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# Close contacts of xenograft recipients: Ethical considerations due to risk of xenozoonosis

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## Abstract

With decades of pre-clinical studies culminating in the recent clinical application of xenotransplantation, it would appear timely to provide recommendations for operationalizing oversight of xenotransplantation clinical trials. Ethical issues with clinical xenotransplantation have been described for decades, largely centering on animal welfare, the risks posed to the recipient, and public health risks posed by potential spread of xenozoonosis. Much less attention has been given to considerations relating to potentially elevated risks faced by those who may care for or otherwise have close contact with xenograft recipients. This paper examines the ethical and logistical issues raised by the potential exposure to xenozoonotic disease faced by close contacts of xenotransplant recipients—defined herein as including but not limited to caregivers, household contacts, and sexual partners—which warrants special attention given their increased risk of exposure to infection compared to the general public. We discuss implications of assent or consent by these close contacts to potentially undergo, along with the recipient, procedures for infection screening and possible quarantine. We then propose several options and recommendations for operationalizing oversight of xenotransplantation clinical trials that could account for and address close contacts' education on and agency regarding the risk of xenozoonosis.

## KEYWORDS

bystander risk, caregiver, clinical ethics, informed consent, research ethics, xenotransplantation

## 1 | INTRODUCTION

Advances in the viability of genetically modified pig organs transplanted into humans have greatly increased the likelihood of clinical xenotransplantation soon moving to clinical trials. The ethical

issues regarding clinical xenotransplantation have been explored for decades,<sup>1–4</sup> mostly centered on animal welfare, risks to the recipient, and the risks posed to the public's health due to potential spread of infectious diseases from animals that may be transmitted to humans through xenotransplantation, termed xenozoonosis. While the absolute risk of xenozoonotic infections remains unknown,<sup>5</sup> there is a consensus guided by the precautionary principle that xenograft recipients should submit to long-term or lifelong health surveillance and monitoring for infectious disease (e.g., regular tissue biopsies, blood

**Abbreviations:** CERCs, comprehensive ethics review committees; IRB, Institutional Review Board; IXA, International Xenotransplantation Association; NExTRAC, novel and exceptional technology and research advisory committee; NIH, US National Institutes of Health; PCMV, porcine cytomegalovirus; RAC, recombinant DNA advisory committee.

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samples, and health questionnaires). If monitoring of the recipient reveals signs of zoonotic disease, the recipient may be required to undergo quarantining. In turn, the risks posed by xenotransplantation raise difficult questions regarding informed consent, privacy, and confidentiality.

As in allotransplantation, a xenograft recipient will likely require an extended period of caregiver support following surgery, involving close interaction with members of their social support system. Therefore, special attention must also be paid to the ethical issues regarding caregivers and close contacts of xenograft recipients, who may not be afforded the dedicated education and protections of formal research participants but conceivably face a higher risk of exposure to zoonosis than the general public. We define close contacts as individuals most likely to have direct, intimate, and/or prolonged contact with xenograft recipients: post-transplant caregiver(s), household contacts, and sexual partners. We exclude from this discussion hospital and research clinicians and staff as their education on and consent for participation in a xenograft recipients care falls under the jurisdiction of occupational health procedures and protections. We argue that given this potential elevated risk, the same long-term infectious surveillance and potential quarantine requirements described above for xenograft recipients—as well as the consequent ethical and logistical issues—might justifiably be extended to recipients close contacts.<sup>5-11</sup>

Surveilling and potentially quarantining a xenograft recipient in the context of zoonosis has been discussed previously, raising concerns about restricting their freedom and eliminating their ability to withdraw from a clinical trials surveillance requirements.<sup>12</sup> Yet extending these potential infringements on individuals freedoms to close contacts has not been discussed at length.<sup>9</sup> Here, we explore the risks to xenograft recipients close contacts related to zoonosis and propose how to address their education on, and informed authorization for, these risks, advocating that these issues need dedicated examination before beginning xenotransplantation clinical trials. While we write from a lens of US practice and regulatory landscape, we believe some of the principles here have global application for any context in which xenotransplantation clinical trials are proposed.

