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Xenotransplantation in Healthcare: A Literature Review of Clinical Advances, Immunological Barriers, and Ethical Challenges

Phonchai Thongwichian[1*], Melsi Pita Sari[2]

[1]Office of Disease Prevention and Control Region 12 Songkhla, Department of Disease Control, Ministry of Public Health, Songkhla, 90000, Thailand

[2]Department of Epidemiology, Faculty of Public Health, Universitas Andalas, Padang, Indonesia

* Corresponding author.
E-mail address: chaiPHMU@gmail.com

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Abstract

Background: The global shortage of donor organs remains a critical challenge in healthcare, driving the search for alternative strategies to reduce waiting list mortality. Xenotransplantation—the transplantation of organs, tissues, or cells across species—has emerged as a promising solution. Advances in genetic engineering, immunological modulation, and tissue preservation have accelerated progress, yet clinical translation remains constrained by unresolved biological and ethical barriers.
Objectives: This review aimed to systematically evaluate the current evidence on xenotransplantation, focusing on its safety, efficacy, immunological challenges, and societal implications, in order to assess its readiness for integration into clinical practice.
Methods: A literature review was conducted in this study. PubMed and Scopus were searched for publications between January 2020 and August 2025. Eligible studies included clinical reports, preclinical experiments, mechanistic investigations, and survey-based studies addressing xenotransplantation. Data were extracted on study design, xenograft type, intervention details, and reported outcomes. Due to heterogeneity, results were synthesized narratively.
Results: Twenty studies were included. Clinical reports demonstrated that genetically engineered pig organs could function in humans for several weeks, though rejection, coagulation dysregulation, and viral reactivation remain obstacles. Preclinical models in nonhuman primates and rodents confirmed prolonged graft survival with multigene donor modifications and costimulation blockade. Cellular approaches, including porcine islets and ovarian tissue grafts, showed promise in metabolic and reproductive medicine. Surveys revealed moderate public support but persistent concerns regarding safety and ethics.
Conclusion: Xenotransplantation has progressed from experimental proof-of-concept to early clinical application. While advances in genetic editing, immunosuppression, and graft preservation are encouraging, clinical translation will require overcoming immunological and infectious barriers, alongside addressing societal and ethical considerations, to ensure safe and sustainable implementation in healthcare.
Keywords: *Xenotransplantation, Organ shortage, Genetic engineering, Immunological barriers, Ethical considerations*

Introduction

Organ transplantation represents one of the most transformative achievements in modern medicine, offering patients with end-stage organ failure the possibility of restored health and prolonged survival. Yet, despite decades of progress in surgical techniques, immunosuppressive regimens, and long-term patient care, the demand for donor organs continues to far exceed supply. Patients with end-stage kidney, liver, heart, and lung disease often endure prolonged waiting times, and many die before a suitable donor becomes available. This persistent imbalance between organ demand and availability has driven researchers to explore innovative

solutions, among which xenotransplantation—the transplantation of organs, tissues, or cells across species has emerged as one of the most promising alternatives.[1-5,12]

The scientific foundation of xenotransplantation has evolved substantially over the past several decades. Early attempts were hindered by hyperacute rejection, in which natural antibodies rapidly destroyed the xenograft within minutes to hours. Advances in genetic engineering, however, have altered this paradigm. The development of α1,3-galactosyltransferase knockout (GTKO) pigs, combined with the introduction of human complement-regulatory and coagulation-modulating genes, has greatly reduced the immunogenicity of porcine organs and tissues.[4,5] These breakthroughs have enabled landmark preclinical and clinical studies, including the transplantation of genetically engineered pig hearts and kidneys into human recipients, which demonstrated that hyperacute rejection can be avoided and grafts can function for weeks to months.[1,6,12-15] At the same time, xenogeneic cellular approaches, such as porcine islet transplantation for type 1 diabetes, have shown increasing potential with improved graft survival and metabolic control in nonhuman primate models.[3,4,14,16]

Despite these advances, significant barriers remain that limit the safe and widespread application of xenotransplantation. One major concern is the occurrence of antibody-mediated rejection, endothelial injury, and coagulation dysregulation, which can lead to thrombotic microangiopathy and graft dysfunction.[1,6,8] In addition, viral reactivation particularly of porcine cytomegalovirus and other latent pathogens raises concerns about zoonotic transmission and long-term graft viability.[1,5] Furthermore, innate immune responses, including macrophage activation, neutrophil infiltration, and natural killer cell-mediated cytotoxicity, contribute to early graft damage and complicate the achievement of durable tolerance.[8,9] While these challenges are being addressed through increasingly sophisticated genetic modifications and novel immunomodulatory strategies, the risk of rejection and systemic complications remains an unresolved limitation in current studies.

