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Introduction

The waiting list for an organ transplant is extremely long (over 100,000 people in the U.S.) and difficult to ascend.[1] Every day, an average of 13 people on the waiting list for a kidney die, while a new person is added approximately every 14 minutes.[2] This is a net-addition of approximately 85 to 90 people being added to that list daily. These circumstances have led scientists to experiment with xenotransplantation, or the transplantation of organs from a non-human donor to a human recipient.[3] While a xenotransplantation could also be considered the act of transplanting an organ between any two differing species, for purposes of this paper a xenotransplant is generally defined and used in terms of a human receiving a non-human organ.[4] Such a procedure, if done properly in both medical and ethical terms, can result in establishing a virtually unlimited supply of donor organs for human use.[5] Pre-clinical trials where non-human primates received organs from differing species (mainly pigs) have already been shown to be effective.[6] After the successful xenotransplantation of a pig's kidney into a brain-dead patient by Dr. Robert Montgomery and his team at New York University (NYU) Langone in New York City in October of 2021, several ethical questions arose. These questions range from the carrying out of the procedure itself on a brain-dead patient, the welfare of and ethical ramifications of using animals in such a procedure, and the role of research moving forward.

Additional research is necessary before pig organs are harvested for xenotransplants on a large scale, and much of this research will have to follow significant ethical parameters. While the October '21 xenotransplant at NYU was done on a brain-dead patient, a living patient who can directly benefit from the procedure should be seriously considered as a soon-to-be recipient. The maintaining of the donor animal's welfare is also of the utmost importance. Ensuring the ethical and healthy raising of these animals is imperative to medically successful and ethically

sound xenotransplantations. Further, Institutional Review Boards (IRBs) will have to grapple with research ethics in a novel fashion, and this paper will help guide them on that journey. A framework for ethical research will be established in this essay, as well as relevant questions answered, all while using normative ethics in an effort at setting ethical norms regarding how we ought to move forward from here. Finally, a framework for future empirical clinical trials will be proposed, with emphasis on maintaining ethical standards.

I. Xenotransplantation

A xenotransplant is, for the general purposes of this paper, when a human undergoes a transplant procedure where they receive animal organs, cells, or tissue.[7] [8] Due to an overwhelming demand for organs that has spanned the last several decades, and the fact that so many people die while waiting for one, scientists have turned to animals for help. What first began with blood xenotransfusions (the act of transfusing blood of one animal blood to one of a different species) from a lamb to a teenaged patient in the late 17th century, has given way to a successful xenotransplantation of a pig's kidney into a human patient in October of 2021.[9] [10]

a. History of Use

The first use of an animal being used for such a procedure was in 1667 when a 15-year-old patient was given lamb blood. Save a nosebleed just under 12 hours after, the procedure was considered a success.[11] However, due to the relatively small amount of blood used and the modern understanding that human and non-human blood do not mix, it was likely not as successful as was thought at the time.[12] In the 19th century, frogs were often used for skin grafts, and the first corneal xenotransplant happened using a pig.[13] [14] In the 1920s, monkey testes were transplanted into male recipients in attempts at "rejuvenation." While experts today question the legitimacy of results from the procedure, where slices of chimpanzee or baboon testicles were

implanted into a human male, there were widespread reports of recipients feeling more energized with very few complications reported.[15] Even if those results may have been akin to placebo effects, the procedures were otherwise deemed successful due to no significant issues.

The 20th century saw several attempts at liver, kidney, and heart xenotransplants using mainly primate (baboon and chimpanzee) organs. Between November 1963, and February 1964, Dr. Keith Reemtsma performed six kidney xenotransplants to varying degrees of success. The ages of his patients ranged from 12 to 46 years old, and most died within two to six weeks of the surgery. A 23-year-old female, however, survived the longest – for approximately nine months – after receiving a baboon kidney. Dr. Reemtsma found that sepsis was more likely to kill the recipient than rejection of the organ and concluded that proper blood type of the donor animal should be a focus of future clinical trials.[16] One of the earliest longest-lasting liver xenotransplantations was performed by Dr. Tom Starzl in Pittsbugh in 1992, when a 35-year-old man survived for 70 days with a baboon liver.[17]

b. Contemporary Use

One of the more promising uses of xenotransplants in humans is the use of non-human hearts in newborns. Hypoplastic left heart syndrome (HLHS) is a condition that affects babies in approximately two out of every 10,000 live births. Without surgery, an infant born with HLHS has a zero percent chance of survival.[18] In 1985, a baboon heart was used in the first ever xenotransplant of an infant. “Baby Faye,” as she is known, survived for 20 days with a baboon heart.[19] Due to the significant lack of human hearts available for neonatal transplants (less than 100 per year in the United States), the necessity and plausibility of neonatal heart xenotransplantations became clear.[20] Additionally, pigs have become the preferred source of organ procurement for xenotransplants in adult humans. This is because non-human primates

(NHP) have various disadvantages, such as having smaller organs that cannot support the physical needs of an adult human. Pigs can also grow to the necessary size for use in an adult human xenotransplant in as little as half a year or less.[21] Further, recent advancements have allowed pigs to be genetically modified so a recipient of their cells, tissues, and organs have a significantly higher chance of accepting the foreign body and not rejecting it.[22]

As medical science progresses, xenotransplants are becoming safer and more tenable. However, as with any medical procedure, there are always risks. As with most modern medicines, tests on non-human primates are the main way xenotransplant experiments are carried out.[23] Since the late '90s, experiments have been done using pig organs into NHPs, specifically testing procedures involving lungs, kidneys, hearts, and livers. One of the main risk-factors that was discovered from these transplant experiments was the possibility of cross-species infection. Therefore, the creation of new immunosuppressive drugs to help recipient's bodies safely accept the foreign organs is an important step in moving forward with xenotransplantation. An emphasis has also been established on continued research into genetically modifying pigs for organ donation while avoiding the usage of wild pigs.[24] This allows for tighter regulation and preventative measures to be put in place to avoid diseased or otherwise unhealthy donors infecting the organ recipient, who could then also potentially pass on those diseases to others within their species.

