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Ethical and Regulatory Challenges of Xenotransplantation

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ABSTRACT

Pig xenotransplantation has re-emerged as a promising strategy to address the global shortage of human donor organs, driven by major advances in genetic engineering, immunology, and transplant medicine. The development of genetically modified pigs, particularly through targeted gene deletions and the introduction of human protective transgenes, has enabled significant improvements in graft survival by mitigating hyperacute rejection, complement activation, and coagulation incompatibilities. The advent of CRISPR-Cas9 technology has further accelerated the production of multi-transgenic pigs capable of simultaneously addressing multiple immunological barriers. Preclinical studies in nonhuman primates have demonstrated unprecedented survival times, with life-supporting pig kidney grafts exceeding one year and pig heart grafts surviving up to nine months under advanced immunosuppressive regimens. These achievements paved the way for landmark pig-to-human transplants, including kidney xenografts in brain-dead recipients and compassionate-use transplants in living patients, which confirmed short- to medium-term organ function in humans. Nevertheless, persistent challenges remain, particularly antibody-mediated injury, innate immune activation, microvascular thrombosis, and long-term graft durability. Infectious risks, especially related to porcine endogenous retroviruses, have been extensively investigated, with no confirmed transmission to humans to date, although continued vigilance is required. Beyond scientific hurdles, xenotransplantation raises complex ethical, regulatory, and societal concerns involving animal welfare, informed consent, public health risk, justice, and long-term recipient monitoring. As of 2025–2026, xenotransplantation stands at a transitional stage between advanced experimental research and early clinical application, holding substantial potential to transform transplantation medicine while requiring careful ethical and regulatory oversight before broader clinical implementation.

Keywords: Xenotransplantation; Bioethics; Regulation; Animal welfare; Public Health

Abbreviation: Gal: Galactose-α1,3-Galactose

Introduction

Pig xenotransplantation is a promising approach to address the critical shortage of human donor organs, with significant recent scientific progress towards clinical application. Researchers have made substantial advances by using genetic engineering to overcome key barriers. Specifically, gene editing techniques have enabled the creation of pigs with modified organs that can potentially survive transplantation into primates [1]. Key breakthroughs include: deletion of xenoantigens that trigger immune rejection; introduction of human 'protective' genes and development of novel immunosuppressive therapies. Recent milestones include extending pig kidney graft survival to over 1 year and pig heart survival up to 9 months in experimental models [2]. Moreover, three recent pig-to-human transplant attempts have occurred, including two kidney xenografts in brain-dead recipients and one heart xenograft [3]. However, challenges remain, including potential immunologic barriers and the need for more sophisticated genetic and immunological strategies. Pig xenotransplantation represents one of the most promising and extensively researched solutions to the critical global shortage of human donor

organs, with decades of scientific progress culminating in recent breakthrough achievements that have brought this technology closer to clinical reality than ever before. The increasing shortage of human cadaveric organs has become the critical limiting factor in the number of transplants performed each year [4].

While some deficit is being met by organs from living donors, this source remains insufficient to address the growing demand. Xenotransplantation using pig organs could provide a comprehensive solution if the associated immunologic and physiologic challenges can be overcome [2]. The pig stands out as the most suitable donor animal for humans due to shared genetic, anatomical, and physiological similarities [5]. Pigs have long been used as research animals and have gained particular importance as potential organ sources because of their compatibility with human organ physiology and their ability to be genetically modified [6]. When organs from wild-type (genetically unmodified) pigs are transplanted into immunosuppressed nonhuman primates, a vigorous host immune response causes hyperacute rejection within minutes or hours [1]. This immediate and devastating response has been the primary obstacle to successful xenotransplantation for decades. The immunologic barriers are fundamentally related to the presence of natural anti-pig antibodies in humans and non-human primates that bind to antigens expressed on transplanted pig organs [7]. The most important of these antigens is galactose-α1,3-galactose (Gal), which activates the complement cascade and results in rapid graft destruction through hyperacute rejection. Beyond hyperacute rejection, researchers identified additional rejection mechanisms including acute humoral xenograft rejection, which occurs when high levels of elicited anti-pig IgG develop if the adaptive immune response is not adequately prevented by immunosuppressive therapy [8].

