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The Viability, Risks, and Benefits of Xenotransplantation as a Solution for Human Organ Shortage

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Abstract: **Xenotransplantation is the process of transplanting organs across different species. Here, we will specifically look at how modern medical technology is developing a way to use pig organs as an alternative for human organs. This would dramatically improve the dreadfully long waitlist times for those in need of an organ transplant. Obviously, xenotransplantation isn't as simple as transplanting pig organs into humans expecting perfect functionality. With xenotransplantation comes risks such as diseases, and scientists are researching to find preparations to prepare for potential hazards. Although more development will need to take place, the future is no doubtedly bright for this new potential alternative to permanently overcome one more obstacle standing in the way of mankind: human organ supply shortages.**

Keywords: **xenotransplantation, organs, transplant, pigs, chronic illness, regeneration.**

I. INTRODUCTION

Since ancient times, our human ancestors were clearly intrigued by the idea of merging human and animal characteristics together[1]. For example, this is apparent in the drawings of the Egyptian Goddess Bastet, a hybrid that takes on the form of a cat merged with a woman. With modern medical technology improving by leaps and bounds over the past decade, this is slowly becoming a reality, but not exactly the way the Egyptians would have imagined it.

Over the past few years, the gap between organ demand and organ supply has continued to grow dangerously apart. In fact, in 2016, 98,000 patients were sent off to a waiting list with 20 percent of those patients transplanted after a waiting time that was "essentially too long to calculate"[2]. By the end of February 2022, 116,690 patients were forced to wait for an organ transplant[3]. The waitlist is only growing as "every 10 min, someone is added to the national transplant waiting list"[4]. However, the bigger problem is that time isn't infinite and forty-two percent of patients on chronic hemodialysis are projected to die in five years. In other words, about forty percent of patients on the waitlist die every five years if they continue to remain waitlisted[2]. This disproportion between organ supply and demand has made it clear that an alternative supply of organs is needed. If not, every day in Europe, 18 patients will die waiting for an organ transplant[4]. However, for the past decade with the advancement of xenotransplantation, the transfer of organs or tissues between two different species which in this case particularly between humans and pigs, scientists believe they may have found the answer[3].

Here we will review the underlying obstacles and barriers that still remain from making xenotransplantation a reality as well as the potential solutions for each using modern medical technology. Moreover, we will also cover all the disease, risks, and viruses if we were to introduce xenotransplantation to treat millions of lives and how it will affect not only the patients, but society as a whole. Ethical and moral issues raised due to xenotransplantation as well as an evaluation of many of the most popular and favored arguments would also be covered. Finally, we will look forward and evaluate how close we are from successfully achieving xenotransplantation with groundbreaking technology such as CRISPR/cas9 and what it can mean for society.

II. HISTORICAL BACKGROUND

Although it may seem that the idea of xenotransplantation from one species to another may seem like a more recent innovation, this concept has had a very long history to get to where it is today. This idea was explored as far back as the 17th century by Jean Baptiste Denis when he attempted to perform xenotransfusion of blood between farm animals to human patients. However, the first ever attempted xenotransplantation of tissues/organs was performed in 1838 in which a "corneal xenotransplantation from pig-to-human" was performed[5].

Nearly a century later, Mathieu Jaboulay, a clinical surgery professor at the Faculty of Medicine located in Lyon, France in 1906, performed a xenotransplantation of a kidney between a pig and a patient. Jaboulay "placed the animal's organ at the bend of the patient's left elbow and connected it to the artery in the upper arm and the cephalic vein by means of a metal ring." Three days later, due to "formation of blood clots in vascular linkups", the transplant was called off[6]. Many more similarly failed attempts were made in successful xenotransplantation during the early 20th century, as scientists "blamed technical obstacles for the disappointing results" instead of "the biological difference between species"[6].

The first real success in the field of xenotransplantation would not come for another few decades until in 1963, Reemtsma showed some promising results after he transplanted chimpanzee kidneys into six different patients. Although five of the six patients were unsuccessful operations due to rejection of the organ or infection, one patient was able to live for nine months, even able to return to her job as a schoolteacher. She would die however due to, what was believed, "an acute electrolyte disturbance"[2].