Recent studies have shown increased length of survival for NHP xenotransplant recipients of pig organs.[25] Non-human primates receiving pig kidneys, lungs, and livers have lived up to 435 days, 195 days, and 29 days, respectively. This is in large part due to the progress made in raising pigs for the specific purpose of xenotransplantation.[26] Researchers have also shown that NHP recipients of pig hearts can live as long as 945 days.[27] In the late 1990s, however, clinical

experiments using pig cells and tissues in humans was temporarily halted by the Food and Drug Administration (FDA) over concerns of non-human viruses being introduced to the human body.[28] Today, the FDA regulates all animal products used in xenotransplantation.[29] Additionally, they have offered an exhaustive set of guidelines for clinicians and researchers to follow when carrying out experiments or studies on xenotransplantation. These guidelines coincide with an application that must be sent to the FDA for approval; this application ensures not only animal welfare is maintained but also works to prevent diseased or infectious animals from being used in human xenotransplants. This comprehensive framework provides both mandatory rules and regulations as well as suggestions to be followed to ensure safe and effective studies.[30]

One of the main aspects of the guidelines put forth by the FDA is that of maintaining animal welfare. The origins of the animals as well as how they are raised and killed are closely followed and documented to keep the animals healthy and, in turn, maintain the health of the human recipients of their organs. This includes tests on the animal's herd, biopsies of whatever part of them is being sought for xenotransplant, and even quarantining of the animal for at least three weeks prior to the harvesting of the animal's body part being used.[31] Implementing and standardizing these practices helps to enhance the efficacy of xenotransplants and the like. Moreover, it allows animals to be genetically modified in attempts at preventing the receiving body from rejecting the skin, cells, tissue, or organ. Careful attention to the donor animal, from semination to embryo health maintenance to slaughter, is important to ensure the safety of the human recipient.[32]

II. NYU Procedure

The xenotransplant at New York University, while remarkable in and of itself, did have various shortcomings. It proved that a pig's kidney can successfully be used in a human recipient. However, the patient's own kidneys also remained intact (although the level of their functionality is unknown), meaning the full extent of the procedure's efficacy is not certain.[33] There was also a missed chance at testing the patient's response to a kidney from a triple knockout (TKO) pig. A TKO pig is one that has had three of its carbohydrate xenoantigens removed. These carbohydrate xenoantigens are generally responsible for the body rejecting the pig organ, which has been demonstrated in NHP xenotransplant experiments.[34] [35] For the NYU procedure, a pig of this nature was not utilized. While it is widely accepted that humans generally do not have the antibodies that would result in a rejection from a TKO pig, this study could have confirmed that, so long as a quick onset rejection did not occur. This is unfortunate because organs from TKO pigs are more than likely going to be the most-utilized pig for future use in xenotransplantation trials and beyond.[36] I hypothesize that a TKO pig was not used in this procedure due to the fact that the patient was braindead. Nonetheless, the NYU procedure was considered a successful one. A significant indicator of success lies in the fact that the patient's body did not reject the organ during the 54hour period that the experiment lasted. Also, important to note is the patient's urine and creatinine levels remained normal comparable to a human-to-human kidney transplant.[37]

a. Procedural Success & Ethical Justifications

While a TKO pig was not used in this procedure, a α1,3-galactosyltransfearse gene-knockout (GTKO) pig was. A GTKO pig has only had the Galactose-alpha-1,3-galactose (alpha gal) removed. GTKO pigs, as have been shown in prior studies, are not the ideal donor pigs for

xenotransplantation procedures.[38] [39] [40] Nonetheless, the removal of the alpha gal from the pig was necessary, as it can prompt a rapid attack on the donor organ by the human immune system.[41] This xenotransplantation did not occur like one normally would, i.e., an organ being implanted into the body. Rather, for observational purposes, the kidney in question was attached to the body via blood vessels in the thigh of the patient and kept in a transparent protective sheath while outside the body.[42] This did not have any impact on the outcome of the study, as the patient's blood was still running through the kidney as it normally would if it had been implanted inside the body.

There are several ethical justifications that would have had to be considered prior to the carrying out of this procedure. Beauchamp and Childress's bioethical theory of principlism (autonomy, beneficence, nonmaleficence, and justice) can offer a normative starting point.[43] Firstly, the patient's wishes must always be upheld, even post-mortem. In this case, the patient was a registered organ donor. Ironically, however, the organ-donor patient in this case was actually receiving one, instead of donating one. Additionally, her family gave permission for the procedure to be done. Together, both of those facets of the case uphold the principle of autonomy.