This leads to activation and injury of the vascular endothelium, causing delayed organ destruction within days or weeks. The development of genetically modified pigs has been the cornerstone of progress in xenotransplantation research. The most significant breakthrough came with the creation of alpha1,3-galactosyltransferase gene-knockout pigs, which do not express the critical Gal antigen that triggers hyperacute rejection [9]. Genetic modification strategies have evolved to include multiple approaches: Deletion of xenoantigens: removal of the three known carbohydrate xenoantigens against which humans have natural preformed antibodies [1]. Introduction of human protective genes: expression of human complement-regulatory proteins such as CD46, CD55 (decay-accelerating factor), and other protective factors [2]. Coagulation system modifications: expression of human coagulation-regulatory proteins like thrombomodulin, tissue factor pathway inhibitor, and CD39 to address incompatibilities between porcine and primate blood coagulation systems [8]. Immune system modulators: introduction of factors such as human TNF alpha-related apoptosis inducing ligand, HLA-E/beta-2-microglobulin, and CTLA-4Ig to modulate cellular immune responses [5]. The emergence of sophisticated molecular tools, particularly Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 gene editing technologies, has significantly increased the efficiency and precision of producing genetically modified pigs for xenotransplantation [3].

These advances have enabled the creation of multi-transgenic pigs that can address multiple rejection mechanisms simultaneously. Nuclear transfer and cloning technologies have also enhanced the ability to generate transgenic pigs with greater efficiency compared to traditional pronuclear injection methods [6]. Importantly, nuclear transfer offers the ability to target gene insertion selectively to specific gene loci and to delete specific genes in pigs with unprecedented precision. Recent experimental results have demonstrated remarkable progress in pig-to-primate transplantation outcomes. Using alpha1,3-galactosyltransferase gene-knockout pigs combined with novel immunosuppressant agents, researchers have achieved 2 to 6 months' survival of heterotopic heart xenotransplants [2]. In life-supporting kidney xenotransplantation, promising survival approaching 3 months has been documented. The most recent achievements represent quantum leaps in survival times. The combination of extensive gene editing and novel immunosuppressive therapy based on blockade of the CD40/CD154 T cell costimulation pathway has extended life-supporting pig kidney graft survival to greater than 1 year and pig heart survival to up to 9 months [1]. These breakthrough results in large animal preclinical models laid the foundation for three historic pig-to-human transplants: two kidney xenografts in brain-dead recipients deemed ineligible for transplant, and one heart xenograft representing the first clinical-grade study of pig-to-human transplantation [3].

Despite tremendous progress, significant challenges remain. Liver and lung xenotransplantation's have not achieved the encouraging survival rates seen with kidney and heart transplantation [2]. When classical acute humoral xenograft rejection is prevented, thrombotic microangiopathy and coagulation dysregulation become more prominent obstacles. The initiating cause of pig cardiac and renal xenograft failure appears to be antibody-mediated injury to the endothelium, leading to microvascular thrombosis development [7]. Contributing factors include preformed anti-non-Gal antibodies, development of low-level elicited antibodies to non-Gal antigens, natural killer cell or macrophage activity, and inherent coagulation dysregulation between pigs and primates. Recent data, including results from the first clinical case, suggest that gene modification alone will not overcome all xenogeneic immunologic barriers, necessitating active and innovative immunologic strategies [3]. A critical concern in xenotransplantation is the potential for cross-species infection, particularly regarding porcine endogenous retroviruses [10]. Comprehensive studies have addressed the discovery and characterization of porcine endogenous retroviruses, examining the risk of zoonotic infections emanating from pigs. Encouragingly, all retrospective studies on patients with pig xenografts have shown no evidence of porcine endogenous retroviruses transmission to date [10]. Additionally, no formal evidence has been presented from in vivo studies in non-human primates or from humans exposed to pig organs, tissues, or cells that porcine endogenous retroviruses infect primate cells [2].