Then in the 1980s scientists would finally realize that to have the highest chance of successfully performing xenotransplantation, pigs would be the ideal source of organs, not primates such as chimps, contrary to conventional belief. However, despite the similarities between pig organs and humans, obstacles persisted as the fact remains that "the 80 million years during which humans (and NHPs) and pigs had been evolving differently had resulted in a complex primate immune/inflammatory response to a pig xenograft", resulting in graft rejection[2].

However, as new breakthroughs and advancements fostered in a new age of genetic engineering during the 1990s, so did xenotransplantation as ideas of genetically modified pigs pushed xenotransplantation closer to reality. Since then, genetic engineering has only moved forward and so has xenotransplantation along with it. With advanced medical and genetic technology of today such as CRISPR/cas9 the future has never been so bright for xenotransplantation[2].

On January 7, 2022, the first xenotransplantation of a pig heart from a genetically modified pig was performed in the University of Maryland on David Bennett Sr. After the 8 hour procedure, Bennett was able to live a healthy life with a healthy heart for two months before passing away due to "graft dysfunction"[7]. Although Bennett did pass shortly after the surgery, this is still undoubtedly a big step forward in bringing xenotransplantation into reality.

III. OBSTACLES

Despite the many breakthroughs achieved in the field of xenotransplantation, scientists still have a few obstacles standing in their way. The four main barriers of xenotransplantation that we will be talking about are Hyperacute Rejection (HAR), Acute Humoral Xenograft Rejection, Cellular Rejection, and finally Coagulation Dysfunction.

The first, and perhaps, the biggest obstacle remains to be a type of immune response called Hyperacute Rejection or HAR. Hyperacute rejection occurs when "preformed human natural antibodies recognize xenogenic endothelial antigens"[8]. This reaction can occur "within several minutes" after xenotransplantation has happened[4]. The main and most problematic xenogeneic antigen in pigs is galactose-α1,3-galactose which is "synthesized by the alpha-1,3-galactosyltransferase (GGTA1) enzyme encoded by the porcine GGTA1 gene"[9]. In fact, "1% of all circulating human antibodies" are made to bind to galactose-α1,3-galactose[3]. What happens is that human antibodies called IgG antibodies in our blood recognize and bind to the foreign α-Gal epitopes, resulting in the " activation of the complement system"[9]. This activation results in the "formation of the membrane attack complex", which "acts as a catalyst for cell membrane penetration by proteins forming transmembrane channels"[4]. As a result lysis, or the destruction, of the endothelial cells occur. This then subsequently leads to the failure of the graft vascular system, meaning the transplantation has failed.

Another type of graft rejection that remains a obstacle towards successful xenotransplantation procedures is Acute Humoral Xenograft Rejection, also known as Acute Vascular Rejection which can occur "days to weeks" once "HAR is under control". Like HAR, acute vascular rejection also involves human antibodies and xenograft antigens, in particular "the swine leucocyte antigen (SLA)". Therefore, when our human antibodies recognize and bind to SLA antigens, it leads to the

"adhesion of NK cells and macrophages, which then invade the interstitial space of the transplanted organ"[9]. Some examples of these significant NK cells and molecules include "NKG2D/UL16 binding protein 1, NKp44, CD28/CD86, and MHC class I". In fact, NK cells seem to play a dramatic role in the success of xenotransplantation as their depletion leads to a prolongation of graft survival"[8]. Next, these cells produce cytokines like "tumor necrosis factor α (TNFα) and interferon γ molecules", triggering a "cascade" that influences "genes encoding adhesion and chemotactic factors". The problem with this is that messing with gene expression with those genes can lead to "adhesion of the recipient's platelets'' forming clots, which inevitably leads to what we call Acute Humoral Xenograft Rejection[9].

The final type of graft rejection that still remains an obstacle is Acute Cellular Rejection or ACR which can occur "several days after transplantation"[4]. The big players of this type of rejection are "CD8 + and CD4 + T cells" interacting with "class I and II SLA molecules". After this occurs, these cells then infiltrate the interstitial space in the xenograft, subsequently causing necrotic foci to form in these areas. This infiltration of T cell and B cell in the xenograft is what we call Acute Cellular Rejection. Other molecules and cells involved in this rejection are "T and B lymphocytes, macrophages and, in part, NK cells"[9]. It is important to note however, that this type of rejection hasn't been given lots of attention until recent years as "intense immunosuppressive agent regimens" are typically used to prevent the previous immune response: Acute Vascular Rejection[8]. However, as the obstacles of HAR and AHXR improves, acute cellular rejection is getting more attention and research in xenotransplantation experiments.