Beneficence and nonmaleficence, or the pursuit of what is best for the patient or research subject and the avoidance of doing harm to them, while still relevant, are slightly less applicable here. Since the patient was brain-dead (thus also considered legally dead), there was no hope of her regaining brain function.[44] Therefore, she could arguably be neither harmed nor helped from this procedure. On a larger scale, however, beneficence can be considered. The advancements this can offer the bigger picture of science are undeniable. While this patient herself did not

inherently receive any meaningful procedure, medicine at large did. This case proved that xenotransplants are a feasible prospect in medical science. Future patients will reap the benefits.

Although the patient at NYU Langone did not benefit from the xenotransplant she underwent, moving forward, others certainly will. This utilitarian outcome is important to note. In utilitarian terms, one should act in such a way that the outcome of one's actions results in the most amount of good for the greatest number of people.[45] Over time, if xenotransplantation becomes a more exact and easily executable procedure, the tens of thousands of individuals on transplant waiting lists can benefit. The clinical utility of xenotransplants is significant, and the patient who underwent the NYU procedure can be considered a catalyst of that clinical usefulness. The nature of medicine and science, while largely rooted in patient care and maintaining beneficence and nonmaleficence, is also broadly utilitarian. Experiments such as this one demonstrate that overarching utilitarian nature; the goal here was not to fix the kidney function of the patient, but to test whether a pig's kidney could be effectively used in a human.

Deontology, or the ethical theory that deals with one's moral duty and how one ought to act, is also an important aspect of xenotransplantation.[46] On the one hand, medical professionals have the obligation to uphold what is best for their patients, as is outlined in the theories of beneficence and nonmaleficence. On the other hand, one of the principles of medical ethics put forth by the

American Medical Association (AMA) says "A physician shall…advance scientific knowledge (and) maintain a commitment to medical education." Further, the AMA states that the physician is obligated to share their findings with the public and their colleagues, also in the name of advancing medicine.[47] Thus one could argue that it is the duty of the physician to pursue

xenotransplantation experiments. The implementation of the NYU procedure on a brain-dead patient, however, creates for a much more nuanced discussion on the matter.

b. Ramifications of Utilizing a Brain-Dead Patient

Carrying out the first ever pig kidney xenotransplantation on a brain-dead patient was by no means a bad place to start. The risk-benefit ratio was simple: zero risk to the patient, significant possible benefit to medicine and science at large. One of the downfalls of using a brain-dead patient arises in questions surrounding resource allocation of the patient's organs. Because the patient was an organ donor, people who were on transplant lists missed out on getting organs since organs must be procured as quickly as possible after brain death.[48] This is, obviously, in the assumption that the patient had organs that were suitable for donation. In utilitarian terms, however, the future benefits of medical advancement trump the individuals in this case.

This then begs the question of how to move forward with future studies. Should additional brain-dead patients undergo this experimental procedure, or are physicians and researchers dutybound to give living patients a chance to directly benefit? We now know that this procedure is possible, however potential living recipients may feel coerced because of terminal prognoses. Should these vulnerable subjects, such as those near death, not be able to receive a xenotransplant, or should they be given the opportunity to extend their life? These are ethical questions that Dr. Montgomery and his team at NYU avoided by using a brain-dead patient, however, are ones that future researchers and IRBs will have to consider.

III. Ethical Considerations

Aside from the complications that arise from the aspect of a brain-dead patient being used in this procedure and those like it, other ethical issues must also be considered when planning future

studies on xenotransplantation. Beneficence and nonmaleficence, or the ensuring of beneficial treatments and avoiding any that can do harm, immediately come into play. As does the right for participants to withdraw from a research study. According to the Declaration of Helsinki, which is the accepted foundation of ethical research on human subjects, any participants should maintain "the right…to withdraw consent to participate at any time."[49] However, because of the early and experimental stages of contemporary xenotransplantation, participants must agree to both a lifetime of monitoring and waive their rights to this withdrawal.[50] [51] Yet, some terminally ill patients may be okay with these stipulations. While that may be the case, the inclusion or exclusion of the terminally ill must be carefully considered, which will be further expanded on shortly.

Patient autonomy, or lack thereof, must also be considered. All the above, as well as normative ethical considerations in regard to animal welfare, will be touched on in this section.

a. Ethical Considerations for Researchers and Institutional Review Boards

Possible negative side effects of a xenotransplantation should not be downplayed. The most severe of which, the body of the recipient rejecting the organ leading to the death of the patient, is a genuine risk in any transplant, whether the organ is from a human or non-human donor. Nonetheless, a terminally ill patient may be okay with such a potential side effect. If researchers subject their participants to possible harm or death, they are not, as long as the patient is deemed to have decision making capacity and given proper informed consent, ignoring the principle of nonmaleficence. Further, in respect to patient autonomy, is the ignoring of that nonmaleficence justified, or is the patient's autonomy compromised due to a terminal prognosis? The terminally ill are generally considered to fall under the umbrella of vulnerable populations.[52] This, however, has not always been the case. Terminally ill patients have had to fight for their rights to be

considered for medical research participation, which was adamantly sought after because of their belief that some procedures, insofar as they are experimental, may offer them their only chance at survival.[53] An IRB should not immediately discount the idea of allowing the participation of terminally ill patients in future clinical empirical studies. Weighing the pros and cons of allowing terminally ill patient participation, and ensuring a hierarchy of possible participants is established, should be a goal of any IRB reviewing research submissions from researchers.