However, researchers interpret these results with caution, recognizing that more basic research and controlled animal studies that more closely mimic the pig-to-human xenotransplantation setting are required for comprehensive safety assessment [10]. The field stands at a critical juncture where initial clinical trials are already underway or anticipated. Trials of islet and corneal xenotransplantation are currently in progress, while trials of pig kidney or heart transplantation are expected within the coming years [7]. The future success of xenotransplantation depends on three key developments: further genetic modification of pigs, introduction of novel immunosuppressive agents that target the innate immune system and plasma cells, and development of clinically applicable methods to induce donor-specific tolerance [2]. A major challenge ahead involves combining the most important and efficient genetic modifications in multi-transgenic pigs suitable for clinical xenotransplantation [8]. The final therapeutic regimen will likely involve a sophisticated combination of modified functional genes in donor organs, development of immunological tolerance to pig antigens, and administration of novel therapeutic agents capable of controlling natural killer cell and monocyte-mediated responses [6]. The interpretation of the main concepts is highlighted in the following text. Xenotransplantation involves the transplantation of organs, tissues, or cells across species barriers, most commonly from pigs to humans.

It has gained renewed attention as a potential solution to the global shortage of donor organs, particularly kidneys. Chronic kidney disease and end-stage renal failure continue to increase worldwide, while the availability of human donor kidneys remains insufficient to meet demand. As a result, xenotransplantation has re-emerged as a scientifically plausible and clinically relevant strategy [2]. Recent advances in genetic engineering, immunosuppressive therapies, and perioperative management have enabled experimental pig-to-human kidney transplants to achieve short- to medium-term graft function. These developments represent a significant milestone in transplantation medicine. However, despite these advances, xenotransplantation continues to raise complex ethical, immunological, regulatory, and societal challenges that must be addressed before broader clinical implementation can be ethically and legally justified [11]. The ethical analysis of xenotransplantation encompasses multiple interrelated domains. One of the most prominent concerns is animal welfare. Genetically modified pigs are bred, maintained in bio secure environments, and ultimately sacrificed solely for the purpose of organ procurement. This practice raises questions regarding the moral status of animals, the justification of their instrumental use, and the obligation to minimize suffering throughout their lives [12,13].

Informed consent represents another major ethical challenge. Candidates for xenotransplantation are often patients with life-threatening conditions and limited therapeutic alternatives. Under such circumstances, it is difficult to ensure that consent is fully voluntary and adequately informed, particularly given the uncertainty surrounding long-term outcomes, risks of rejection, and potential infectious complications [14]. Xenotransplantation also raises public health concerns. Unlike conventional transplantation, the risks associated with xenotransplantation extend beyond the individual recipient. The potential transmission of zoonotic pathogens introduces societal risks, transforming individual clinical decisions into matters of collective ethical responsibility. This raises questions about whether individual consent can ethically justify risks borne by the broader population [14,15]. Issues of justice and equitable access further complicate the ethical landscape. Xenotransplantation is expected to be costly and technologically demanding, at least in its initial phases. There is concern that access may be limited to privileged populations or well-funded healthcare systems, potentially exacerbating existing health inequities. Finally, philosophical, cultural, and religious concerns persist regarding the blurring of boundaries between human and animal life, contributing to public ambivalence or resistance toward xenotransplantation [13,16]. Due to its experimental nature and potential societal impact, xenotransplantation is subject to exceptionally strict regulatory oversight.

