

# Genetic disenchantment and xenotransplantation: diminishing pigs' capacity to experience suffering through genetic engineering

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## ABSTRACT

One objection to xenotransplantation is that it will require the large-scale breeding, raising and killing of genetically modified pigs. The pigs will need to be raised in designated pathogen-free facilities and undergo a range of medical tests before having their organs removed and being euthanised. As a result, they will have significantly shortened life expectancies, will experience pain and suffering and be subject to a degree of social and environmental deprivation. To minimise the impact of these factors, we propose the following option for consideration—ethically defensible xenotransplantation should entail the use of genetic disenchantment *if* it becomes possible to do so and if that pain and suffering cannot be eliminated by other means. Despite not being a morally ideal 'solution', it is morally better to prevent unavoidable pain until a viable non-animal alternative becomes available.

## INTRODUCTION

Xenotransplantation—the cross-species transfer of live cells, tissues or organs—has been studied for decades to bridge the gap between the increasing demand for human tissues and organs and the current shortfall. Solid organ transplantation, which this paper is concerned with, is of particular importance for xenotransplantation. In the USA, over 100 000 persons are currently awaiting a human organ. Yet, over a dozen patients die each day while waiting for a transplant.<sup>1</sup> Xenotransplantation could be one way to address the shortfall of transplantable organs. While we believe that alternate means of increasing organ supply should continue to be developed,<sup>1</sup> solid organ xenotransplant research has continued with the hope of achieving clinical status within the next decade or two.

The pig is the primary animal being considered as a source of organs for humans for several reasons—similar sized organs, close physical and anatomical similarity to humans, ease of breeding enough source animals, low risk of cross-species infection (xenozoonosis) and their rapid growth to adult size in ~6 months.<sup>2</sup> The pigs will be genetically engineered and specifically bred and housed in designated pathogen-free (DPF) conditions. These conditions deviate from the typical environmental conditions of pigs. They will be deprived of being outdoors, not permitted to be in a 'natural' habitat and may lack some of the communal

interactions that pigs typically enjoy. Then, at some point in the pigs' lives, they will be anaesthetised, the transplantable organs will be retrieved and the pig will be euthanised when the organs are surgically removed.

Issues of animal ethics and rights are inherent in xenotransplantation, which we are sensitive to and the breadth of which is beyond the scope of this article. Here, we raise an ethical concern that has not been adequately explored regarding xenotransplantation—animals with complex mental and social lives, with the capacity to suffer, will be deprived of their ordinary state and have the potential to experience pain, suffering and distress because of this deprivation. While the specific details remain unclear, the pigs likely need to be restrained to undergo regular blood sampling, biopsies and other invasive testing that will involve physical and psychological suffering. To ameliorate potential suffering, one could ensure that the facilities where the pigs would be raised are designed in a way that minimises such suffering. Moreover, any medical tests would use analgesia, and general anaesthesia would be used when organ retrieval is indicated. These two options, from the little that is known publicly about the housing conditions of the genetically modified pigs and the surgical procedure itself, seem to already be in place to some degree. Still, these solutions may not eliminate all sources of potential suffering, such as the young piglet being separated from its mother or the lack of a 'natural' habitat where the animals can live and thrive.<sup>3</sup> Here, we present a proposal for consideration and deliberation—ethically defensible xenotransplantation should entail the use of genetic disenchantment if it is demonstrated that such pain and suffering cannot be eliminated by other means. This proposal is informed by Shriver's prior work on animal disenchantment in industrialised animal agriculture and is predicated on two assumptions regarding xenotransplantation.<sup>4</sup> Our analysis will proceed under the following two assumptions: (1) xenotransplantation research will inevitably continue, and (2) causing pain and suffering requires sufficient justification. Given that xenotransplantation research involving pigs will continue, researchers have a moral responsibility to eliminate as much pig pain and suffering as possible. We argue that genetic disenchantment could therefore be pursued insofar as it is effective at eliminating pain and suffering that cannot be mitigated by other means and does not compromise the transplanted organ.