The principle of justice is relevant here. The Belmont Report, another widely accepted framework for the ethical use of human subjects in research, expands on this. According to the report, justice in this type of research considers who should or should not be aided by the research and who should or should not be subject to the possible negative ramifications of it.[54] Researchers should carefully consider who they choose for xenotransplantation experiments. The report goes on to identify the dichotomy of social and individual justice, wherein individuals should be sought in a fair manner and there should be an "order of preference" established in regard to groups of subjects. This order of preference refers to the idea that some groups of potentially vulnerable populations may only be used under certain conditions. Those conditions mainly fall under the lifesaving potential that underlies their participation, as long as autonomy and informed consent are upheld, which will be examined further later in this paper. Conversely, if a patient is willing to participate in a dangerous procedure, they could be found to not be able to make their own decisions due to the possible risks involved.

In the same vein, some who abide by specific religious doctrine(s) can be deemed decisional enough to *forego* life-saving treatment that is otherwise minimally risky. For example, someone who considers themselves a Jehovah's Witness can refuse a blood transfusion that could save their life. While this is a dangerous choice, it is generally the norm in clinical healthcare to

respect this decision of the patient on religious grounds. This decision is only respected, however, if the patient is able to prove without a doubt that they have the mental capacity to make this decision in that they understand all the risks involved doing so.[55]

An adult deemed decisional can disallow a medical team to perform a procedure that could save their life, despite relatively minimal risk, justified for religious reasons. Thus, a decisional adult should be able to participate in dangerous research that could help advance medical science on grounds of autonomy and the three theories of normative ethics. This individual could see it as their duty to help others and participate in the pursuit of the greater good and increasing the body of knowledge. They could see their own ethical virtue as being in jeopardy if not allowed to follow through with the research study. Lastly, the consequences of their participation could help countless others. A utilitarian lens gives this person not only the credence to follow through with participating, but also the moral high ground thanks to the positive consequences for the greater good that could follow.

Aside from the various ethical problems that arise out of the use of human subjects in such experimental procedures, animal ethics also play a large part. The ethical treatment of animals is especially important in xenotransplantation, given that animal organs are being used in humans. In 1959, Russell and Burch coined the “Three Rs” in an attempt at maintaining the lowest amount of suffering in animals used for research. The Three Rs are replacement, reduction, and refinement. Researchers should attempt to replace animals with other modes of research whenever possible, reduce the number of animals used as much as they can, and refine experiments to minimize the physical and emotional distress of the animals while ensuring maximal welfare.[56] [57] The FDA has guidelines in place to ensure much of the above, but it is still imperative that IRBs also keep the welfare of the animals in mind.

While the Three Rs offer a solid starting point for animal ethics in research, they sometimes fall short in terms of xenotransplantation. For instance, even if the number of animals used in the initial research is minimized as much as possible, the ultimate goal of xenotransplants is to raise animals so humans can use their organs. This would result in animals raised en masse for purposes of harvesting them for their organs, similar to farm-raised animals being raised for human consumption. One way around this could be the use of artificial organs. Although the science and technology on this is advancing, it is still in its infancy.[58] [59] That said, the refining of xenotransplantation studies to minimize animal suffering should be a main priority of researchers. Thus, everything from the raising of the animals to the ethical slaughter of them should be kept in check by both researchers and IRBs. In this regard, something such as a collaboration with the Institutional Animal Care and Use Committee (IACUC) could be beneficial here.

b. Institutional Review Boards Upholding Normative Ethics

When it comes to any research involving human subjects, vulnerable populations must not be manipulated into participating. In xenotransplantation studies, terminally ill patients are the most vulnerable population in question. However, they can also receive the most benefit from these studies. Because of this risk-benefit ratio, informed consent must be kept in check, which will be expanded upon later. A terminally ill patient may be more than willing to undergo the necessary long-term supervision and waiving of their rights to withdraw from the study, if in return there is hope for a prolonging of their existence. While a clinical xenotransplantation study may directly break the guidelines of participant withdrawal outlined in the Declaration of Helsinki, a xenotransplantation may also allow a patient to stave off death and give them a second chance at life. A patient who is terminally ill can still be deemed to be of sound mind with decision-making

capacity. If this is the case for a given person, and they are willing to participate in such a study, should they be prevented from doing so?

This obviously puts IRBs in an ethical quandary. While it is their job to protect individuals from harm, one could make the case that they have also become too paternalistic over the years. "People should have the right to choose whether to be involved in any study for which they meet the inclusion criteria, provided they are given accurate information, are not coerced and are mentally competent," says Dr. David Shaw of University of Basel's Institute for Biomedical Ethics.[60] He goes on to say that the possible participant should be the one to decide if the risk is too great, not the IRB. Dr. Shaw is likely giving significant credence to the participant's autonomy. Afterall, he says if people are able to risk their lives skydiving and bungee-jumping, they should also be able to participate in potentially life-ending research, especially if society at large (and themselves) could benefit from it.[61] He is hinting here at both the aspects of informed consent and the risk-benefit ratio.