Finally, one of the biggest challenges in successfully carrying out xenotransplantation is coagulation dysfunction. Even after the big three of "hyperacute rejection, AHXR, and the T cell response were successfully controlled", graft failure still proceeded to occur[2]. During coagulation dysfunction, "thrombotic microangiopathy" develops which leads to "fibrin deposition and platelet aggregation, resulting in thrombosis within the blood vessels of the graft and ultimately ischemic damage". As coagulation disorders start to develop the patient starts to suffer from "systemic consumption coagulopathy" inevitably leading to their death[9]. So, how does coagulation dysfunction develop in the first place in xenotransplantation? This dysfunction in the coagulation system is first initiated by the "activation of the vascular endothelial cells by antibody, complement, and/or innate immune cells". This essentially results in a change of the cells from an anticoagulant to a procoagulant state[2]. This dysfunction is further escalated by the incompatibilities between "pig and human thromboregulatory molecules". To elaborate, although the binding process between Pig thrombomodulin and "human thrombin" is acceptable, both Pig thrombomodulin and its cofactor,pig endothelial protein C receptor, prove to be very poor in activating protein C. In conclusion, this incompatibility between pigs and human thromboregulatory will inevitably result in poor regulation of the coagulation system if xenotransplantation does ever take place, resulting in dysfunction of the coagulation system and graft failure.

IV. SOLUTIONS

Although there may be some questions and doubts on how scientists will come about to approach the obstacles of xenotransplantation, with modern medical technology, scientists are optimistic that they have found solutions. The four solutions we will talk about will address the four main obstacles to xenotransplantation consisting of Hyperacute Rejection (HAR), Acute Humoral Xenograft Rejection, Cellular Rejection, and finally Coagulation Dysfunction.

If the main problem and cause of Hyperacute Rejection is the "Galα(1,3)Gal antigen" in the pig xenograft, the simplest solution is to get rid of it. This can be achieved by "inactivation of the gene encoding GGTA1" and replacing its wild-type with a "mutant variant", which prevents the gene from encoding the enzyme in the first place. One method scientists are using to apply this genetic modification is "intracytoplasmic microinjection of CRISPR/Cas9 vector" which is proven to increase survival for embryos by avoiding "penetration of the pronuclear membrane". However, although the Galα(1,3)Gal antigen is the most problematic antigen, it is not the only antigen that human antibodies are against. In fact, the genes encoding "cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH)" and "β1,4-N-acetylgalactosaminy ltransferase (β4GalNT2)" also have proven to cause Hyperacute Rejection. Luckily, similar methods used to genetically modify and remove the "Galα(1,3)Gal antigen" can be applied to these two other genes[4.] Therefore, it is the combination of the "inactivation of porcine *GGTA1*, *CMAH* and *β4GalNT2* genes" using technology like "ZFNs, TALENS, and CRISPR-Cas9" that proves to help reduce Hyperacute Rejection[7] . Last but not least, the final modification to help eliminate the barrier of Hyperacute Rejection regards the complement system. Xenotransplantation results in "complement activation with formation of the membrane attack complex(MAC)" which ultimately leads to graft failure which is part of Hyperacute Rejection. Scientists may have found a solution in that the insertion of "human complement regulatory proteins, such as CD46 (membrane cofactor protein), CD55 (critical for C3 activation), and CD59 (MAC-inhibitory protein) significantly reduces Hyperacute Rejection[8].