Regulatory authorities generally require extensive preclinical data demonstrating safety and efficacy, particularly in nonhuman primate models, before approving any human application. Donor animals must be bred and maintained in highly controlled, bio secure facilities to minimize infectious risks [14,17]. Another defining regulatory feature of xenotransplantation is the requirement for long-term, often lifelong, monitoring of recipients. This surveillance may include periodic clinical evaluations, laboratory testing, and biological sample collection. Such requirements raise concerns related to privacy, autonomy, and the proportionality of regulatory obligations imposed on recipients [14,17]. Regulatory approaches to xenotransplantation vary significantly across jurisdictions. Differences in ethical standards, biosafety regulations, and approval pathways create the risk of regulatory arbitrage, sometimes referred to as "xenotourism", in which patients seek experimental procedures in countries with weaker oversight. Additionally, the involvement of commercial entities in the development of genetically modified donor animals introduces further regulatory complexity, including issues related to intellectual property, conflicts of interest, and cost control [15,18]. Pig kidney xenotransplantation represents the most advanced and extensively studied application of solid-organ xenotransplantation. Early research relied on nonhuman primate models, which demonstrated that genetically modified pig kidneys could sustain life and renal function for prolonged periods under intensive immunosuppression.

These findings laid the foundation for experimental human studies [11,19]. More recently, genetically modified pig kidneys have been transplanted into brain-dead human recipients as a means of evaluating organ function and immune responses in a human physiological environment. These studies demonstrated urine production, creatinine clearance, and other indicators of renal function, while also revealing early immune-mediated injury and inflammatory responses [11,20]. In limited cases, pig kidneys have been transplant-

ed into living human recipients under compassionate-use protocols. These cases provided proof of concept that pig kidneys can function in humans for weeks to months. At the same time, they highlighted persistent challenges, including antibody-mediated rejection, microvascular injury, coagulation abnormalities, and infectious risks. Collectively, these studies underscore both the promise and the limitations of current pig kidney xenotransplantation strategies [15,19]. In Brazil, xenotransplantation remains confined to experimental research and ethical debate. Although Brazil has a well-established public organ transplantation system and significant expertise in transplant medicine, no specific regulatory framework currently authorizes xenotransplantation in humans. Brazilian scholars and bioethicists emphasize the central role of national regulatory authorities, particularly Brazilian Health Regulatory Agency (ANVISA), as well as research ethics committees and biosafety legislation, in any future consideration of clinical xenotransplantation.

There is broad consensus that legal adaptations, public engagement, and alignment with international standards would be essential prerequisites for the ethical and safe introduction of xenotransplantation trials in Brazil [21]. A pioneering study, led in part by Brazilian researchers, mapped in detail how the human immune system responds to the first living human recipient of a genetically modified pig kidney. Involved deep molecular profiling (transcriptomics, proteomics, metabolomics) [22]. Initial adaptive immune reaction: shortly after transplant, the patient's body recognized the kidney as foreign and activated cellular rejection mechanisms, mainly via T lymphocytes; this type of response was partially controlled with standard immunosuppressive drugs. Persistent innate immune activation: even with immunosuppression, the innate immune system (especially monocytes and macrophages) stayed active against the graft; this ongoing activation may compromise the long-term survival of the organ if not specifically addressed. New biomarkers and insights: the researchers identified porcine donor-derived cell-free DNA (dd-cfDNA) in the patient's blood, suggesting it could be a sensitive marker for early graft injury or rejection. The study confirms that xenotransplantation is feasible, but also shows that controlling only the traditional adaptive response (T cells) is not enough. The innate immune system plays a significant role in ongoing rejection that current immunosuppressive treatments don't fully control.