To justify the inclusion of living patients in these studies, informed consent, which the Belmont Report also touches on, should be a significant aspect of the pre-study qualifications. For a participant to be able to give informed consent, three criteria must be met; all relevant information must be disclosed to the potential participant, they must be able to prove a complete understanding of it, and lastly, once these parameters are met, they must have voluntarily agreed to participate. It also says extra care must be taken in regard to vulnerable populations, which include "the very sick."[62] A way of ensuring a patient is not unduly coerced into participation can be done via the 'sliding scale' approach. The sliding scale "requires an increasingly more stringent standard as the consequences of the patient's decision embody more risk."[63]

This approach, according to Dr. James F. Drane, has three standards of application in evaluating the decisional capabilities of a patient, from the least dangerous and in their best interest, up to potentially exceptionally risky treatments wherein a patient rejects the potentially life-saving care.[64] A parallel can be seen here with participants of xenotransplantation studies. As opposed to refusing a life-saving intervention, rather, they are pursuing it, even though it may be extremely dangerous to their well-being. This risk-benefit analysis must be done by the participant deemed to also be of sound decision making capacity and analyzed by researchers in the realm of the sliding scale.

The less benefit but the greater risk that a person faces if participating in the study, the more decisional they should be deemed. This is the gist of the sliding scale. This approach should be applied by researchers seeking living patients for xenotransplantation studies and cross-checked by the IRB. That said, a patient undergoing a xenotransplant procedure faces substantial risks, but also significant benefit. A terminal prognosis may be extended by days, weeks, or months. However, due to the inherent dangers of a xenotransplantation, they must be able to properly communicate an understanding of the specifics of the procedure. These types of procedures are on the high end of the sliding scale, where a patient must be able to show that they fully understand all the risks and benefits involved and know exactly what will be happening to them before, during, and after the procedure.

Potential participants may be less able to be truly autonomous in their decision-making due to "certain social and existential conditions."[65] Their assessment of a risk-benefit analysis could be skewed due to existential threats they may be facing. Further, it should be ensured that the patient is considering participation of their own volition, and not to appease loved ones. Researchers then should utilize this sliding scale method in considering xenotransplant study participant's

levels of informed consent. By extension, an IRB should be sure the sliding scale approach is being applied to the proper extent due to the inherent dangers of the study. Here, I propose a three-step process of ensuring that a patient fully understands the possible ramifications of their decision. This entails the patient submitting three requests of intent to participate in such research – two written, and one verbal.

In the handful of places throughout the United States where physician assisted suicide is legal, there are strict regulatory rules surrounding the practice. For instance, in many states patients must submit two written requests as well as an oral one.[66] [67] When this is done, it shows that the patient is of sound mind and able to make their own decisions regarding their own care. If this is the norm in life-ending procedures like assisted suicide, this should also be applied to those who wish to participate in potentially life-ending studies. In sum, a patient who wishes to be involved in a xenotransplantation study should provide two written requests and a verbal statement of intent, all of which proving that they fully understand the risks involved yet are still willing to participate.

An additional advantage of appropriately applying the sliding scale is the fact that it can uphold virtue ethics. Virtue theory is concerned with how one's actions reflect their general moral character.[68] It implies that doing right or wrong is an intrinsic part of who someone is and is one of the main theories of normative ethics. If virtue is sustained by the individuals carrying out a given study, then it is more likely the study itself will be conducted ethically.

Virtue theory can be applied to the sliding scale and risk-benefit analysis. If a physician ensures that a patient has complete understanding of a procedure before undergoing it, it can be generally concluded that they have upheld ethical standards in their medical care. Similarly, if a researcher or team makes sure that a possible research participant is not being coerced and is

deciding to partake in potentially dangerous research of their own will and is of sound mind, they can be thought of as being virtuous. They are preserving moral character and doing what is right, and not taking advantage of an otherwise uninformed patient. Any negative side effects the participant may experience (e.g., death after a xenotransplant) do not make the researcher any less virtuous so as long as the participant was deemed properly decisive.

When considering participants for xenotransplantation studies, a hierarchy of possible participants should be established. This can be modeled off an already existing criteria for organ transplant recipients suggested by Dr. Carol S Lin and Dr. Shannon L Harris in the *Journal of Multi-Criteria Decision Analysis*. This system is based on urgency, efficiency, benefit, and equity. Urgency is in relation to the risk of the patient dying while waiting for an organ; efficiency takes into account the possibility of failure versus the expected quality of life after the transplant; benefit attempts to find patients that withstand the highest possibility of a beneficial outcome, and equity touches on the idea that every patient has the right to an organ transplant.[69] Medical research teams can mirror this system in determining who to include in clinical xenotransplantation studies.

The establishment of urgency in considering transplant recipients attempts to ascertain how long a patient may survive *without* the transplant.[70] Those who are deemed to be at a higher risk of death in temporal terms are placed higher on the list of possible recipients. The efficiency and benefit aspects are slightly more subjective in that they attempt to predict the quality of a patient's life *after* the procedure. Efficiency considers the unique nature of each patient and how their lifestyle habits or general qualities could affect the transplant and their recovery.[71] For example, someone with substance abuse issues or who is obese may be deemed to be less qualified for a transplant due to the negative effect their lifestyles may have on their body's

ability to heal and accept an organ from a foreign body.[72] Furthermore, the concept of benefit in determining transplant recipient hierarchy suggests physicians reflect on the nature of the patient's life post-transplant. Studies have shown the giving of an organ to someone who has "the greatest transplant survival benefit" will reduce death rates in the transplant recipient population at large.[73] [74] Naturally, the pursuit of a quality life and the avoidance of deaths should be of the utmost importance to researchers. Equity, however, is slightly more nuanced, as it is considered a way of contemplating possible recipients in an impartial manner. While not inherently problematic, the nature of equity is often recognized via a first-come first-served basis. This simplified way of deciding organ allocation can disregard other factors such as general levels of health of a given patient.