Next we have the proposed solutions to Acute Humoral Xenograft Rejection which prevent success of xenotransplantation through the formation of clots. A solution to this problem can be seen in the "ectoenzyme present in the vascular endothelium and in blood cells" known as CD39 which specializes in the "regulation of clotting and inflammatory processes." Furthermore, CD 39 also " inhibits platelet aggregation triggered by adenosine triphosphate (ATP) and adenosine diphosphate (ADP) release". It is able to achieve this by "hydrolyzing" this ATP into adenosine which acts as a "strong platelet aggregation inhibitor." A similar enzyme called CD73 also performs similar activities. In conclusion, the implementation of both "hCD39 and hCD73 genes" will essentially greatly increase adenosine production, reducing incidents of Acute Humoral Xenograft Rejection. Another significant solution is genetically modifying and adding"anti-inflammatory and antiapoptotic genes" such as "Heme oxygenase 1 (HO-1)" and "Zinc finger protein A20". Heme oxygenase 1 is able to "contribute to the protection of cells against apoptosis, free radical formation and inflammation" while Zinc finger protein A20 works by "inhibiting the activity of the nuclear factor kappa-light-chain-enhancer of B cells (NF-κB) and inhibits TNF-mediated programmed cell death". Through the introduction of these genes, protection is available to be made to porcine endothelial cell, reducing Acute Humoral Xenograft Rejection[4]. Last but not least, the final solution discussed here will regard macrophages. It is no secret that macrophages play an essential role in Acute Humoral Xenograft Rejection and are known for its "direct toxic effect". However, this obstacle can be eliminated by introducing the CD47 gene in pigs. CD47 is able to recognize and bind to the "Human signal-regulatory protein α (SIRPα)" resulting in the prevention of "macrophage-mediated autologous phagocytosis". This essentially is able to save the destruction of xenograft cells, and therefore reduce Acute Humoral Xenograft Rejection occurrences[9].

Another obstacle that scientists may have potentially overcome is Cellular Rejection. T- lymphocytes are one of the cells/molecules contributing to the problem of cellular rejection, but they need the "T-cell receptor (TCR) binding to major histocompatibility complex (MHC) molecules on antigen-presenting cells" to function in the first place. Therefore, to deal with the T-cell response, scientists have proposed to implement the "human dominant-negative mutant class II transactivator (CIITA-DN) transgene", which not only blocks the "human T cell response" but also is able suppress "class II SLA molecules" and "class I SLA molecules" which are two major players in causing cellular rejection9. Another clever approach to counteracting cellular rejection is implementing the "HLA-E" gene which protects the endothelial cells from the infiltration of the likes of "NK cytotoxicity", "macrophage cytotoxicity", and other cells/molecules involved in cellular rejection[4].

Last but not least, the final proposed solutions regard the obstacle of coagulation dysfunction. The significance of "endothelial cell protein C receptor (EPCR)" has not been overlooked by scientists as a crucial approach against coagulation dysfunction. In fact, EPCR has the ability to help regulate "anti-inflammatory, anticoagulant, and cytoprotective signaling". Studies have already been performed showing that cells with EPCR display lower signs of "human platelet aggregation" which reduces the risk of developing "thrombosis" and the subsequent consequence of the dysfunction of the coagulation system. Another approach can be seen with an enzyme called "CD39" "or ectonucleoside triphosphate diphosphohydrolase-1 (NTPDase 1), encoded by the ENTPD1 gene." The reasoning behind its potential to overcome the obstacle of coagulation dysfunction is that it plays a role in regulating the coagulation system itself. More specifically its role is to "inhibit the formation of clots". With this essential ability to help regulate the coagulation system, studies have already proven that cells expressing CD39 have already shown lower signs of "myocardial ischemia and reperfusion injury". The final solution scientists have found to address the problems with the coagulation system is regarding the issue of "Lethal thrombocytopenia" and subsequent graft rejection. Thrombocytopenia is caused by "Human platelet sequestration" which is when the "asialoglycoprotein receptor (ASGR)" binds to human platelets resulting in their phagocytosis. However a simple solution, using advanced genetic modification technology, is to inactivate the "ASGR1 gene" which codes for ASGR, therefore preventing subsequent graft rejection[9].

V. DISEASE AND RISKS

With the many benefits and possibilities that can come with xenotransplantation comes with an equal amount of risks as well. The fact remains that in xenotransplantation, we are transplanting actual pig organs into our human bodies and with it the many microorganisms that can potentially cause zoonosis. The risks of zoonotic infection and disease are endless as pig organs can transmit a "wide range of bacteria, parasites, and viruses"[7]. Just some of the infectious viruses that can spread as seen from previous allotransplantation is "the human cytomegalovirus, the HIV-1, the hepatitis C virus, and the rabies virus"[10]. Furthermore, the list goes on as "West Nile fever, rabies, toxoplasma, and HIV" are just some of the many more infectious risks that come with xenotransplantation[5].