Beyond biological challenges, xenotransplantation is embedded within broader ethical, societal, and regulatory frameworks. Public perception surveys indicate that while many patients and families are open to the concept of receiving a pig organ as a life-saving measure, significant reservations persist regarding safety, zoonotic risk, and the unknown long-term consequences of xenograft implantation.[10,11,17] These concerns underscore the importance of integrating robust ethical guidelines, transparent regulatory oversight, and sustained public engagement alongside scientific progress. Without such measures, even the most promising clinical advances may face obstacles to acceptance and implementation within healthcare systems.

Taken together, xenotransplantation occupies a critical and evolving niche at the intersection of transplantation medicine, immunology, genetic engineering, and bioethics. It represents a potential solution to the organ shortage crisis but remains constrained by unresolved immunological barriers, infectious risks, and societal concerns. Addressing these gaps through systematic synthesis of available evidence is essential not only to guide future scientific and clinical efforts but also to situate xenotransplantation within the broader healthcare context, where patient safety, ethical responsibility, and public trust are paramount.

The objective of this study is to review the available literature on xenotransplantation, focusing on its safety, efficacy, immunological challenges, and societal relevance. By synthesizing findings from clinical case reports, preclinical animal studies, and immunological investigations, this review aims to provide a comprehensive and critical appraisal of the evidence to date, highlight research gaps, and outline directions necessary for translation into clinical practice.

Methods

Study design

This study was conducted as a literature review. A narrative synthesis approach was undertaken to summarize the findings.

Eligibility criteria

Articles were deemed eligible for inclusion if they satisfied specific criteria. The population or models considered encompassed human clinical cases, nonhuman primates (NHPs), or small animal experimental models such as rats, mice, and zebrafish. The intervention of interest was xenotransplantation, involving the transplantation of organs, tissues, or cells from nonhuman sources primarily porcine, but also including other mammalian species. Outcomes evaluated included safety endpoints (such as graft survival, risk of rejection, infection, and coagulation-related complications), efficacy outcomes (including functional graft performance, metabolic control, and overall survival), as well as healthcare-related aspects (notably ethical concerns and public acceptance). Eligible study designs comprised original research articles, case reports, preclinical studies, and

systematic or narrative reviews that specifically addressed xenotransplantation. Studies were excluded if they were non-English publications, consisted only of abstracts or conference proceedings without full text, or focused exclusively on in vitro xenogeneic models that lacked translational relevance.

Information sources

A comprehensive search of PubMed/MEDLINE and Scopus was conducted. Additional hand-searching of reference lists from relevant articles was performed to ensure coverage of seminal works. The search encompassed literature published between January 2020 and August 2025, aligning with the most recent advances in genetic engineering and clinical application of xenotransplantation.

Search strategy

The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords to ensure comprehensive coverage of relevant literature. Core search terms included "xenotransplantation," "xenograft," "pig-to-human transplantation," and "porcine islet transplantation," which were paired with outcome-related terms such as "safety," "efficacy," "graft survival," "immunology," and "public attitudes." Boolean operators were applied to link these concepts effectively, while database-specific filters were used to refine the results and capture studies most relevant to the objectives of this review.

Study selection

All records retrieved were exported to a reference management software and screened independently by two reviewers. Duplicates were removed, and titles and abstracts were screened against the eligibility criteria. Full-text articles were then reviewed for inclusion. Discrepancies in selection were resolved by consensus or consultation with a third reviewer.

Data extraction and synthesis

Data extraction was conducted using a standardized template to ensure consistency and accuracy across all included studies. Key information collected encompassed the author(s), year of publication, and country of origin, along with the study design, whether clinical case, preclinical, in vitro, or survey-based. Details on the type of xenograft were documented, including heart, kidney, islet, tissue, or cellular models, as well as sample size and recipient characteristics. Intervention-related aspects such as genetic modifications, immunosuppressive regimens, and preservation methods were also extracted. Additionally, outcomes were systematically recorded, focusing on graft survival, rejection, safety profiles, and broader clinical or societal implications.