Potential downfalls of this suggested model occur in that many factors are subjective. Not every physician will always give the same prognosis, and the determination of a patient's quality of life is largely up to them. Further, a given patient could potentially lie about their perceived quality of life in an attempt at being considered for the research study if they learn a higher or lower QOL would give them a better chance of acceptance into the study. Nonetheless, establishing a protocol for choosing recipients of life-saving organs can subvert issues surrounding resource allocation and questions of trust. Potentially life-saving resources should be given to those who qualify based on previously determined conditions.[75]

An IRB must strive to encapsulate normative ethics in studies they approve, not only to maintain morality but also to safeguard trust. This includes the trust of the public regarding medical research in general, the IRB trusting the work of the researchers, and the individual research subjects trusting the investigators carrying out the study.[76] Maintaining these facets of

trust is imperative for researchers to be able to properly carry out their studies. If any of these facets of trust become compromised, so too does the possibility of future research.

In choosing recipients of an organ xenotransplantation, the main factors for IRBs to make sure researchers uphold are autonomy, informed consent, and the hierarchy in relation to justice. This also works to maintain the trust of the public for research studies. While many aspects of healthcare today are unnecessarily politicized, this is a way to avoid that politicization of clinical studies while avoiding controversies surrounding who is and is not chosen for these procedures. The public should trust that researchers are choosing participants in a fair and just manner, and that IRBs hold them to it. Thus, a strict protocol for xenotransplantation recipients must be implemented. This implementation should have an emphasis on the hierarchical model upholding nonmaleficence, beneficence, and justice. Due to the potentially controversial nature of resource allocation in transplant surgeries, this can ensure that those who will benefit the most from them are the ones who will undergo them.

Besides maintaining the ethical aspect of studies involving human subjects, animal ethics must not be forgotten. There are already several rules and regulations in place to ensure the ethical raising of pigs for xenotransplants, as provided by the FDA.[77] However, researchers and IRBs must be sure that the pigs are ethically sourced. For example, there are significantly different regulations for pigs raised for human consumption compared to pigs raised for scientific and medical testing. Pigs raised for livestock purposes do not fall under the same federal guidelines as those that are raised for research; they are significantly less strict.[78] [79] Thus, if IRBs are not diligent as to where the pigs (or any animal) used in xenotransplantation experiments come from, researchers could get around strict federal guidelines by seeking out livestock as opposed to animals raised purely for research purposes.[80]

Proper raising and screening of animals used for research is important for more than just purposes of animal safety. While any human-to-human transplantation has risks of infection, a xenotransplantation has additional, more serious risks. These risks pose a threat to not only the individual receiving the animal organ, but also to society at large. The death of a patient who received lamb's blood in the 17th century led to the banning of xenotransfusions in Paris.[81] [82] Although steps have been taken to reduce the possibility of animal-to-human transmission of infectious disease, that risk is never zero. Similarly, if a patient does become infected after a xenotransplantation, the risk of other humans then also becoming infected from an animaloriginated pathogen rises.[83] This has been documented multiple times in recent history, most notably in a Marburg virus breakout in Germany in 1967 and an Ebola outbreak in Zaire in 1976.[84] [85] [86] In both instances, a single human infected by an animal led to dozens of other infected humans. The Ebola case resulted in four waves of infection in humans, eventually killing 88 percent of the over 200 people infected.[87] [88] Thus, risks to society at large must also be accounted for and studies designed to reduce the possibility of those risks as much as possible.

While the deontological nature of researchers is to uphold the best interests of both research participants and society at large, consequentialism is also relevant. Consequentialism defines the ethical nature of an action as being solely based on the outcomes of a given act – its consequences.[89] Thus, it comes down to the Institutional Review Boards who approve these studies to maintain all the above. The four ethical principles, as well as duty to keep the public safe, should be sought. In terms of beneficence, upholding animal ethics and allowing terminally ill patients to partake, under the right circumstances, is imperative to this. Further, while it would be easy to continue to use brain-dead patients for xenotransplantation experiments as was done by Dr. Montgomery at NYU, beneficence for the patient is nonexistent. A brain-dead patient

cannot benefit whatsoever from the procedure. While it was a good place to begin, now that it has been *somewhat* proven to work in a human recipient, living patients should be next in line. If an IRB disallowed terminally ill patients or researchers leave them out of studies altogether, nonmaleficence and justice would not be upheld. This is because it is wrong to withhold someone from participating in research that may be beneficial to them, especially if they can give informed consent and have a terminal prognosis.[90] Thus, if a patient can benefit from a given study, but they are not allowed to participate in it, nonmaleficence falls to the wayside, and justice is lost.

The well-being of the given animal being sought in pre-trial stages directly correlates with the well-being of the human recipient of the animal organ, as well as society at large, as has been demonstrated. Therefore, IRBs should ensure that the animals used for research are properly raised, slaughtered, and tested for any harmful viruses or disease. The established FDA guidelines should be followed, from insemination of the embryo to the multi-day quarantine of the animal before being killed, and everything in between. Additionally, the animal must be properly genetically modified (using GTKO or, preferably, TKO pigs) to further ensure the human recipient's body has the highest chance of accepting the organ.