The transplant was performed in March 2024 at Massachusetts General Hospital on a 62-year-old man with end-stage kidney disease. While the procedure was a major scientific milestone, the patient died about two months later, likely due to an unrelated cardiac condition. Xenotransplantation, which involves the use of organs from other species - such as genetically modified pigs—has been increasingly regarded as a promising strategy to address the global shortage of donor organs. In this context, detailed immune profiling plays a crucial role, as it enables a deeper understanding of the mechanisms underlying graft rejection. By elucidating both adaptive and innate immune responses involved in this process, such analyses provide essential insights that support the development of more effective therapeutic approaches aimed at improving immune suppression and long-term transplant outcomes. Xenotransplantation is the medical practice of transplanting organs, tissues, or cells from one species into another, most commonly from animals to humans. It usually involves: source animals, primarily genetically modified pigs; targets: humans with end-stage organ failure (kidney, heart, liver); goal: address the severe shortage of human donor organs [5]. Pigs are used because their organs are similar in size and function to human organs, they reproduce quickly and are easy to breed and they can be genetically edited to reduce immune rejection and infection risk. Common genetic modifications include removing pig genes that trigger hyperacute rejection, adding human genes that regulate blood clotting and immune response, inactivating porcine endogenous retroviruses [23].

The principal challenges involve immune rejection, inflammation with coagulation abnormalities, infection risk, and long-term graft survival. Immune rejection remains a major obstacle, as humans can mount strong adaptive immune responses mediated by T lymphocytes and antibodies, as well as innate immune responses involving macrophages and the complement system. In addition, cross-species biological differences may trigger excessive inflammation and abnormal coagulation, increasing the risk of clot formation. Another important concern is the potential transmission of animal-derived viruses, although this risk is currently subject to strict monitoring and control. Finally, while short-term outcomes of xenotransplantation have shown significant improvement, long-term graft survival and durability continue to be actively investigated [15]. At present, xenotransplantation has not yet entered routine clinical practice. Nevertheless, several experimental transplants, particularly involving kidneys and hearts, have been successfully performed in living patients. In some of these cases, the transplanted organs functioned for periods ranging from weeks to months, demonstrating the technical and biological feasibility of this approach. Ongoing research is now primarily directed toward achieving more effective immune regulation, with special emphasis on controlling innate immune responses, in order to improve graft survival and enable broader clinical application in the future [11].

This field holds substantial clinical and scientific importance, as it has the potential to save thousands of lives each year by expanding the availability of transplantable organs. By increasing access to viable grafts, xenotransplantation may significantly reduce the time patients spend on dialysis or on transplant waiting lists. Moreover, it represents a major frontier in modern medicine, integrating advances in transplant surgery, genetics, and immunology, and paving the way for transformative innovations in patient care [20]. Brazil has no specific regulatory norm yet authorizing xenotransplantation trials in humans; any future clinical use will require adaptations of ethical and legal frameworks, including Brazilian Health Regulatory

Agency (ANVISA) approval and bioethics committee oversight [21]. As of 2025–2026, the field of xenotransplantation is in a transitional phase between advanced experimental research and early clinical application. Studies have demonstrated that genetically modified pig kidneys are capable of functioning in humans and in brain-dead model systems for extended periods, highlighting the biological feasibility of the procedure. Genetic engineering plays a central role in these advances, particularly through multi-gene editing and the introduction of human transgenes, which are essential strategies for reducing innate immune rejection. Nevertheless, immune responses remain complex, involving macrophage activation, antibody-mediated injury, and the engagement of costimulatory pathways. Although clinical cases to date are limited, they have provided valuable insights for refining immunosuppressive protocols and xenograft monitoring strategies, thereby supporting the safe and progressive development of this field [11,19,20].

Conclusion

Xenotransplantation using genetically modified pigs represents a potential paradigm shift in addressing the organ shortage crisis. While significant scientific and technical hurdles have been overcome, the path to routine clinical application requires continued innovation in genetic engineering, immunosuppression, and safety protocols. The recent achievements in extending graft survival and the initiation of human clinical cases mark xenotransplantation as closer to clinical reality than ever before, offering hope for thousands of patients awaiting life-saving organ transplants.

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Conflicts of Interest

No conflict of interest.

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