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ORIGINAL ARTICLE

In defense of xenotransplantation research: Because of, not in spite of, animal welfare concerns

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Abstract

It is envisioned that one day xenotransplantation will bring about a future where transplantable organs can be safely and efficiently grown in transgenic pigs to help meet the global organ shortage. While recent advances have brought this future closer, worries remain about whether it will be beneficial overall. The unique challenges and risks posed to humans that arise from transplanting across the species barrier, in addition to the costs borne by non-human animals, has led some to question the value of xenotransplantation altogether. In response, we defend the value of xenotransplantation research, because it can satisfy stringent welfare conditions on the permissibility of animal research and use. Along the way, we respond to the alleged concerns, and conclude that they do not currently warrant a cessation or a curtailing of xenotransplantation research.

KEYWORDS
animal welfare, precautionary principle, research ethics, transgenic pigs, xenotransplantation

1 | INTRODUCTION

A defender of xenotransplantation envisions a future in which transplantable organs can be safely and efficiently grown in transgenic pigs—those that have been genetically modified to reduce immunogenicity and increase physiological compatibility with the human body.[1] There is reason to be optimistic that this future is not far off, evidenced by the registration for a phase I clinical trial to begin with 20 patients with end-stage kidney disease.[1] Within the last year, researchers attached genetically-altered porcine kidneys and hearts to "brain-dead" bodies,[2,3] and a transgenic pig heart was transplanted into a living but severely ill patient in a procedure that was granted emergency authorization.[4,5] In each case, no hyperacute rejection of the organ was reported before the studies were terminated.[2]

There are significant practical barriers to overcome, to be sure, but this paper will set these issues aside to focus primarily on ethical concerns about animal welfare in the research setting, specifically whether a net benefit to human beings can be reasonably expected. Research involving animals will continue to be needed to address other ethical concerns involving clinical safety, patient autonomy, and public health, among others. Given how unique xenotransplantation is compared to our other use of and research on pigs (i.e., indefinitely breeding a species of pigs to serve as a supply of organs for human transplantation), this line of research, as L. Syd Johnson observes, "requires its own ethical justification" (p. 362).[6] The unique challenges and risks posed to humans that arise from transplanting across the species barrier in

[1] Pigs are considered ideal candidates for growing human organs and much of the research has focused on them. Adult pig organs are a similar size to adult human organs; we know a lot about pig cells, anatomy, and so on because our familiarity with porcine valve replacement and previous xenotransplantation experiments; pigs mature at a fast rate; they are easy to raise in a laboratory; there are fewer prohibitions on pig research compared to nonhuman primate research; and pigs produce a lot of offspring in a relatively short time period.

[2] However, in the study by Porrett el al [3] there was some evidence of thrombotic microangiopathy; one of the kidneys produced minimal urine; and ineffective creatinine clearance was observed, and so despite the largely positive outcomes, several challenges still remain.

addition to the costs borne by non-human animals leads her to conclude that it is "the wrong solution to an urgent problem" (p. 363), which calls into question the value of the research. Our paper defends the value of this research because we believe it can satisfy stringent welfare conditions on the permissibility of animal research and use. Along the way, we respond to some of the unique challenges raised with pursuing xenotransplantation and conclude that while there are genuine concerns and limitations to the research, they do not warrant a cessation or a curtailing of the research.

2 | NECESSARY CONDITIONS FOR PERMISSIBLE ANIMAL RESEARCH

Our defense of xenotransplantation is limited in scope. First, it is not intended to sway "abolitionists" who reject all forms of non-human animal research.[7] We contend that the development and use of transgenic pigs in research and medicine satisfies the necessary conditions for morally permissible animal research. While there are competing accounts of what makes for permissible animal research, that is, how to weigh human versus animal interests, we focus on the account set forth by DeGrazia and Sebo.[8] Since their account sets a high bar for the permissibility of animal research, showing how xenotransplantation satisfies it provides a reason for optimism about how this line of research can survive scrutiny. We therefore grant for the sake of argument DeGrazia and Sebo's assumption that "persons" are to be treated as ends in themselves and their interests are to be weighed more heavily than those of "nonpersons" in deciding what is permissible. It is fair to wonder who counts as a "person" in their view and if neonates or very young infant patients are among them. Nonetheless, we shall assume that transgenic pigs are not persons in the relevant sense of the term and that the subset of humans listed for transplant, which includes neonates and young children, are persons. Second, as already indicated, we will not directly engage ethical concerns that do not concern research on pigs.[3] While there is reason to worry about patient autonomy, fair distribution, and informed consent, these are beyond the scope of the paper.