Ultimately, a respect for patient autonomy and the pursuit of the greater good must be upheld. Dr Shaw's ideas on people being able to consent to dangerous or life-threatening research are again relevant here. If someone has a terminal illness, and they can potentially benefit from the research, then they should not be barred from participation. An IRB can justify researchers' request to allow participation of vulnerable patients if, according to the Belmont Report, "appropriateness of involving them (is) demonstrated."[91] Because a vulnerable person may have a diminished capacity to consent, one way of protecting such subjects is by reducing

the risks they may encounter in given research that is unlikely to beneficial.[92] In doing so, researchers can be sure to uphold the principle of nonmaleficence. However, forbidding someone who is terminally ill from participating in a potentially life-saving study, could in and of itself be considered maleficent, while also completely disregarding beneficence. When it comes down to it, to some participants, a prolonged life could be better than no life at all. This could be for several reasons including, but not limited to, more time with loved ones, and the altruistic aspect of helping humankind at large.[93] Utilizing the hierarchy of possible patient participants will help researchers and IRBs deem who is most fit to partake. Maintaining these standards will allow researchers to preserve various ethical principles, from virtue ethics to consequentialism, deontology, and utilitarianism.

IV. Suggestions for Future Research

Moving forward, additional xenotransplantation research must be carried out. This is crucial to advancing and perfecting the procedure in the goal of making it more widely available for patients around the world on transplant waiting lists to directly benefit from. The foundation has been laid by all prior studies and has received a newfound social awareness and excitement thanks to the recent pig kidney xenotransplant at NYU. Thanks to these recent advancements, and the fact that the NYU xenotransplant was largely effective, the obvious next step is to continue studies on the efficacy of the procedure on living patients who have something to gain.

a. **Proposal for Future Clinical Study**

The next phase of xenotransplantation studies should be carried out via empirical clinical research studies. Doing so will enable additional clinical studies to be done that will all contribute to the larger goal of moving past clinical trials and into the execution of this procedure on a wide scale as a normal practice in healthcare. In sum, getting organs to those who need them. However, to get to that point, researchers must submit proposals to IRBs, and persons on those boards must be able to thoroughly understand those proposals to reject or accept them. Because of the unique nature of these studies in that they are so new to the clinical realm, proposals must be extensively contemplated, as they will likely set the precedent for many that follow. After all, there is no supreme IRB that sets standards for future studies, but rather cases and ethical resolutions set precedents and flow into and influence each other in a temporal fashion.[94]

These proposals should touch on the four levels of research proposed by Kon: lay of the land, ideal versus reality, improving care, and changing ethical norms.[95] In providing an overview of current practices and insight into ideal clinical practices versus what happens in reality, researchers can offer an understanding as to why a given study is important. Additionally, elaborating on how the study can improve care and thus alter how ethical norms are upheld moving forward, can further justify the research proposal.

Thus, the format of a research study proposal to an Institutional Review Board will be utilized in this section to replicate the general pursuit of researchers seeking approval for clinical trials of xenotransplants using living patients. A statement of research will be established, followed by the purpose and significance of the study along with research design and procedures. Next, an elaboration on instruments used, sample selection and size, and the recruitment of

subjects as well as insight to informed consent procedures will be provided. Finally, data collection and methods of analysis followed by subjects' rights in the study will be explored.

The statement of the research question should be relatively simple while encapsulating the entire idea of the study in a single sentence. Something along the lines of "Are kidney xenotransplantations viable in humans?" could prove to be too vague. An emphasis should be placed on specific organs being tested, efficacy, and the question of side effects. For example: "What is the efficacy of a xenotransplantation involving a pig kidney onto a living human subject and what possible side effects arise?" This encapsulates the overall goals of aspects to test and observe in the research: the organ being tested, the efficacy of the procedure, and the possible risks to the patient.

The statements of purpose and significance are important. They are essentially elaborations on the research statement that work to justify the reasoning behind the pursuit of the study in the first place. The purpose of clinical xenotransplant trials, for instance, is to gain insight into the efficacy of modern medical science's ability to carry out these procedures. It not only tests the technology but also the wherewithal of the physicians carrying them out. The significance of the study lies in the use of living patients. The procedure has been demonstrably effective in both non-human primates and brain-dead patients, thus the next logical step is to perform a xenotransplantation on a living participant who can directly benefit from it. The results of the study will be significant in that they will offer future researchers and clinicians insight into how to move forward with xenotransplantation – both empirically in trials and in the eventual execution of them as a clinical norm. Well-articulated statements of purpose and significance give the IRB insight into two of the four levels of research touched one earlier, namely improving care and changing ethical norms. The proper carrying out of clinical xenotransplant

trials on living patients will work towards improving future care of patients, while also progressing the evolution of ethical norms in healthcare.

The design of the empirical study will be largely empirical where both qualitative and quantitative data will be collected. Comprehensive health records of participants will be gathered and maintained throughout the study, which will last as long as the patient as living and, likely, for a short time after their death. Quantitatively, many statistics will be gathered, such as urine and creatinine levels, blood cell counts, and number of days of survival following the procedure. Procedurally, the data will be gathered by collecting all prior health records and through maintaining of patient data throughout and after the procedure. While much of the data will eventually be made public, identifying information such as names will be omitted.

Instruments utilized in this study could include questionnaires distributed to the patients before and after their procedures, as well as data from interviews. Both quantitative and qualitative data can be gathered from these, such as quantified pain levels (pain scales of 1-10), quality of life, and expectations of the future. Given the complexity of the procedure, both structured and nondirective interviews could be used to obtain an understanding of the patient that is as comprehensive as possible.