<sup>1</sup>For example, by adopting novel policy measures to increase living and deceased human organ donation and the development of bioengineered organs.<sup>1</sup>



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## THE INEVITABILITY OF FURTHER XENOTRANSPLANTATION RESEARCH

Our first assumption is empirical—xenotransplantation research will inevitably continue for the foreseeable future.<sup>5,6</sup> This is based on the fact that the incidence and prevalence of organ failure are increasing, and therefore, the demand for organs will follow a similar pattern.<sup>7</sup> Johnson observes that the shortage of organs is caused by too few people choosing to donate their organs—either when they die or as living donors—and that alternative strategies to increase the number of human donors should render the need for xenotransplantation unnecessary.<sup>3</sup> For example, she notes that adopting a presumed (opt-out) consent model has increased organ donation in several countries; however, there remains no definitive evidence to support the contention that doing so in isolation is effective.<sup>8</sup> Even Spain, widely considered the gold standard for organ donation, still has an insufficient number of organs and an increasing kidney transplant waitlist.<sup>9</sup> So leaving any ethical arguments aside for now, the fact remains that attempts around the world, thus far, to increase the number of human donors to the level necessary have been largely unsuccessful. Importantly, the number of human organs available for transplantation will always be limited because only a fraction of people who die are eligible to donate their organs—in the UK, it is only ~1%.<sup>10</sup> Similarly, the expectation of increasing the number of living donors to the level required belies the disincentives and costs of doing so.<sup>11</sup> Consequently, novel attempts to identify a source of organs to meet the demand are likely to continue until the disparity has been addressed.

While there have been criticisms of xenotransplantation from ethicists and scientists alike,<sup>3</sup> there has been a steady increase in the number of xenotransplant studies conducted—the goal is for xenotransplantation to move into the formal clinical trial phase and to one day become a viable therapeutic option. Animal-to-animal xenotransplant research is ongoing; baboons with genetically modified pig hearts have survived more than 150 days,<sup>12,13</sup> while a monkey with a genetically modified pig kidney survived for 2 years.<sup>14</sup> In 2022 and 2023, researchers at multiple institutions in the USA performed studies of both kidney and heart xenotransplantation. Researchers at New York University and the University of Alabama at Birmingham have also performed genetically modified pig kidney-to-human decedent studies.<sup>15–17</sup> Researchers at the University of Maryland Medical Center performed a genetically modified pig heart-to-human transplantation in January 2022 and September 2023, with the recipients living for 6 and 8 weeks post-transplantation, respectively.<sup>18</sup> The path towards formal clinical trials seems to have been paved, and the University of Alabama at Birmingham has submitted its plan for a phase 1 clinical trial.<sup>19</sup>

## MORAL RESPONSIBILITY TO MINIMISE SUFFERING AND PAIN

Our second assumption is ethical—causing suffering and pain requires sufficient justification.<sup>20,21</sup> By pain and suffering, we mean the phenomenal or conscious awareness of hurt or deep discontent resulting from the frustration of one's desires. If one causes suffering and pain without a good reason, they should seek to mitigate it. For example, kicking a toddler for fun is morally wrong, but pushing a toddler out of the way of an oncoming car to prevent her from being hit is morally permissible—in both cases, pain is inflicted and an evaluable reason for causing that pain. The principle also seems to be true when applied to causing non-human animal pain. A person is justified or permitted in allowing her dog to be vaccinated, which involves causing the dog pain, because of the ensuing good that results from being

vaccinated, namely, being protected from disease. However, if the person allows the veterinarian to poke her dog with needles just for fun, this would be unjustified because, at the very least, poking a dog with needles for fun is a bad reason to poke a creature capable of experiencing pain. So, it seems clear that inflicting suffering and pain on another creature is permissible *only* with good reason and sufficient justification, and greater suffering and pain requires greater justification. To deny that causing suffering and pain to another creature requires good justification is to court moral callousness that few would be willing to accept, and we assume that this ethical tenet is generally considered uncontroversially true.

## MORAL RESPONSIBILITY AND XENOTRANSPLANTATION

That causing pain and suffering requires sufficient justification means that, in the case of xenotransplantation, researchers should not cause unnecessary pain and suffering to pigs. Stated differently, there should be good reason to cause suffering and pain to pigs. Some might argue that the line of research is unethical for precisely this reason—there are alternatives to xenotransplantation to increase the availability of transplantable organs, and so, xenotransplant research is unnecessary. Whether the alternatives are as promising as xenotransplantation to mitigate the organ supply shortage within the next decade or two is subject to debate. Importantly for present purposes, xenotransplant research will continue for the foreseeable future, and given that it will continue, the issue is how researchers are to minimise or otherwise eliminate unnecessary pain and suffering.