3 | EXPECTATION OF SUFFICIENT NET BENEFIT

DeGrazia and Sebo offer three necessary conditions for the moral permissibility of animal research. The first condition is that the proposed research must offer important and unique benefits that outweigh the risks to human beings to justify the harm caused to pigs. This requires, as they explain, that "the benefits [of the research] cannot be obtained, ethically, without animal research"(p. 422), meaning there is no ethical or feasible alternative to using animals. The xenotransplantation defender must therefore show three things: first, transgenic pigs offer a significant net benefit for humanity, meaning there is no feasible, currently available alternative to using them; second, the benefit to humanity has to outweigh the costs that may accrue to human beings, which in the case of xenotransplantation means that the potential risk of xeno-zoonotic disease must be acceptably low; third, the unique benefit to humanity justifies the harm to animals, which includes everything from research on the pig for the purpose of genetic engineering, to breeding, and housing transgenic pigs in a biosecure environment, an environment much different than their natural habitat, for the sake of killing them.

Although this first condition is rightfully demanding, there is good reason to expect a sufficient net benefit that can only be gained by research on transgenic pigs. Genetically altering pigs for the sake of perfecting a transplantation method has the potential to bring about several significant benefits, including a lifesaving therapy that would shorten the time spent requiring dialysis and waiting for an organ to become available, as well as reduce waiting list mortality. Even with strong organ donation support in the United States, the number of people needing an organ has risen sharply over the past couple of decades. In 1991, there were 6953 donors and 23 198 people on the organ waiting list; in 2019, the number of donors jumped to 19 267 while the number of people on the organ waiting list skyrocketed to 112 568.[9,10] There were over 90 000 people on the kidney transplant waitlist in the United States in 2020 but only 23 643 kidney transplants were performed.[11] In China there are estimated to be 300 000 patients in need of an organ transplant but only about 16 000 transplant surgeries are performed each year.[12] The quality of life for a person waiting for an organ that may never come is reduced, as that person may be unable to perform various activities, consume various foods, and maintain a job, and, if in need of a kidney, must undergo dialysis, along with the significant chronic and acute physical suffering that accompanies it.[13,14] On average, 17 people die each day in the United States waiting for an organ that never comes.

While it is unlikely that xenotransplantation could solve this crisis all by itself, it nonetheless has a role to play alongside other solutions. Other proposed solutions, which vary in their feasibility and acceptability, include increasing healthcare access, building more ICUs, training more surgeons, expanding donation criteria, furthering research on lab-grown organs, and creating a market for kidney transplants.[15] Johnson argues that because these options do not involve the general problems raised by animal welfare and the problems unique to xenotransplantation itself, they are "much preferable" to xenotransplant research (p. 364). Yet this does not follow if high ethical standards for animal welfare in xenotransplantation research can be met. Ultimately, it is likely that the organ shortage can only be addressed through a multifaceted approach, whereby xenotransplantation will be one of the approaches utilized.[16]

Indeed, there is some evidence to suggest that the alternative policies may not be enough. Looking at the implementation of policies aimed to promote organ donation in Singapore, Lee and colleagues

[3] The history of animal use in xenotransplantation has been a bloody affair involving more than pigs. Chimpanzees and other non-human primates have been used along the way with little success. We do not claim that past research would meet the criteria we aim to satisfy in this paper. Rather, we narrow the scope of our project to the use of transgenic pigs in research and development of medical therapies that will help promote formal clinical trials in humans and safety in xenotransplantation more generally.