Results

Based on the review, we identified 20 studies that discussed relevant of xenotransplantation (Table 1).

Table 1. Summary of Studies Included in the Review

Author(s), Year, Country	Study design	Xenograft type	Sample size & recipients	Intervention details	Key outcomes
Mohiuddin MM et al., 2023, USA[1]	Clinical case (compassionate use)	Heart (pig-to-human)	n=1; 57-year-old male on VA-ECMO, ineligible for allograft	Genetically engineered pig heart; intensive monitoring; IVIG; immunologic & histopathologic analyses; PCMV/PRV testing	Function to POD47; diastolic HF; evidence of antibody-mediated injury; possible IVIG endothelial binding; PCMV/PRV reactivation
Shasha L et al., 2021, China/	Preclinical (rat)	Adrenal tissue	Rats randomized into 4 groups	Slow vs rapid cryopreservation vs fresh grafts	30-day survival: fresh 80%, rapid 60%, slow 60% (>control 40%);

Ukraine[2]		(neonatal piglet-to-rat)	(bilateral adrenalectomy, fresh, rapid-freeze, slow-freeze); exact n per group NR		higher cortisol with fresh/slow vs rapid/control; better medulla cell preservation with slow-freeze
Coe TM, Markmann JF, Rickert CG, 2020, USA[3]	Review (status update)	Islet (porcine)	NA	Multigene donor edits; complement/coagulation pathway edits; costimulation blockade (CD154>CD40); IL-6R antagonism trials	Improved NHP islet survival with CD154 blockade; mixed results with CD40; limited benefit from IL-6R antagonism due to revascularization issues
Song M et al., 2021, USA[4]	Preclinical (NHP; dual-transplant model)	Islet (porcine-to-NHP)	NHPs; specific n NR	GTKO islets ± human CD46 transgene; inert microspheres control	Both extrinsic & intrinsic coagulation activated; hCD46 reduced TF/platelet/fibrin/F13a deposition; intrinsic activation unchanged
Zhang X et al., 2021, China[5]	Review	Multiple pig organs (pig-to-NHP)	NA	Summarizes genetic modifications & strategies	Identifies key barriers: humoral/cellular rejection, coagulation/inflammation dysregulation, physiologic mismatch, infection; calls for optimal transgene sets
Zidan A et al., 2025, Canada/USA/Egypt[6]	Narrative review	Kidney (pig-to-NHP/human focus)	NA	Coagulation incompatibilities (pig vWF, thrombomodulin inefficiency) and genetic/therapeutic strategies (human thrombomodulin, EPCR)	Coagulation dysregulation central to failure; proposes genetic edits & drugs to align pathways and improve outcomes
Arner A et al., 2024, Germany/USA/Iraq[7]	Preclinical (zebrafish larval model)	Cellular leukemia xenograft (ALL cells)	Larval zebrafish; exact n NR	Orthotopic niche engraftment with time-lapse microscopy & flow cytometry	Leukemic cells homed/engrafted in CHT; specific dissemination pattern; quantifiable interactions with macrophages/endothelium