This is important because several scholars have argued that pigs will experience a lot of suffering and pain. Hughes was one of the first to raise this concern, stating that ‘the need to keep donor animals free—as far as possible—from infectious agents may require them to be raised in isolation, and the genetic modification necessary to achieve compatibility with humans may impair health and cause suffering in the donor animals’.<sup>22</sup> Currently, it seems that the pigs used for xenotransplantation will need to be bred and raised in DPF environments in perpetuity—not only during the initial research phases of xenotransplantation but also if/when it becomes a viable clinical option, and the raising of such pigs will have to scale up to meet demand. Concerns have also been raised with xenotransplantation that are centred on this very issue of breeding and housing pigs in a non-natural environment that prevents them from exercising their natural behaviours and involves frequent manipulation, including blood sampling.<sup>3,23,24</sup>

One response would be to insist that high welfare standards are being met or exceeded. WHO has recommended that DPF facilities should have high standards of animal welfare.<sup>25</sup> There is some evidence that facilities have been trying to address this responsibility, for example, by permitting genetically engineered pigs to be housed and sleep with other members of their species so that they can develop social relationships, have sufficient space to walk around rather than being confined with limited space allowance and are provided with stimulating toys and food treats to encourage playful and varied activity.<sup>ii</sup> Due to concerns about vertical viral transmission, it is necessary to wean genetically engineered piglets from the mother after the first week, but they can remain around other piglets and are not isolated. A pragmatic reason also exists for maintaining high welfare

<sup>ii</sup>This information is based on personal email correspondence with David Cooper describing his experience at one facility in the USA responsible for raising genetically modified pigs for xenotransplantation.<sup>2</sup>

standards—it helps to ensure that unnecessary attention is not diverted away from the primary goal of xenotransplantation. Arguably, it is in the interest of biotechnology companies—due, at a minimum, to public relations—to permit genetically engineered pigs to have the best possible lives within the confines of what is possible, reasonable and safe. Moreover, unhealthy, stressed pigs may compromise organ quality. Despite attempts to address certain aspects of animal welfare, in some cases doing more than what is legally required, xenotransplantation will still involve a degree of environmental and social deprivation, medical testing and procedures, all of which carry the potential for suffering and pain in genetically engineered pigs. In other words, it would appear that there is plenty of suffering and pain inherent in the research itself, and as such, there is suffering and pain that cannot be mitigated.<sup>26</sup> If this pain and suffering is morally concerning—which we assume is the case—then attempts should be made to mitigate it as far as possible.

Another option has been offered by Moen and Devolder, who describe an approach termed ‘palliative farming’ in which animals raised as a food source are administered drugs to relieve stress and pain.<sup>27</sup> This approach would be unlikely to succeed in xenotransplantation, as these drugs would be metabolised by the liver and excreted by the kidneys—the very organs that would be used as xenografts in the human recipient—which could lead to unanticipated problems. We can only speculate, but there is a risk that the administration of regular analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) during the maturation process could potentially result in some degree of renal impairment. For example, there is evidence in humans that regular analgesic and NSAID use can adversely affect renal function,<sup>28–30</sup> and a 7-day course of some NSAIDs in healthy pigs was shown to result in mild damage of the renal tubules, though this was not deemed clinically significant.<sup>31</sup> So, it is possible that regular administration of these kinds of drugs could compromise the xenograft and therefore may not be an appropriate option in the context of xenotransplantation. Admittedly, it is worth noting that the justification for ruling this proposal out is weakened when applied to organs other than the kidneys. However, given the significant role of optimal kidney function, any compromised renal function could have a wider negative effect on the other organ systems.

In sum, researchers should mitigate unnecessary suffering and pain. Xenotransplantation research will involve pigs in suffering and pain, not all of which is eliminable through environmental changes or palliative care. If there is a way to eliminate or otherwise reduce their suffering and pain without compromising the organ, then researchers should pursue it.

### THE CASE FOR GENETIC DISENHANCEMENT

Pigs are already genetically altered for xenotransplantation research. Genetically engineered pigs for xenotransplantation are created using somatic cell nuclear transfer and are genetically modified to prevent hyperacute and acute vascular rejection and to reduce the risk of xenozoonosis. Specific genes like the sugar molecules GGTA1, Neu5Gc and B4GALNT2 are also knocked out in genetically modified pigs to reduce their immunogenicity and prevent hyperacute rejection. The advent of CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 genome editing systems has made the process of adding or deleting genes more efficient, precise and cheaper. Importantly, for the prospect of genetically disenchanting pigs, the reproductive process provides ample opportunity to do so.