report, "Despite new legislation (HOTA) in Singapore, the utilization of cadaveric donor livers showed no increase in the last 3 years" (p. 315).[17] For those in American hospitals, Wynn and Alexander report that "the total number of organ donors increased <2% annually over the subsequent 4 years" (p. 325).[18] Looking at data from Canada, Gill and colleagues report, "There has been no significant increase in the number of deceased organ donors in Canada over the past decade." (p. 1580).[19] Dominguez and Rojas found a similar pattern in Chile—presumed consent legislation did not improve organ donation rates.[20] Finally, in a comparison between countries that adopt an opt-in versus an opt-out organ donation policy, Arshad and colleagues report, "our data demonstrate no significant difference in deceased donation or solid organ transplantation activity between opt-out versus opt-in countries" (p. 1453).[21] Although Ahmad and colleagues found that an opt-out model increased the deceased donation rate and deceased transplantation rate in Spain,[22] Etheredge concludes that based on the longitudinal data from countries with opt-out models for the past 20–30 years, the data are largely inconclusive as they are contradictory and offer no definitive proof that switching from opt-in to an opt-out model, alone, is a significant contributory factor to increased donation.[23] Therefore, it is *possible* that changes to organ donation systems can increase the pool of available organs. However, even in Spain, which is universally considered the gold-standard for organ donation systems, patients still die waiting for an organ transplant, and so, adopting the donation system should not be viewed as a panacea. Perhaps with time things will change, but for now researchers have no decisive reason to think xenotransplantation research should be excluded from the options to be pursued in the effort to maximize the organ supply.

Moreover, we are much further advanced in our approach to creating transgenic pigs than we are in the development of functional lab-grown organs. Current methodologies, De Los Angeles and colleagues report, "are not compatible with producing complex three-dimensional tissues, such as transplantable organs" (p. 334).[24] It is also unlikely that we will be able to grow human organs artificially without the use of animal hosts. As Tarifa and colleagues report, "the possibility to use organoids to generate whole viable organs for transplantation appears remote" because organs require broader biological systems to promote healthy growth over time (p. 287).[25] Therefore, they conclude that "whole organ engineering is still far from a therapeutic application and most probably it will require the use of animal organs as scaffolds" (p. 288).

Of course, the preceding does not show the impossibility of solving the organ transplant crisis through other means. Yet even if it did, it is instructive to compare and contrast two ideal scenarios: perfected xenotransplantation versus perfected allotransplantation in which "perfected" means we can meet "organ demand." The costs of allotransplantation in the perfected state involve the ongoing negotiation of death criteria (who, at least, counts as a non-living person?), the dead donor rule (keep it or leave it?), and the optimal method for obtaining organs (gift, conscription, or market?), and the burden the procurement process places on the sick and dying at the end of life (surgical interests versus palliative care interests). No matter how these issues are adjudicated, all of the costs will be incurred by persons. Yet, a significant portion of these costs would shift to non-persons in perfected xenotransplantation. Transgenic pigs promise to provide organs to patients quickly, since pigs take around 5 months to mature, and given their large litter size, they promise a scalable solution to the organ transplant crisis. This by itself does not settle the issue, because xenotransplantation could cause infectious diseases that harm persons, but that is an additional reason why *research involving animals* is needed so that we might be able to avoid these costs.[4] Pressing the "research on animals" button offers a good chance at securing a better future for people in organ failure.

Regarding infectious disease, concerns are often raised about the potential for xeno-zoonotic diseases being transferred from transgenic pigs to human xenograft recipients and the potential for an epidemic or pandemic event. There is no shortage of zoonotic diseases — those transmitted from animals to humans — which include HIV/AIDS, Ebola, rabies, West Nile virus, coronaviruses, and swine flu. Importantly, a virus can be benign in one species and pathogenic in another, and this impact is evidenced by the 2 million deaths that occur annually from just 13 zoonotic diseases.[26]