## 2 | POTENTIAL XENOZOONOTIC RISK TO CLOSE CONTACTS OF XENOGRAFT RECIPIENTS

Although pigs grown in designated pathogen-free facilities have helped decrease the fear of zoonosis, the pig heart transplanted into a patient in January 2022 showed evidence of contamination with porcine cytomegalovirus (PCMV).<sup>13</sup> While PCMV appears isolated to the porcine tissue, the implications of infection with other porcine viruses in humans remain unclear. Medical research often involves at least some degree of risk for non-participants. For example, in human challenge trials, participants volunteer and give informed consent to be exposed to a pathogen. Modern research ethics guidelines, as well as the protocols reviewed by institutional review boards (IRBs), place an emphasis on the welfare of the individual participant, but there is

unaddressed risk to close contacts who may also be exposed. There has been recent interest in the ethical dimensions of risk to clinical trial non-participants who could be negatively affected and how to balance the costs and benefits of the implementation of such trials.<sup>14-16</sup>

Following allotransplantation, caregivers are needed for household tasks, transportation to follow-up appointments, support for medically related tasks, medication adherence, assistance with daily life activities, and wound and/or line care. The role that a caregiver might fulfill in xenotransplantation is expected to be very similar to that for allotransplantation. Therefore, the caregivers of xenograft recipients, along with their household and sexual contacts, plausibly face an increased risk of exposure to zoonotic infections that may be spread via contact with bodily fluids and secretions.

Risks presented to a recipient's close contacts could include: (i) risk of acquiring a novel pathogen (zoonosis) from the xenograft recipient due to proximate and frequent contact, (ii) stigma associated with acquiring a novel transmissible disease<sup>17</sup>; (iii) guilt caused from transmitting a novel disease to others (with the potential to precipitate an epidemic or pandemic); (iv) violations of privacy and confidentiality, and (v) possible infringement on freedom if quarantine is deemed necessary because of signs of zoonosis. Moreover, for immediate caregivers of adults, and especially caregivers of xenograft recipients who are children, as well as for members who live in the same household as a recipient, the choice to decrease their interactions to mitigate their own risk *after* the xenotransplant may not be an option. Developing guidance on how close contacts should be informed of and allowed to provide consent or assent for risks posed to them is therefore imperative.

## 3 | EDUCATION AND CONSENT FOR POTENTIAL RISK TO CLOSE CONTACTS

In clinical trials, participants are informed of the potential risks and benefits of the study and asked to provide explicit informed consent stating that they understand and accept the terms. In xenotransplantation, the risks of zoonotic infections, however small, are not limited to the individual recipient and may have implications for the wider community.

There are notable parallels and precedents for guidelines tailored to individuals who come into close contact with certain patient groups, such as vaccination recommendations specific to close contacts of immunocompromised individuals and guidance around close contact with individuals with known SARS-CoV-2 infections.<sup>18,19</sup> It is similarly vital to consider whether and how close contacts should be informed of, and asked to provide consent or assent for the risks of xenotransplantation. We broadly describe five options:

**Option A:** Only the xenograft recipient needs to provide consent to the xenotransplant and agree to lifelong (or long-term) monitoring.

**Option B:** In addition to the requirements of *Option A*, the xenograft recipient, prior to xenotransplantation, should provide a list of members of the same household/close contacts, sexual partners, and caregivers for record keeping and future possible contact tracing. All

individuals listed would be educated on the risks of xenozoonosis and potential monitoring, and provided with an assent form that contains the basic elements of informed consent, but does not require a signature or other declaration of agreement.<sup>20</sup>

**Option C:** In addition to the requirements of *Option A*, the xenograft recipient, prior to xenotransplantation, should provide a list of close social contacts, to include close friends, members of the same household, sexual partner(s), and caregivers. These contacts would be informed of the potential risk of xenozoonosis and provide formal informed consent and baseline blood samples, similar to those obtained from the xenograft recipient, with additional monitoring possibly required if signs of infection develop in the recipient.<sup>5</sup>

**Option D:** The scope of risk to individuals beyond the recipient necessitates consideration beyond just close contacts, but anyone who could be deemed a bystander with a risk of potential exposure. This is especially challenging, involving the problem of the infinite regress: if an immediate caregiver needs to provide their informed assent or consent, then so should others who may also encounter the xenograft recipient or immediate caregiver. Neighbors, schoolmates, schoolteachers, work colleagues, other family that come into contact would also, in such a model, be at some level of risk and need to provide their authorization. Strict adherence to a principle of protecting all persons who are at some theoretical risk would seem to produce an increasingly long list of persons needing protection.<sup>21</sup> From this position, in addition to the requirements of *Options B* or *C*, the xenograft recipient would be required to provide a list of contacts and contacts of contacts, as well as future contacts updated in perpetuity.

