# Xenotransplantation and Clinical Ethics

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## Introduction

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

## Background of Clinical Ethics in Xenotransplantation

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

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

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

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

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

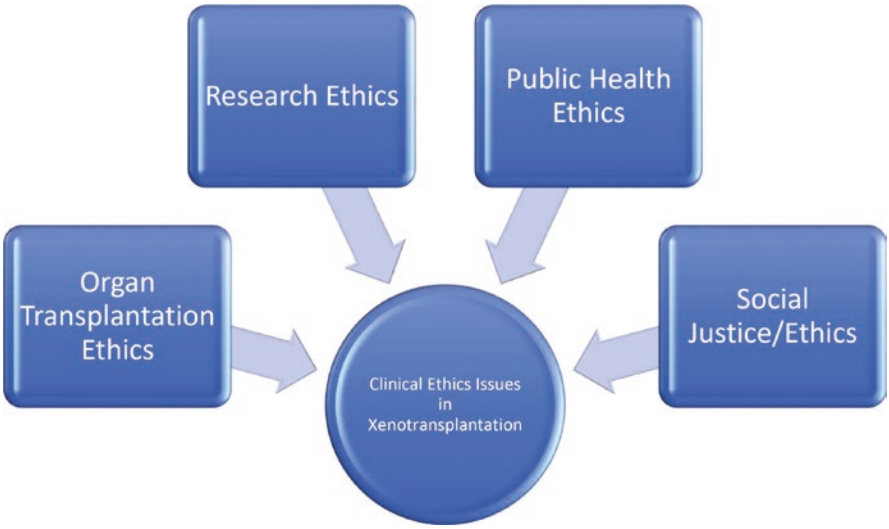


**Fig. 4.1** Clinical ethics issues in xenotransplantation and areas of applied ethics

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

## Autonomy, Patient Rights, and Informed Consent

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

### Right to Withdraw

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

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

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

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

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

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

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

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

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

## Right to Withdraw from Medical Treatment Adherence

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

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

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

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

## Right to Withdraw from Post-Transplant Monitoring

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

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

## Ulysses Contracts

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

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

## Risks to Third Parties

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

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

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

## Enforcement of Treatment and or Monitoring

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

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

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

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

## Practical Considerations in Providing Informed Consent for Xenotransplantation

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

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

## Pediatric Contexts

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

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

## Justice, Equity, and the Allocation of Scarce Medical Resources

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

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

### Allocation of Xenografts

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

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

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

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

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

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

## Xenotransplant Failure, Relisting, and Retransplantation

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

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

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

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

## Expanded Access

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

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

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

## Fair and Equitable Access to Xenotransplantation

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

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

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

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

## Conclusion

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

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