However, although many of these zoonotic diseases do pose some amount of risk, the most significant viral infection that we need to look out for is the Porcine Endogenous Retrovirus or PERV. To put it shortly, PERV is a "functional, vertically transmitted proviruses derived from retroviral infection of the host germline cells" that are found in pig[11]. For this particular virus, the PERV has recorded a copy number with a range as far as 100[9]. There exist three known "subgroups" known as PoERV-A, B and C which all "use different receptors to infect cells"[12]. The difference between these subgroups is that while PERV A and B infect human cells in vitro, PERV C only infects pig cells[10]. Moreover, PERV A and B are present in the "genome of all porcine breeds" while PERV C's presence is "reduced"[9]. However, all PERVs possess the ability to "to induce immunodeficiency and tumors" and therefore primarily targets "human tumor and immortalized cells"[10]. Still, scientists still admit that there is an unknown in terms of the sheer amount of potential for PERV to "infect human cells in vivo" and also their "capacity to cause disease in immunocompetent subjects, let alone in those who are iatrogenically immunocompromised"[12].

VI. MEASURES AND PROCEDURES TO PREVENT INFECTION/DISEASE

Keeping the many risks and infectious concerns in mind, we will now evaluate how these risks can be potentially controlled to decrease the probability of emergencies as much as possible. The first measure we should take is raising these pigs in stable cohorts instead of individual isolation, as this would provide us a way to make an evaluation of the microbiological status of the entire group. Obviously these pigs would need to be at an exceptionally qualified health status, so the usage of "gnotobiotic surgical techniques" was proposed to meet these standards. These herds of pigs would then be isolated in an area with "barrier air filters and strict biosecurity" to ensure the least exposure to infectious agents as possible. Next, the process of deriving the "actual organ source pigs" consists of first naturally farrowing and then undergoing "segregated early weaning" to ensure the least transmission of infectious agents from the breeding herd. These selected cohorts, consisting of 10 to 20 pigs, will be isolated from the breeding herd into a separate quarantined room, at least a month before organ excision. Both the breeding herd and the cohorts will be strictly isolated from each other and any other contact with tight biosecurity. "Positive (above atmospheric) air pressure gradients of high efficiency particulate (HEPA) filtered air" even has the ability to block any airborne infectious agents as well. Even the pig's diet will be strict as it is kept vegetarian, sterilized, and excluded with antibiotics to ensure guaranteed safety[12]. If that wasn't enough, these laboratories also consist of "donor pig screening strategies for up to 100 microorganisms", displaying just how much precaution has been taken for all possible situations[10]. Any caretakers entering the facility must also be cleared of any viruses or infectious agents, and are required to wear sterilized clothing and even shower each time, even when just moving from one cohort to another[12].

Despite all these strict measures and security being taken to ensure no infectious contact in the facilities, there still must be routine monitoring of each pig throughout its entire life. A physical examination and serologic testing of the pigs in the cohorts, shortly after its separation and early weaning, must be taken. Serologic testing must also be repeated again "at two months" and another during the "transfer to the final quarantine barrier". Furthermore, "Bacteriologic screening of nasal and fecal swabs" and a checkup for parasites in a "pooled fecal sample" must be carried out every single month. Moreover, blood from the pigs must be examined in cultures in case the pig is in the "asymptomatic bacteremic phase of an infection" and will receive the "relevant antimicrobial therapy" depending on the results[12].

Now you might be wondering what would occur if one pig in a cohort is infected with a pathogen. Because it is part of a cohort, wouldn't the whole group be unavailable for transplantation? It depends on how early the pathogen has been detected. The "culling" can either take place in the entire facility, just the one group, or only a handful of infected pigs to prevent further spread. These infected pigs would undergo treatments of "narrow spectrum anti-microbials." However, in general, if a pathogen is found, unfortunately all proceedings should be stopped immediately until confirmation has been made that the pigs aren't infected[12].

