantation Require Novel Ethical Justification*

Proponents of using pigs as sources of organs have argued that ethical concerns are mitigated by the existing use of these animals for meat[46, 47]. At present, and around the world, pigs are killed in the hundreds of millions annually. Many are kept, transported, and slaughtered in conditions that frequently raise concerns about inhumane treatment[48-50]. Additionally, pigs are

already used in biomedical research as a translational model, a bridge between small animals like mice, and humans[51]. That pigs are already used and killed for food and research does not justify their use for XTx. Animal tissues sourced from abattoirs, or other experimental contexts, are not under consideration for XTx[52]. Categorically different pigs conceived, raised, and killed under very different conditions would be used for XTx. Novel uses of pigs raise novel ethical concerns, and must be judged and morally justified on their own, and not in comparison to the treatment their kind experiences in other contexts. Consider, for example, that humans are killed in war. Arguably, a defensive war in which enemy combatants are killed can be just[53], but that in no way justifies the killing of humans for other reasons and purposes (such as for their organs). And the use of captured combatants in biomedical research is explicitly prohibited by international law and convention[54,55]. Thus, even if the killing of pigs for meat or in existing biomedical research *could* be morally justified, that justification would not apply across all possible uses and killings of pigs. Moreover, killing intelligent, emotional, social creatures like pigs in agriculture and research, while common, is hardly without ethical controversy[56,57]. The genetic modification and use of pigs as sources of XTx organs, and experimentation on pigs for that purpose, requires its own ethical justification.

Although they are not used as organ sources, NHPs are still used in XTx experiments, as recipients of organs from genetically modified pigs[58]. NHPs are also killed for food in some countries and cultures, but they are not bred, grown, and raised in captivity in the way that pigs are. A superficial justification for using pigs to grow organs, grounded in their killing for meat, would not plausibly extend to using NHPs. Following the principles and practices that regulate research with animals, the use of NHPs in novel XTx research requires justification grounded in the specifics of the research, and its speculative benefits for humans balanced against the burdens

and harms for the animals used[59]. Consistent with the widely-endorsed framework of the 3Rs (Replacement, Reduction, and Refinement), the potential for using alternative, non-NHP and non-animal experimental models and techniques is a relevant, but frequently ignored, consideration as well[60,61]. A calculus that honestly weighs those factors is not likely to favor using NHPs (or pigs) in XTx research.

*Infection Control and Pig Well-Being*

The potential for transmitting zoonotic disease has prompted recommendations for the breeding, housing, and isolation of animals destined to give up their organs for XTx. Precautions to prevent transmission include prohibitions on the use of wild-caught animals, and captive, free-ranging animals (or what is sometimes euphemistically called "humanely-raised" livestock), and animals that can come into contact with other organisms that might harbor infectious pathogens. This requires, essentially, keeping the animals indoors for their entire lives. Other measures include quarantine, and frequent, potentially stressful blood sampling and tissue biopsy of animals for known infectious agents. As described by the Nuffield Council,

> The major stress factors are the need for restraint, which may be physical and/or drug-induced, the process of removal to operating areas and the need for recovery if anaesthesia has been used. Some species can be trained for such procedures, but with pigs it is not so easy because of their size and resistance to restraint[62].

It will often be necessary to house animals in isolation and in sterile facilities, which can significantly diminish well-being in highly intelligent and social animals like pigs, by preventing the expression of natural behaviors (such as digging and rooting in the dirt, wallowing in mud–pigs really do like to do that–and playing), and restricting interactions with conspecifics,

resulting in stress and boredom[63]. If it is also necessary to isolate NHPs used in pig-to-primate experiments, the negative effects on well-being will be similar.

> Even if isolation is not required, in order to keep animals free from infection, the environment will have to be kept relatively sterile and therefore be easy to clean. So it is likely to consist of monotonous textures and to be free of items which might enrich the life for the animal, but which might also harbour infectious organisms. Human contact, which can be advantageous for animals in captivity, may have to be minimised since human beings harbour some diseases (such as influenza) that can be passed on to pigs[64].

Additionally, infection control would require birth by caesarian section to reduce the risk of maternal-fetal transmission, and "the use of methods such as artificial insemination (AI), embryo transfer, medicated early weaning, cloning, or hysterotomy/hysterectomy and fostering [to] minimize further colonization with infectious agents"[65]. Such measures would result in numerous invasive and stressful procedures for the sows used to breed piglets, and would also severely and negatively impact the emotional and psychological well-being of pigs, who are highly social animals with strong maternal-infant bonds[66-68].