Pigs are carriers of porcine endogenous retroviruses (PERVs), which pose risks to human health. The worry here is twofold. First, the xenograft recipient may be infected with a pathogen that was undetected in the porcine source, causing symptomatic or asymptomatic disease. A transferred pathogen could be dormant within a recipient for a period of time before it expresses itself and causes any detectable symptoms. Or, a pathogen could express itself soon after transplantation. The severely ill recipient of a genetically-altered porcine heart, David Bennett, Sr., died 2 months after the transplant, and it is believed that an undetected porcine cytomegalovirus (PCMV) was partly to blame.[27] Second, zoonotic transference can spread from the xenograft recipient to others, creating an epidemic or even pandemic disease. As Johnson explains, "everyone in the world is at risk from an XTx-related [xenotransplantation-related] infection, not merely the individual xenograft recipient"(p. 360); she goes on to say the "unknown and unquantifiable risks of [xenotransplantation] include the possible unleashing of zoonotic diseases that could potentially affect the entire world"(p. 364).[6]

A defender of xenotransplantation must admit to these concerns of zoonotic disease and be willing to forgo xenotransplantation as a possible solution to the organ demand problem if further research on zoonotic diseases reveals that the risks involved are too high. If we have learned anything from the ongoing SARS-CoV-2 pandemic, it is that infectious diseases stemming from animal reservoirs pose a significant danger to humanity. However, we think the concerns warrant caution, not a cessation of the research altogether, and that we have reason to think these worries can be eliminated or otherwise minimized to an acceptable level.

Transgenic pigs can be reared in such a way as to minimize risk of xeno-zoonoses. For example, one study showed that early weaning of

[4] That there may not currently be a study design involving animal models that is relevant for determining zoonotic risk, does not mean that there will not be one. If or when such a study design becomes available, it should be pursued.

piglets eliminated PCMV altogether.[28] Not all zoonotic diseases can be eliminated through rearing techniques, because PERVs are found in the pig genome. Fortunately, research is progressing on better detection and genetic deletion of PERVs in transgenic pigs. One team of researchers were able to gene-edit pigs resistant to classical swine fever virus,[29] while another team of researchers were able to inactivate all 25 PERV copies, which were then used in somatic cell nuclear transfer to produce piglets; no reinfection was observed.[30] Yang et al. succeeded in inactivating 62 copies of proviruses in the pig genome, creating PERV-inactivated pigs.[31] Moreover, certain antiretroviral drugs and vaccines are available and could be used to prevent PERV infection, as well as RNA interference technologies.[32] In any event, the results from research on the transmissibility of retroviruses should function as a limiting factor for xenotransplantation. If it proves to minimize risk to acceptable levels, and it certainly appears that way, then it should go forward; if not, then not.

That said, it is important to bear in mind that many of the zoonotic concerns are still conjectural at this point in time. As Denner explains, "no PERV transmission has been observed in clinical trials transplanting pig islet cells into diabetic humans, in preclinical trials transplanting pig cells and organs into nonhuman primates with remarkable long survival times of the transplant, and in infection experiments with several animal species" (p. 1).[32] PERV infection has only ever been observed in vitro, not in vivo.[33] While this is good news, it must be balanced with the report that the first genetically-altered porcine heart recipient did, unexpectedly, have a PCMV infection which is associated with a reduction in survival times of porcine xenografts in non-human primates.[34–36] Yet the value of this discovery is that we now know that more sensitive methods for screening PCMVs are needed. Learning how to better filter them out will increase the chance of graft survival and lower the risk of the possible spread of zoonotic disease. This only bolsters the reasons for research to continue in order to establish better methods of detection, prevention, and mitigation; there is certainly no reason to halt this research.