Several scholars over the past two decades have begun arguing for a position of genetically modifying non-human animals to decrease or altogether eliminate the ability for certain types of pain and suffering. Genetic disenchantment<sup>iii</sup> in the context of animals describes their genetic modification to better suit their environment in response to the suffering involved in factory farming and medical research.<sup>32</sup> Adam Shriver<sup>4,33</sup> has defended the use of genetic disenchantment concerning industrialised animal agriculture or factory farming, but similar arguments have since appeared concerning research animals.<sup>34</sup> A basic overview of the arguments that have been offered so far is necessary to present our argument for genetic disenchantment in animals used for xenotransplantation, which builds on and expands on this work. Arguably, genetically engineered pigs’ lives are much better than those of animals used in factory farming and other kinds of research, so, the case for disenchantment may be somewhat weaker.

The crux of Shriver’s argument is that, in the context of factory farming, a technological solution may exist today or in the future to eliminate an animal’s capacity to suffer. He posits that ‘genetically modified livestock who have a reduced capacity to suffer would lead to better consequences than maintaining the status quo: specifically, it would lead to a world in which there is much less unnecessary suffering’.<sup>4</sup> The alternative, namely, the elimination of factory farming altogether, is practically unfeasible considering the growing demand for animal meat products. Accordingly, genetic disenchantment offers a preferred alternative to the status quo on grounds of animal welfare.

Devolder and Egel argue that ‘tackling the problem of research animals’ continued suffering by using gene editing to create disenchanting research animals with a reduced capacity for suffering, in particular from pain’ is a worthy pursuit.<sup>34</sup> After all, the use of animals in research is growing, not diminishing, and so, genetic disenchantment offers a feasible way to minimise animal pain and suffering. Abolition of animals for use in research is, therefore, both unlikely and unfeasible until a technological alternative that is at least as efficacious is discovered; the next best option is to explore how pain and suffering can be minimised in xenotransplantation research. This is best described as the defeatist argument for genetic disenchantment—we cannot eliminate the use of animals for research, but we can work towards eliminating animal suffering.

Our argument for genetic disenchantment of pain and suffering for pigs used for xenotransplantation, like work that precedes ours, can be made on the following grounds. The argument can be expressed as follows:

1. Unnecessary pain and suffering in animals should be prevented where possible.
2. Rearing genetically engineered pigs in an unnatural milieu has the potential to cause significant pain and suffering.
3. Further refining the pigs currently being used for xenotransplantation so that they lack certain aspects of conscious pain would prevent significant suffering and pain without compromising their organs. (a) They may be rendered insentient in such a way that they can grow like normal pigs but have no higher-level brain function, that is, animal microcephalic

<sup>iii</sup>The distinction between disenchantment and enhancement is not always clear.<sup>3</sup> For example, what might be considered a disenchantment could be characterised as an enhancement in a different context or vice versa. Take, for instance, a soldier who undergoes genetic modification to reduce the pain and suffering experienced during combat. This would be like the approach taken in this paper for pigs for xenotransplantation. However, in the soldier example, this would likely be termed ‘enhancement’. Hence, the distinction is not always clear.



lumps. This would eliminate all pain and suffering. Or (b) they can be disenanced in a more piecemeal manner, for example, by moderating the corticotropin-releasing hormone, which affects cortisol production and behavioural displays of stress. While there may be concerns that piecemeal disenancement may promote more suffering than otherwise, this seems to be an empirical question, one that requires us to breed such animals and observe their welfare.

4. Therefore, further refining source pigs to disenance them of certain pain and traits could decrease their suffering and pain without compromising the organ and be advantageous over the status quo.
5. Therefore, ethically defensible xenotransplantation should entail the use of genetic disenancement when it is possible to do so.

While we are aware that xenotransplantation does not align with the totality of the 3R (Replacement, Reduction and Refinement) principles in animal research, we do believe our argument is in line with the principle of refinement. In animal research, the 3R framework, developed by Russell and Burch in the mid-20th century, is an approach that commits to replacing animals used in experiments with insentient matter, reducing the number of animals used in research and refining experiments, which would include ‘any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used’.<sup>35</sup> Under the 3R approach, researchers have a moral onus to reduce pain/suffering whenever possible. If genetic disenancement becomes viable, it would prima facie fit the 3R framework principle of refinement. Importantly, genetic disenancement—along with well-designed DPF facilities and evidence-based animal husbandry practices—can help to address some of the animal welfare concerns with xenotransplantation research that have been raised, namely, the concerns that this research is inherently unpleasant and painful for pigs.<sup>36</sup> If done well, there will be minimal harmful psychological or physical suffering. However, despite taking reasonable measures to mitigate any physical pain and suffering associated with xenotransplantation research, some will likely remain. It is because of this that genetic disenancement is ethically defensible—should it become technologically possible to do so.