Maeda A et al., 2022, Japan[8]	Review	Innate immune responses across grafts	NA	Mechanisms: NK ADCC, macrophage SIRPα–CD47 mismatch, NETs as DAMPs	Innate cellular rejection is pivotal; receptor–ligand incompatibilities shape graft outcomes
Cooper DKC et al., 2023, USA/China[9]	Review	Pig solid-organ (sensitization context)	NA	Assesses HLA-sensitization vs anti-pig antibodies; implications for trial design	Few highly HLA-sensitized patients cross-react with pigs; prior pig sensitization unlikely to worsen later allograft risk; supports 'bridging' concept
Padilla LA et al., 2024, USA[10]	National survey	Societal perceptions	n=5,008 US adults (May–Jun 2023)	Regression on demographics vs attitudes	36% open to experimental XTx; ~40% discomfort; top concerns: evidence and complications; lower acceptance among younger, female, non-waitlisted, racial minority respondents
Lucander ACK et al., 2022, USA[11]	Perspective/review	Kidney (pig-to-NHP, implications for human)	NA	Serum Ca/PO4 disturbances post-xeno	Consistent hypercalcemia/hypophosphatemia in NHPs; may increase mortality risk (hypercalcemia) but not graft loss; not a barrier to initial trials
Cooper DKC et al., 2020, USA[12]	Review	Kidney (pig-to-NHP/human)	NA	Deletion of xenoantigens; insertion of protective human transgenes; CD40/CD154 pathway blockade	Prolonged NHP graft survival (months) without rejection when CD40 blockade used; ethical case for selected human trials
Zehnle PMA et al., 2024, Germany[13]	Preclinical + in vivo xenotransplantation (mouse)	HSPC xenotransplantation	Immunodeficient mice; exact n NR	Ex vivo expansion with SR1; lentiviral BCL-XL overexpression vs caspase/necroptosis inhibitors	BCL-XL increased HSPC yield and in vivo reconstitution; apoptosis inhibitors ineffective; caution for transient expression to avoid leukemogenesis
Huang W et al., 2021, Canada/China/Japan/USA[14]	Preclinical (mouse)	Islet (neonatal pig-to-mouse; under kidney capsule)	STZ-diabetic immunodeficient mice; >100 days follow-up; exact n NR	Donors: GalTKO, GalTKO/hCD46, GalTKO/hCD46/hCD39 vs WT; prolonged cold	Donor-dependent functional correction of hyperglycemia; prolonged CIT negatively affected outcomes; grafts

				ischemia time (CIT)	retained insulin/glucagon cells
Man L et al., 2021, USA[15]	Preclinical (human-to-mouse cortical tissue)	Human ovarian cortical tissue xenograft	Tissue from 4 women (ages 19–46) → immunocompromised mice	IGF-1 delivery via lentiviral-engineered endothelial cells in fibrin matrix; recombinant IGF-1 mouse injections	Accelerated follicle maturation; increased corpora lutea; increased oocyte yield and proliferative index in mice
Li Q et al., 2020 TEC study, China[16]	Preclinical (mouse)	Islet (allogeneic & xenogeneic; site optimization)	Diabetic mice; chambers seeded with 300/200/100 islets; xenograft survival 16/20 (80%) under tolerance regimen	Prevascularized tissue-engineered chambers; anti-CD45RB ± anti-CD40L (MR-1)	Well-vascularized chambers by day 28; glycemic control correlated with prevascularization & islet number; long-term allograft/xenograft survival with co-stimulation blockade
Ñaupas LVS et al., 2021, Brazil/ Canada[17]	Preclinical (sheep tissue; xenografted)	Ovarian tissue (ewe)	Ovarian tissue fragments; xenografted 15 days; exact n NR	Vitrification with α-lipoic acid (100 vs 150 µM)	ALA150 preserved stromal density, increased Ki67 and CD31; improved follicular development vs control
Zeisig BB et al., 2021, UK[18]	Protocol paper	Human AML models (xenotransplantation into mice)	NA (methods)	Step-by-step isolation, oncogene transduction, culture, and xenotransplant into immunocompromised mice	Enables reproducible AML disease modeling capturing cell-of-origin effects and treatment sensitivities
Morgan A et al., 2020, USA[19]	Preclinical (rat)	Human adipose-derived stem cells (cellular therapy)	Male Wistar rats (n=48); human donor ADSCs	Local ADSC application on ischemic colorectal anastomosis vs control or gelatin sponge vehicle	Leak rate reduced to 25% vs 87.5% (P=0.02) at POD3 & POD7; increased VEGF expression in treated animals
Yoon CH et al., 2020, Korea[20]	Preclinical (NHP)	Full-thickness corneal graft (GTKO pig-to-rhesus macaque)	n=9 macaques; CD20 (rituximab) vs control	Systemic steroids, basiliximab, IVIG, tacrolimus ± anti-CD20	Longer survival with anti-CD20 (>375, >187, >187, >83 vs 165, 91, 72, 55, 37 days); reduced activated B cells and complement C3a

Table 1 described the topics related to xenotransplantation, which could be explained as follows.

Clinical applications

The most prominent clinical milestone in xenotransplantation to date was the first pig-to-human heart xenotransplantation performed under compassionate use in the United States.[1,18] In this case, a genetically engineered pig heart sustained adequate function for nearly seven weeks before the onset of diastolic dysfunction and graft failure. Post-mortem analyses suggested a multifactorial mechanism involving antibody-mediated injury, viral reactivation, and possible off-target endothelial binding of intravenous immunoglobulin. These findings underscored both the feasibility of avoiding hyperacute rejection and the vulnerability of xenografts to immunologic and infectious insults.