Finally, a significant ethical concern is the use of animals for serial, sequential organ or tissue procurement (for example, of tissues that might regenerate, like the liver, or of paired organs like kidneys, lungs, and corneas, or of pancreatic islets and skin). This would result in multiple and repeated restraint, anesthesia events, surgeries, and recoveries, along with repeated, painful testing and biopsy procedures[69]. Where such sequential use is not prohibited by animal welfare regulations or laws, the likelihood exists of severe and prolonged suffering and harm. Given the expense and investment in resources involved in breeding and rearing infection-free,

genetically modified pigs, it is unlikely that pigs will be "wasted" by killing them when they still have valuable, viable organs and tissues. Moreover, the alternative, the one-time use and killing of multiple animals, may be better from a welfare perspective if it results in less suffering, but would involve many more deaths of conscious, intelligent, emotionally complex creatures.

The breeding, confinement, and slaughter of pigs for meat can cause significant suffering and harm, but it is also clear that the breeding, confinement, and killing of pigs to grow organs for XTx, or NHPs for pig-to-primate XTx experiments, can result in different but no less harmful physical and psychological suffering. And as is true of animal experimentation in general, the level of suffering and distress experienced by animals is frequently underappreciated and underestimated by the committees that review research protocols[70], while the speculative benefits to humans are exaggerated[71].

**The Wrong Solution to an Urgent Problem**

This paper has described several existing ethical tensions in XTx that argue against pursuing it as a solution to the organ shortage:

- Current recommendations for lifelong infectious disease surveillance of xenograft recipients are in tension with the rights of human research subjects to withdraw from research at will.
- Those same recommendations are in tension with the rights of privacy and confidentiality of xenograft recipients in light of recommendations that their close contacts be informed of the risk of zoonotic infection.
- Parental/guardian consent for lifelong surveillance of pediatric xenograft recipients is in tension with a child's right to an open future, and is categorically different from consent

that commits a child to lifelong immunosuppression. An individual may refuse ongoing immunosuppression at the risk of their own health and life, but refusal of infectious disease surveillance presents a potential risk to public health, and may be subject to justified coercion.

- Individual consent to transplant is in tension with public health threats. The unknown and unquantifiable risks of XTx include the possible unleashing of zoonotic diseases that could potentially affect the entire world. No individual can consent to that risk, or to infringe on the rights of others, nor can one dismiss one's moral and social obligations to others through simple consent or decree.
- XTx amplifies the existing tensions concerning justice in organ transplantation. The benefits and burdens of XTx are unlikely to be equitably distributed, in much the same way that the current global organ market exploits and burdens persons in lower income countries for the benefit of wealthy recipients. Xenotourism would exacerbate existing inequities.
- The prevention of infectious disease in animals used for their organs is in significant tension with the best practices of animal care and animal welfare, requiring isolation; sterile, ethologically inappropriate housing; and invasive reproductive procedures that would severely impact the well-being of intelligent, social creatures like pigs. Serial, sequential use of an animal would result in prolonged and severe harm, in violation of the spirit of animal welfare regulations. Moreover, the use of animals for XTx is in tension with the 3Rs, and in particular Replacement, as several viable alternatives to XTx and the use of sentient animals are currently available or in development.

The genetic modification and breeding of pigs as a source of transplantable organs is only one of several possible solutions to the chronic organ shortage. Despite decades of work, XTx is still speculative, and several significant medical and ethical obstacles remain before clinical trials with humans could be seriously considered. Moreover, as the SARS-CoV-2 pandemic has tragically demonstrated, there is an urgent need to treat zoonotic pandemics as grave threats to both humanity and to the other creatures who share the planet. It would be prudent to now pump the brakes on XTx experimentation given that threat.

Other possible solutions to the organ shortage do not implicate the several and significant ethical concerns for humans and animals, and for that reason are much preferable to continuing the effort to "outwit evolution" or outrace the next deadly pandemic. They include: better therapies to prevent and treat the illnesses (like hypertension, diabetes, and heart disease) that result in organ failure; tissue regeneration and repair of damaged organs[72]; and developing human-based and human-relevant methods for growing organs that leverage existing research on 3D bioprinting[73], and creating organoids from stem cells[74, 75]. Procuring organs from expanded criteria donors is possible right now, and has been shown to increase the number of available organs[76], saving lives without the risks of XTx.

Ethical concerns about animal and human well-being alike are heightened in the context of XTx because the shortage of transplantable organs is a *social engineering* problem, not an animal engineering problem[77]. There is a shortage of organs for transplantation because too few people *choose* to donate their organs after death, or as living donors. That problem can be solved by low tech, social engineering that includes carrots and sticks to encourage donation, presumed (opt-out) consent for donation–which has successfully increased donation in several countries[78]–and improving communication with potential donor families[79]. All of these strategies target the

organ shortage at its source: the paucity of human donors. The animal in need of modification, if the organ shortage problem is to be solved with the urgency it requires and deserves, is the human animal.

**Notes**


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