**Option E:** At least during an initial clinical trial, the xenograft recipient should remain an inpatient with strict contact precautions for a predetermined minimum period until the risk of xenozoonosis is considered to have substantially reduced.

Contemplating these options, we propose that *Option B* best strikes a balance between respect for individuals and the feasibility of implementation. We believe the risks undertaken by close contacts of xenograft recipients must be acknowledged and addressed by providing the information needed to facilitate their own decisions about interactions with the recipient; *Option A*, representing the general current status quo, would therefore not suffice. However, close contacts should not be treated in the same manner as xenograft recipients, as suggested in *Option C*. According to the 2018 Common Rule in 45 CFR 46, collection of biospecimens, such as blood samples, meets the definition of human subject research, making close contacts additional research subjects. Not only does this option seem logistically challenging, but it raises the question of whether eligibility for xenotransplantation trials would be contingent on informed consent and blood sampling from this wider circle of individuals. Such a scenario would create too high a threshold for participation in xenotransplantation trials for some potential recipient.

The issue of infinite regress of authorization, as described in *Option D*, underscores the necessity of creating thoughtful and deliberate parameters for which people face risks that are convincingly higher than those of the general public. Informing an ever-expanding group of the potential risks would require dedicated personnel tasked with

continuous tracking of widening webs of social contact, rendering this approach largely impracticable.

Finally, while *Option E* would limit interactions between the xenograft recipient and non-clinical close contacts during the trial period, there is currently little or no information on how long this period would need to be. This would render *Option E* to be questionable because it is possible that some porcine infections (perhaps hitherto unknown) may be latent and only manifest several months or years after the xenotransplant.<sup>5,22</sup> Hence, such a waiting period would not be a practicable or definitive solution toward the objective of protecting those in close contact with the xenograft recipient. Furthermore, it may result in the patient being maintained in hospital for much longer than is necessary, thus exposing him/her to the additional risk of contracting a hospital-based infectious agent that may be resistant to most antibiotic therapy. However, it must be noted that it would be possible and may even be prudent to implement *Option E* for a limited period as part of inpatient recovery immediately post-transplant in order to limit contact that the recipient has with others during this period. This solution would not, however, be feasible in the long-term, as argued above, and would need to be followed by another option, such as *Option B*.

#### 4 | OPERATIONALIZING PROTECTIONS FOR CLOSE CONTACTS

As close contacts of xenograft recipients are not direct research participants, they fall outside the protections of human subjects afforded by IRBs, and their risks are generally not attended to in informed consent conversations and documentation prior to procedures. However, considerations of how to regard and protect close contacts can be informed by scholarship on bystander (i.e., non-participant) risk in the clinical research setting.

For almost 2 decades, Kimmelman has made the argument that more conversation on bystander risk is needed.<sup>14,15</sup> He argues that extending research protection to bystanders would promote non-maleficence, public health, well-being, and would not infringe upon a person's autonomy as it would enable the bystander to make decisions concerning their own welfare.<sup>23</sup> At a minimum, Kimmelman argues that ethics policies should "incorporate some language stating that investigators and ethics committees should consider a protocols harms and burdens to non-research participants."<sup>23</sup> More recently, he has contended that IRBs should be expressly charged with protecting bystanders in human research.<sup>24</sup> Conversely, Wikler's contention is that IRBs are mandated to examine the interests of research subjects and the scope of IRBs should not be immediately expanded to include bystanders without first looking for less onerous alternatives.<sup>21</sup>

Shah et al, writing of bystander risk in the context of human challenge trials, propose that, "[i]t is important to protect all research bystanders because they may be unable to protect themselves; obtaining their consent might be impossible in some cases and problematic in others."<sup>15</sup> They go on to "propose that agencies funding biomedical research establish databases of reviewers qualified to serve on ad hoc Comprehensive Ethics Review Committees (CERCs)" to "conduct

proactive review of research programs.”<sup>15</sup> Such committees would conduct reviews of proposed research studies with the aim of assessing risk to bystanders. The advantage of this approach is that it would go beyond the reach, and not further strain the capabilities, of an IRB.