In general, we should avoid imposing an unsatisfiable burden of proof on xenotransplant research to prove its safety before human subjects can be involved. This betrays an overreliance on precautionary reasoning in the ethics of innovation, that is, how to best manage the risks posed by emerging technologies. One example of overreliance is Fovargue and Ost's argument that formal clinical trials in xenotransplantation should be prohibited based on precautionary reasoning.[37] They reason that the non-zero risk of a novel infectious disease pandemic means that permitting formal clinical trials would knowingly expose the population to an unknown and unprecedented risk that could not be outweighed by the benefits to an individual recipient. Precautionary reasoning is commonsensical insofar as the status quo is acceptably good; there should be a presumption against putting it at risk through uncertain decisions, so the burden is on innovators to show that their research will not increase the overall risk to it. The tendency, though, is to just assume the status quo is acceptably good, which it may not be, and to only focus on the potential risks of the research and none of its potential benefits while offering no guidance about what level of safety is adequate. While some precautionary measures are warranted in the face of uncertainty, uncertainty by itself, even of a worst-case scenario, does not generally justify a moratorium on potentially beneficial research. If it did, then the only acceptable forms of research would be those that pose no risk whatsoever, an impossible standard to meet. We need to continue to learn more about the likelihood of the risks involved, and at this point, there is not enough evidence to demonstrate the risks posed by xenotransplantation are unacceptable. It must also be remembered that precautionary measures incur their own costs, both in terms of forgoing and delaying the potential benefits of an activity while simultaneously imposing their own burdens on those required to meet them. In the case against xenotransplantation, further extending the known mortality and morbidity of people awaiting organ transplant must be accepted to ensure a "no risk allowed" safety standard to avoid an unknown threat of a pandemic that could very well be preventable or mitigable. We therefore share the same assessment of Veatch and Ross who write that, "at this point," the precautionary approach to xenotransplant is "overly burdensome relative to the potential benefits that such research could provide."[38]

Settling the question of zoonotic risk through further research will also help determine the seriousness of another objection to xenotransplantation, what we call the "no end in sight" objection. According to this objection, since the risks of zoonotic communicable infection are unknown, long-term or lifelong monitoring of the research subject is recommended in current guidelines, which conflicts with the subject's fundamental right to withdraw from an experiment at any time. Compounding the objection is that it is not clear that the right to withdraw can be totally waived and the use of "Ulysses contracts" to bind subjects to past decisions without the benefit of their lived experience is suspect at best.[39,40]

This is another limiting objection to xenotransplantation research. While it is justifiable to ask subjects to forgo the right to withdraw for a limited amount of time, it is hard to justify for an unlimited amount of time. If subjects, along with sexual partners and other close contacts, such as friends and family members, must indefinitely submit to constant and invasive bio-surveillance measures such as digital-device monitoring, regular checkups, blood tests, and tissue samples, and perhaps periods of forced isolation, then so much the worse for xenotransplantation research. It is not something that researchers can reasonably ask human subjects to do (nor is it practical for research sponsors and there is a lack of enforcement mechanism), and the "submit to it or no organ for you" condition places an undue burden on the subject's decision making. All the more reason, then, to continue working with animal models to lower the risk of infection and the severity of communicable disease. Some degree of monitoring will inevitably need to be in place (as follow-up is always needed post-transplant) but minimizing the degree of it as much as we can through further animal research is a worthy pursuit. Nor should we discount the altruism that research subjects may have to further scientific study in this area. If "challenge trials" involving novel infectious agents already spreading through the population can be justified for vaccine development purposes, then trials involving known agents could be justified on a similar basis.[41–43] We could potentially develop a vaccine for the general population in advance or quickly enough to ward off a pandemic. The point

is that further research may well serve to provide ways that mollify or even undermine the "no end in sight" objection altogether.

Recall that DeGrazia and Sebo's first condition is that "the net benefit of animal research for humans is sufficiently important that it serves to justify the harms to animal subjects (once differences in moral status between humans and nonhumans are taken into account)" (p. 424).[8] It is admittedly nebulous how to weigh the moral status of animals with the benefit to humans, but in light of the promise of xenotransplantation to mitigate the organ crisis with significantly less harm to persons, our cost-benefit analysis suggests that the expected benefit does in fact justify the harm befalling pigs. If any animal research is morally permissible, it is permissible on account of saving human lives, which is exactly the reasonably expected outcome of xenotransplant research.