Despite all these proceedings being made to prevent infection spread towards the pigs, the risk of the Porcine Endogenous Retrovirus (PERV) will not be affected as PERV is not transmitted by pathogens, but rather are encoded in the pig's genome. So how have scientists proposed to prevent this virus? Using advanced technology such as CRISPR/cas9, scientists are now able to specifically "target the polymerase gene of PERV elements", therefore mutating them and causing the inactivation of these elements[13]. Other advanced technology that can be used is the use of RNA interference(RNAi). When scientists "transfected" pig fibroblasts with small amounts of RNAi "by the polymerase III H1-RNA gene promoter which corresponds to a highly conserved PERVsequence region", PERV expression in these transgenic pigs was "significantly inhibited"[11]. Another approach, although not fully developed, is the "Zinc-finger nuclease technology" which can work to actually delete the virus from the pig genome itself[5]. However, other methods do exist that do not require complex gene

editing modifications to the pig. One way is to specifically choose pigs that have low signs of PERV in their genome. Another way is that the patient can take a vaccine to help counter the virus when receiving the transplantation.

Finally, antiretroviral drugs can also be taken to fight against PERV[10]. Although many of the approaches proposed by scientists are still under development and can be seen as theoretical, PERV "will likely be treatable" and any "pandemic infection seems improbable"[7].

VII. MORAL AND ETHICAL RAMIFICATIONS

Although the reality of having an infinite supply of organs does have its advantages, there are still many moral and ethical arguments that must be considered and evaluated for xenotransplantation. However, before we go over these ethical considerations, we must first go over why "ethical decision making" on xenotransplantation can be a "special challenge"[14]. The first reason ethical judgment may be difficult on xenotransplantation is the possibility of zoonosis, affecting not only the patient but the general public as well. One particular virus that scientists are looking out for is the "porcine endogene retrovirus" (PERV) in pig cells that can be transferred to humans[14]. The second reason is that the uncertainties of xenotransplantation are "inherent in the system" and not a matter of "not having done enough research"[14]. The fact is that there still remains too much unknowns, as although research can estimate the many risks of xenotransplantation, it is only that: an estimate. "Wait and see" is not ethically justifiable to make decisions and these uncertainties must be taken into consideration[14].

The first argument that will be put into evaluation is morality of the treatment of animals. The harvest of organs from pigs would no doubtedly result in the death of the animal. Not only that, but the pigs for their whole life would be kept in "sterile, laboratory like conditions" which is even worse than in "agricultural breeding"[9]. They would be subjected to frequent testing and "the inability to roam freely and behave normally could be emotionally harmful"[15]. However millions of animals are already being harvested everyday for food for the sake of human survival. In fact, 1.3 billion pigs were being harvested worldwide for food in 2019 alone. The number of pigs needed to supply dying patients with organs is "vanishingly small" compared to those already annually harvested to feed billions worldwide. Still, "while taking the life of a species with a lower degree of sentience could be considered wrong," generally this is justified when it is a matter of life and death between a fellow human being or a pig, especially when there are no other alternative solutions[15].

One of the most popular arguments against the ethics of xenotransplantation is the "playing god" argument. This argument argues that "mixing of tissues from different organisms into a single being" interferes with "the natural order of things"[15]. By "reshuffling the order of nature intended by God" we are essentially "assuming" the same status as God by creating an unnatural life form, and thus are acting in an unethical manner[14]. However, one problem with this argument is that it is based on the assumption that "everything natural is good/right, and everything unnatural is bad/wrong"[1]. By arguing that xenotransplantation is "unnatural", the stance is taken that the definition of unnatural is "elements" that "are made by humans and involve interventions in nature", while being natural is simply what is carried out in nature without any human intervention whatsoever[1]. Applying this interpretation of what it means to be unnatural vs. natural, one may say that natural disasters or sickness/disease can be seen as natural as they are without human intervention and therefore good/right. Continuing on with this interpretation, one may also conclude that "all attempts to prevent natural disasters or administer medicine" by humans is unnatural so therefore "unethical" and bad/wrong[1]. However, despite being "unnatural", these human interventions were made with good intentions to save millions of lives. The same can be said for xenotransplantation too.