Sample and selection size of participants will be simple: only a single patient will participate in the study. Due to the novel nature of the procedure, careful attention must be given to the patient. As for recruitment of the subject, the hierarchy of transplant recipients should be utilized. Someone who can benefit the most from the procedure, such as a terminally ill patient, but who also has the highest probability of long-term survival, should be sought. Recruitment also largely depends on the geographic location of the study. For example, if the study is being carried out by a research team in Pittsburgh, a participant in Pittsburgh will be sought. A team in Pittsburgh

should not be seeking out patients in Seattle for their study, for both practical as well as ethical reasons. The recruitment process will utilize physicians within the Pittsburgh healthcare system by asking them to suggest potential candidates whom they think would qualify and benefit.

The informed consent procedure of subjects in a xenotransplantation trial is unlike that of other clinical studies. For example, a patient, once committed to the study, cannot withdraw once the procedure has taken place. Consent must be established multiple times throughout the process. Additionally, to avoid coercion and ensure a patient is acting autonomously, a patient who wishes to be involved in a xenotransplantation study should provide two written requests and a verbal statement of intent, all of which proving that they fully understand the potential risks and are still willing to participate. The informed consent form that the patient signs must also explicitly state the fact that the participant cannot withdraw from the study once the procedure has been completed and must be willing to undergo tests and follow-up appointments indefinitely. Once an organ has been surgically transplanted, the participant is essentially a participant for life. Lastly, the patient must understand the risk to them is great. Death is a possible risk in xenotransplant procedures.

A significant amount of data will be collected in this study, from nearly every aspect of the medical care to the patient's medical history and results of both the procedure and all future visits. Additionally, audio and video from interviews may be utilized, however identifying data must be redacted. Besides interview data, questionnaires and surveys administered to the patient will be collected, in attempts at establishing as comprehensive an understanding of the procedure as possible.

The subjects' rights regarding this study will be maintained as normal in that personally identifying information can and will be withheld from any data made public or seen by anyone

other than the principal investigator and their team. However, much of the data, such as survey data and bodily function, will not be protected. This is unique due to the highly publicized nature of the study – much of the resulting information should be made publicly available for other researchers and medical professionals to use moving forward in future clinical trials. The patient will be made aware of this, and emphasis will be made on the fact that their name will be replaced with a number (e.g., Patient 1).

b. **How This Theoretical Empirical Research Can Sustain Above Ethical Arguments**

The ethical parameters described throughout this paper should be maintained in any future empirical research. These parameters of normative ethics can be maintained in several ways. It comes down, in large part, to the IRBs and the researchers working together in a transparent manner. The interdependent nature of the IRB and the researchers works like a system of checks and balances. Together, those on the IRB and the researchers submitting proposals can shape the framework of the study in such a way that it maintains ethical integrity.[96]

The use of living participants with a terminal diagnosis can directly benefit from a xenotransplantation. Thus, they should be sought first in this study. This upholds the principle of beneficence in that it gives someone a chance of living longer. It also works to ensure nonmaleficence since passing over possible participants who can benefit from a potentially lifesaving procedure are not disregarded. Sometimes doing nothing is worse than doing something, and that would be the case if this procedure, which has been proven to work on a human, was not implemented using living patients who have something to gain. The principle of justice is also relevant here – it would not be just for a research team to continue using brain-dead patients when it is now medically accepted that a pig kidney can be used in a human body. Furthermore, autonomy is upheld so long as the patient is cognizant of all the risks and benefits

and can demonstrate a full understanding and appreciation of them. If deemed to be able to make their own decisions, and the research team follows through with the three-request rule described above (two written and one oral request of the procedure) then a living patient in need of a kidney can ethically participate.[97]

Utilizing the hierarchy of xenotransplantation eligibility can also work to sustain ethical factors. Choosing participants who urgently need a kidney and are close to dying, but who are also otherwise relatively healthy (non-smokers, etc.) and predicted to have the best chance of surviving the surgery will sustain ethical research. Autonomy, once again, is also at play here. The study should seek out a patient who understands the risks involved and volunteers to be on the hierarchy of possible recipients of the non-human organ. These are all significant factors in helping medical teams and IRBs justify proceeding with such a procedure.

V. Conclusion

Medical science has reached a point where allowing a living patient to receive a pig kidney is not only feasible, but also has a likelihood of success. The general success of the NYU Langone xenotransplantation demonstrates the viability of the procedure and the urgent need to replicate it on a living patient who can benefit. The fluidity of the laws surrounding xenotransplantation through the years are now becoming rigid and regulated. Dr. Starzl, who led many of the 20th century xenotransplantation experiments in the U.S., once said he believed that over-regulation in the past had stifled the possibility of experimental procedures.[98] Now, however, this is no longer the case.

Proper guidelines and laws established by the FDA are allowing for the healthy obtaining of organs. Further, the World Health Organization has published international guidelines and recommendations for countries to follow when conducting such trials, including the maintaining

the health of animals, recommendations on long-term monitoring of these studies, maintenance of regulations worldwide, the necessity of the allowance of xenotransplantation studies in a given country when appropriate regulations are enacted, all while remaining transparent and assessing the outcomes. [99] [100] Society's regulatory advancement surrounding xenotransplantation, combined with modern ethical discourse, has provided a way forward for this research. Thanks to the NYU procedure, there is both a newfound public interest aspect and starting point for future clinical studies. This should encourage other medical teams and transplant surgeons to continue the work of Dr. Montgomery, and to do so on living patients. This paper can act as an ethical starting point for such procedures.

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