4 | TRANSGENIC PIGS MUST HAVE LIVES WORTH LIVING

DeGrazia and Sebo's second condition is that "animal subjects' lives be worth living," meaning that "once their lives begin, they are expected to be worth continuing for the duration of their lives" (p. 424). The idea is that their lives are, on the whole, positive or of sufficient quality so as to not render killing them an act of a kindness. They explain, "if it would be a kindness to kill them humanely at any point, that would entail that the lives were at that point not worth continuing" (p. 424). Part of the justification for this conclusion is that it is wrong to bring into existence a creature whose life is not worth living; another part of the justification is that those who bring these creatures into existence stand in a relationship to these animals that involves the researcher in a protective relationship. As parents have obligations to children they bring into the world, so too do the researchers have obligations to the laboratory animals they bring into the world. Practically, then, pigs should be given "comfortable living conditions, adequate food, exercise, and access to conspecifics" and be subjected to minimal harm (p. 424).

Yet there is no compelling reason to believe that the measures taken to reduce zoonotic risk — keeping the pigs indoors in sterile environments for the entirety of their brief lives — would be incompatible with existing regulations designed to safeguard animal welfare. The United States Department of Agriculture's (2019) *Animal Welfare Act and Animal Welfare Regulations* requires that all animal research be approved by an Institutional Animal Care and Use Committee to ensure: (1) that minimal pain is inflicted on the animals; (2) that no alternative to using animals is available; and (3) that the animals are provided with veterinary care "sufficient space to allow each animal to make normal postural and social adjustments," and access to "wholesome, palatable" food "free from contamination and of sufficient quantity and nutritive value to maintain all animals in good health" (p. 231).[44] In their review of recent xenotransplant research, Cozzi and colleagues note that facilities "for rearing specific pathogen-free (SPF) or DPF [defined pathogen-free] pigs follow high welfare and safety standards" (p. 11).[45] Researchers are also able to satisfy the law's requirement for the use of sedatives and anesthesia with procedures that involve or would otherwise cause discomfort as well as the provision of painless euthanasia after procedures that would otherwise cause severe or chronic pain or distress.[44] Second, there is good reason to think that transgenic pigs will be treated well independently of legal regulations. In order to maximize the health of the transplantable organs and minimize zoonotic concerns, transgenic pigs will not be housed in cramped, miserable cages, nor will they live in their own waste as is often the case on industrialized farms. To reduce psychological and physiological stress that can be transmitted to organs, transgenic pigs will have stimulation, including toys and possibly conspecifics.[46] They will not be slaughtered in massive slaughtering factories that increase stress and pain; rather, in order to ensure the safe retrieval of organs, transgenic pigs will be as painlessly sedated as possible. In other words, there is a compelling reason inherent in xenotransplantation research itself to treat transgenic pigs as well as possible and to minimize pain.

Critics have a response: transgenic pigs will still suffer and be harmed in a variety of ways, and the *Animal Welfare Act* is not always enforced. Bernard Rollins observes that, although their welfare will be better than most other pigs, their living situation will "be equally deficient in accommodating the animals' biological and psychological natures" (p. 4).[47] Entwistle and colleagues note the chronic care, isolation, and sterile lab environment "could be emotionally harmful" (p. 992)[48] for transgenic pigs. Johnson is more explicit:

> These pigs are genetically modified and cloned, and must be bred and housed using infection-control measures like artificial insemination, embryo transfer, Caesarian births, and isolation in sterile environments without contact with other animals, preventing the expression of their natural behaviors. Their use would require frequent blood and tissue sampling, which in pigs requires restraint, including drug-induced restraint.[49]

The argument is that, despite efforts to provide transgenic pigs with the best life possible, the research requires confinement, pain, suffering, and death, and the suggestion might be that death would be a mercy for transgenic pigs.