VIII. CONCLUSION

Although immense progress has been made over the past few years, a few more steps must be overcome to bring the future to reality. So how close are we? The "genetic manipulation" that has been modifying pigs currently were made to "overcome the innate immune response" that causes graft rejection. However, with the current limited "drug therapy" scientists hope in the future to develop pigs that would even be able to "control the adaptive immune response", achieving "immunologic tolerance" and preventing graft rejection[2]. That is where CRISPR/cas9 comes in. This groundbreaking technology has already helped reduce graft reduction drastically, but to completely achieve immunologic tolerance, changes and developments will have to be made in the future. CRISPR/cas9 still struggles against off-target mutations and "modifications of the basic system" in the future will be necessary to achieve immunologic tolerance. Although the "research into the ideal modified pig" is still currently ongoing, it is simply "a matter of time", with help from groundbreaking technology such as CRISPR/cas9, before xenotransplantation becomes a reality[9].

With xenotransplantation making progress each and every day, one can't help but wonder how it will all fit into society in the future. However despite the many benefits that come with xenotransplantation, looking into the future, xenotransplantation will come with challenges to integrate into society. The first challenge will be the expensive price tag of this therapy. Although "competition among companies" may seem to help balance the costs, if history is any indication, this rarely happens with medical therapies. Therefore, only those with "private insurance" or wealth in society will truly have access to xenotransplantation[15]. Furthermore, this can result in an "unintended effect" of actually increasing the waiting time for organs, as the availability of pig organs would actually decrease the demand for human organs. Therefore, those with financial struggles who can't afford xenotransplantation will be forced to wait extended waiting times for allotransplantation as the supply of human organs decreases[15]. Therefore, looking into the future, "a world wide network" is essential in being able to provide access to xenotransplants at an "acceptable cost" and a "reasonable time frame" for everyone in society[11].

A second challenge may come with the potential risks of the zoonosis aspect of xenotransplantation that can not only affect the patient but the whole world. Therefore, it is important to look forward and consider regulation at the international level. Without this uniformity in regulation, "the potential for problematic tracking and abuse persists" now for allotransplantation, but also for xenotransplantation in the future[15]. Without uniformity on the international level in regulation, the world will see an increase in xenotourism from all around the world "seeking less expensive or more immediate treatment." This will only dramatically increase the risk for zoonotic diseases on the international level. Furthermore, private companies are already planning to "create their own genetic modifications to the donor organs." This results in "proprietary" information regarding these genetic modifications preventing an "independent analysis of risk." In conclusion, if xenotransplantation were to be implemented into society, "rigorous oversight" will be a necessity for the protection and health of society as a whole[15].

We have come a long way to get to this point in the progression of xenotransplantation today and it's only a "matter of time" before it becomes a reality[9]. With "prolonged survival of cellular and solid organ xenografts", "administration of newer costimulation blockade agents", and access to genetically modified pigs with technology such as CRISPR/cas9, only a few more developments now stand in the way from the future. Although the future will hold some unknowns and challenges on implementing xenotransplantation into society, one thing is clear and that is international collaboration will be essential on managing this groundbreaking technology and securing a "vibrant future"[5].

IX. REFLECTION

Before we conclude this paper, I would now like to provide some of my own thoughts and beliefs after presenting the facts on the topic of xenotransplantation. Obviously I will be reflecting and focusing on the ethics of xenotransplantation and address the question of whether we as humans should introduce such technology into our society. However, to me, it is not simply a yes or no question as there are too many aspects and uncertainties to deal with on this question. For example, looking at the zoonotic aspect of the risk of xenotransplantation, like I said before, the fact remains that there are still too much unknowns as no matter how much research is applied, we can never predict exactly what will happen when we introduce millions of pig organs into the bodies of the public. There could potentially arise a new virus that slipped out of the researcher's noses and even cause a pandemic spread, possibly a lot worse than what we currently are experiencing. However, looking at the benefits of xenotransplantation we have the potential to solve one of society's nagging problems which is the dreadfully long waitlist time for patients. In fact, this problem has even affected me as my own pastor has a friend currently being waitlisted and is not projected to survive by the time an organ is available. Although it will be at the expense of pigs raised in laboratory settings harvested for organs, my personal opinion is that the logic provided by some of the popular arguments I relayed earlier makes perfect sense to me as we currently are already benefiting at the expense of pigs every day from food. The amount needed to satisfy the required amount of organs needed from xenotransplantation is miniscule compared to the millions of pigs harvested for food on a yearly basis.

In conclusion, I believe with the right preparations and organized regulations from an international corporation, xenotransplantation should definitely be introduced and the risks should be taken just as every other scientific breakthrough has had.

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