Housing such a committee within a funding agency, though, presents inherent conflicts of interest. While governmental agencies such as the US National Institutes of Health (NIH) fund xenotransplantation research, much of the funding also comes from industry entities that hold patents for genetically modified pigs and/or organs. These private sector entities have a clear financial incentive to see clinical trials advance. In this context, then, requiring a for-profit funder (private industry) to establish CERCs to assess bystander risk may not be advisable. However, housing something akin to a CERC within an academic medical center or governmental agency, such as the NIH, would have the advantage of bringing oversight and uniformity to the process.

It has been previously argued that adopting a system to review xenotransplantation research that is similar to the NIH’s Recombinant DNA Advisory Committee (RAC) or the Novel and Exceptional Technology and Research Advisory Committee (NEXTRAC) could be beneficial.<sup>14,25</sup> Through a public forum, the RAC was used to review research that involved novel technologies and the ethical concerns they raised. The RAC made recommendations for consideration but did not establish regulatory guidance. Similarly, NEXTRAC makes recommendations on ethical and safety matters of emerging biotechnologies. These two systems display the precedent of bodies external to an IRB that provide additional recommendations on novel ethical matters in research.

Analogously, a global organization with prominent expertise in the field of xenotransplantation, such as the International Xenotransplantation Association (IXA), could develop guidelines on how an institution that is preparing for clinical xenotransplantation trials approaches risk to close contacts of xenograft recipients.<sup>25</sup> While no system will guarantee complete education, acceptance, and compliance, we suggest approaches that can begin to address education and assent for close contacts within the framework of *Option B* described above. Education of close contacts could take place in a private hospital conference room or via telemedicine where a multi-disciplinary team is present to provide information and answer questions or concerns. The team would comprise of members of the healthcare team, social workers, therapists, and/or past xenograft or transplant recipients, and should include an independent patient advocate. Another approach could entail a requirement for a general educational session for those who are considering receiving a xenograft, together with their caregivers, household contacts, and sexual partners.

Importantly, we have intentionally focused our discussion on the processes of education and assent for close contacts, as these represent important aspects of xenotransplant clinical trials that have thus far been largely unattended. We recognize that applying any of the frameworks above to mitigate risk for recipients and close contacts may not be applicable to all xeno organs or cells since the level of potential infective risk can vary by tissue.<sup>26</sup> However, the protocols and infrastructure that will be required for zoonosis surveillance and potential quarantining lie outside the scope of

what we aimed to examine, but require dedicated exploration and operationalization. The need for longitudinal monitoring in xenograft recipients has been widely discussed, yet no viable implementation and enforcement mechanisms for such a burdensome and logistically challenging commitment exists today.<sup>27</sup> Extending such monitoring to close contacts would require further economic and logistical investments.

## 5 | CONCLUSIONS

The issue of risk to close contacts of xenograft recipients—caregivers, household contacts, and sexual partners—is a pressing concern given the advent of forthcoming xenotransplantation clinical trials. Yet, discourse on how to address this risk is lacking. Inability to withdraw from surveillance, infringements on freedom and privacy, potential risk of infection, and unnecessary monitoring are possibilities for those interacting closely with a xenograft recipient. Investigators should require that potential xenograft recipients have caregivers willing and capable of providing post-transplant support while remaining aware and informed of their own potential risks. The education of close contacts, and their provision of assent to the risks of their involvement, should be a fundamental component of xenotransplantation research design. Implementation of these measures will require guidance from major societies such as the IXA, as well as institutional bodies separate from the IRB, tasked with consideration and oversight of these protections.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work in this paper.

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