## RESPONSE TO OBJECTIONS

It is important to reiterate that our argument assumes that xenotransplantation research will continue. If it continues and we have a moral responsibility to eliminate or minimise pain and suffering as much as possible, then our conclusion follows. Proponents of animal rights criticise xenotransplantation because animals ought not to be used in this way. Here, we do not take a stand on the ethical permissibility of xenotransplant research; we only assume that it will continue. A proponent of animal rights can agree that if the research continues, which it will, it is better to eliminate pain and suffering as much as possible. We do not think this commits one to a defeatist attitude, for it is compatible with arguing that the research should not continue. In other words, one can consistently maintain (a) that xenotransplant research should stop for reasons of animal rights and (b) that, if it continues, it is better for the pigs if they are genetically disenanced.

Arguments against disenancement have been offered. Murphy and Kabasenche draw on an ecofeminist lens to argue that disenancement extends a domination-oriented resolution to animal suffering that is predicated on a perceived moral—or other—superiority to justify the subordination of animals.<sup>37</sup> If the benefits of xenotransplantation could be brought about

without having to harm animals, then this would be both preferable and morally obligatory. Murphy and Kabasenche note that if society valued the capacities of animals, we would try to improve the experience of animals, rather than removing their capacity to experience.<sup>37</sup> This objection echoes other animal welfare frameworks that focus on the biological capacities of an animal and the moral and prudential value of animals having the opportunity to realise their biological capacities.<sup>38</sup>

We agree that researchers should do everything to improve pig well-being and that, perhaps, the continuation of xenotransplantation research suggests that society does not value the capacities of pigs. Our argument merely assumes that this line of research will continue and that pigs will continue to be genetically altered for organ transplantation. As such, these animals will likely suffer in profound ways, and their suffering may not be mitigable in environmental ways. For instance, researchers will not allow these animals to roam free on a habitat reserve until time for organ retrieval. This is why we think genetic disenancement may be worth pursuing.

That our argument presupposes that xenotransplantation is ongoing despite ethical objections allows us to sidestep common concerns about genetic modification more generally. To reject further genetic disenancement because it violates the integrity of the animal<sup>39</sup> or that it is part of a broader system of oppression<sup>37 39 40</sup> is irrelevant to our argument precisely because these concerns apply to xenotransplant research more generally, which is not going to stop anytime soon. Maybe these concerns show that xenotransplant research should stop; maybe they do not. Our point is that since it is not going to stop, further genetic alteration may be required because of our moral responsibility to eliminate pain and suffering when it is possible to do so.

Perhaps the most worrying criticism is that genetic disenancement could result in scientists creating ‘animal microcephalic lumps’ that are in a state of ‘brain death’ whereby they have no higher-level brain function. We agree that this would be ethically problematic because even though it would entail no capacity to suffer, it would remove the possibility of *any* kind of experience—let alone positive experiences—and the formation of meaningful relationships. Rather, we argue along the lines of more piecemeal disenancement (ie, 3b); however, while this would preserve the capacity for positive experiences, it may still negatively affect animal welfare. For instance, if a pig’s capacity for experiencing pain was eliminated, the pig may be unaware of a broken limb, or it may be unable to experience fear, the social benefits that result from experiencing fear and the role of pain in learning; indeed, the pig may not be able to experience many pleasures that result from or are intertwined with experiences of pain.<sup>41</sup> This concern is well taken—perhaps, we must concede that this criticism represents one of the primary risks associated with the disenancement of the pigs used for xenotransplantation. Nevertheless, those responsible for them in the DPF have an interest in ensuring that the pigs are cared for and are not routinely injuring themselves and potentially compromising their organs.<sup>iv</sup>

## CONCLUSION

If—following formal clinical trials—xenotransplantation is shown to be safe and clinically effective, it will introduce the

<sup>iv</sup>As we have noted already, the case for disenancement in xenotransplantation is weaker compared with factory farming, and therefore, we would expect it to be perfected in this area first and later adopted, *if* feasible, for xenotransplantation.<sup>4</sup> This is important because the process of perfecting disenancement would itself involve a degree of pain, suffering and failure.

novel and potentially large-scale use of genetically modified pigs for ongoing research and clinical purposes. However, xenotransplantation may entail some degree of deprivation, pain and suffering for animals that we know have complex mental and social lives. Thus, we have argued that *if* it becomes possible to genetically disenhance pigs to lack or diminish their capacity for pain and suffering, then there may be an obligation to do so. We understand that the use of—and disenchantment of—animals for research is not morally ideal, but until there is a viable non-animal alternative, then reducing or removing unavoidable pain and suffering is morally preferable. Additional research is needed to try to empirically verify if and to what extent pigs are affected by their unnatural housing conditions.

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