These concerns are well-taken. If the regulations cannot be satisfied, then the xenotransplant defender should insist that, rather than ending xenotransplantation research altogether, researchers should engineer transgenic pigs to reduce their capacity for suffering. As with other facets of genetic engineering, this is not a far-fetched possibility, for it has been demonstrated that researchers can modify affective pain or felt pain awareness but not nocioception.[50] There is a growing literature in defense of welfare-based arguments for engineering out animals' capacity to experience pain, specifically animals used in industrialized animal agriculture and animal research.[51–54] If we engineer transgenic pigs to lack the enzymes in the brain that are responsible for affective pain experiences, then transgenic pigs would not experience subjective, phenomenal pain, though they may still experience pleasure and display pain-related behavior. Importantly, though, transgenic pigs would live a brief life of some pleasure and little to no phenomenal pain; there will not be pressing animal welfare concerns for perfected

xenotransplantation, for their lives would be worth living, meaning that they experience more pleasure than pain overall. The high degree of existing genetic manipulation required to engineer transgenic pigs means that were it scientifically possible to achieve this outcome there would be ample opportunity to do so.

In the meantime, as research continues on pigs and researchers are unable to eliminate or minimize pain through genetic engineering, the xenotransplant defender can insist that this cost must be borne without being carried away by the rhetoric. On the one hand, it is a moral cost that this research causes transgenic pigs some pain, and the defender is sensitive to this. On the other hand, it is not as though these pigs undergo constant painful procedures and it is far from clear to us whether their lives are not worth living. The nature of the research warrants blood sampling, a sterile environment, and other lack of niceties, which is not to be confused with an environment devoid of toys or conspecifics, for the benefit of humanity. Common practice, for example, is to use pigs from "closed herds" for xenotransplantation.[55] To not test for infection threatens the well-being of a person, who—recall—has higher moral standing than a transgenic pig. While there is a dearth of research on transgenic pig welfare, which allows critics to speculate more negatively than may be warranted, existing research does not support the claim that transgenic pigs' lives are not worth living. Martelli et al.'s study on transgenic pigs intended for xenotransplantation found no significant differences on various welfare metrics compared to non-transgenic pigs, suggesting to them that there is "no significant undesirable effect" as a result of genetic engineering (p. 815).[56] If there are ways to promote transgenic pig welfare without compromising safety, then the xenograft defender is all in favor. But as it is, the burden is on critics of xenotransplantation to show that transgenic pigs do not have lives worth living.

5 | NO UNNECESSARY HARM TO TRANSGENIC PIGS

DeGrazia and Sebo's third necessary condition for morally permissible research is that "animal subjects not be subject to unnecessary harms," meaning "that no harms should be imposed on subjects unless they are strictly required to carry out the study in a scientifically valid way" (p. 425–426).[8] This means that transgenic pigs are not unnecessarily deprived of basic goods, such as water, food, socialization, mobility, and the like; it also means that transgenic pigs are not subject to unnecessary interventions, such as unnecessary blood draws or injury. For reasons already stated, the xenotransplant defender thinks there is compelling reason to treat transgenic pigs as well as possible: healthy and happy pigs are integral to healthy organs. There is also compelling reason to edit them to eliminate phenomenal suffering. If this is done, there is no reason to think unnecessary harm will befall them and every reason to think their suffering will be minimized. Of course, if the research demonstrates a pattern in which the pigs are clearly subjected to unnecessary harms, then so much the worse for the research. However, research on transgenic animal welfare thus far does not support this.

6 | CONCLUSION

It is important to highlight, lest someone think otherwise, the xenotransplant defender is in favor of pursuing other avenues for increasing the availability of transplantable organs; it is just that they have good reason to think they will not be enough in the short term. Until better alternatives are available, transgenic pigs could provide a feasible solution to the problem in the relative short-term. As Caplan and Parent explain: "xenotransplant should not be the end-goal, but an intermediate marker on the path to organs bioengineered with the intended recipient's tissues or mechanical options" (pg. 1205).[57] Animal research will inevitably be necessary to reach this future. We have argued that porcine-based xenotransplant research can satisfy stringent requirements for animal research, because it can produce a significant net benefit to human beings while avoiding bad outcomes for the pigs involved, namely making their lives not worth living and subjecting them to unnecessary harm.

CONFLICT OF INTEREST

Christopher Bobier, Daniel Rodger, and Adam Omelianchuk declare no conflict of interest. Daniel Hurst is a paid consultant to a working group on xenotransplantation ethics at NYU.

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