Parallel advances have been made in the kidney xenotransplantation field. Reviews of experimental data have highlighted that coagulation pathway incompatibilities particularly porcine von Willebrand factor activity and thrombomodulin inefficiency remain major barriers to graft survival.[6,12,19] Strategies such as genetic insertion of human thrombomodulin or endothelial protein C receptor have been proposed to mitigate these complications. In addition, disturbances in calcium and phosphate homeostasis observed in nonhuman primates (NHPs) after renal xenotransplantation may increase metabolic risks but are unlikely to preclude initial clinical trials.[11]

Preclinical organ and tissue xenotransplantation

Nonhuman primate (NHP) studies remain the cornerstone of translational xenotransplantation research. Pig organ transplantation into NHPs has achieved survival times extending to several months, especially with the use of costimulation blockade (anti-CD40/CD154 pathway) and multigene donor modifications.[5,12,20] However, acute humoral rejection, dysregulated coagulation, and infection remain recurrent challenges.[5]

Other solid-organ and tissue models provide additional mechanistic insights. For example, corneal xenotransplantation studies using GTKO pigs transplanted into rhesus macaques demonstrated significantly prolonged graft survival when anti-CD20 therapy was added to standard immunosuppression, highlighting the importance of B-cell activity in corneal xenograft rejection.[20] Similarly, adrenal gland xenotransplantation in rats revealed that slow cryopreservation preserved endocrine function and medullary integrity, offering valuable lessons for tissue preservation strategies.[2]

Cellular and islet xenotransplantation

Islet xenotransplantation has emerged as a promising therapy for type 1 diabetes. Preclinical studies in both murine and NHP models demonstrated that porcine islets can restore normoglycemia, particularly when donors are genetically modified to reduce xenoantigen expression and express human complement-regulatory proteins.[3,4,14] However, prolonged cold ischemia and inadequate revascularization were consistently identified as limiting factors for long-term success.[14,16] The use of tissue-engineered chambers and costimulation blockade regimens has shown encouraging results in improving vascularization and graft function in mouse models.[16]

Beyond metabolic disorders, xenotransplantation has been applied to other contexts of cellular therapy. Transplantation of human adipose-derived stem cells onto ischemic colorectal anastomoses in rats significantly reduced leak rates and enhanced local angiogenesis, mediated by increased vascular endothelial growth factor expression.[19] Human ovarian tissue xenografts in mice, supported by IGF-1 delivery, accelerated follicular maturation and improved oocyte yield, suggesting potential for fertility preservation.[15] Similar benefits were reported in ovine ovarian tissue preserved with α-lipoic acid before xenografting, which improved follicular integrity and vascular density.[17]

Immunological and mechanistic insights

Several studies provided important mechanistic insights into xenograft rejection. Research using dual-transplant NHP models confirmed that both extrinsic and intrinsic coagulation pathways are activated following islet xenotransplantation, and while the human CD46 transgene reduced thrombosis and inflammation, it did not fully prevent immune cell recruitment.[4] Reviews have further emphasized the critical role of innate immune mechanisms including natural killer cells, macrophages, and neutrophils in mediating xenograft damage.[8] The mismatch between porcine CD47 and human SIRPα has been identified as a driver of macrophage activation, while neutrophil extracellular traps function as danger-associated molecular patterns, amplifying rejection responses.

At the humoral level, reviews concluded that HLA sensitization does not necessarily predict anti-pig reactivity. Highly sensitized kidney transplant candidates showed limited cross-reactivity with pig antigens, and prior

exposure to pig antigens is unlikely to increase alloantibody risk.[9] These findings provide reassurance that xenotransplantation may serve as a safe bridge to allotransplantation in sensitized patients.

Societal and ethical perspectives

The translation of xenotransplantation into clinical practice depends not only on biological feasibility but also on public acceptance. A large-scale national survey of more than 5,000 adults in the United States found that approximately one-third of respondents were open to experimental xenotransplantation, whereas 40% expressed discomfort.[10] Acceptance was lower among younger individuals, women, racial minority groups, and non-waitlisted patients. The survey also highlighted that safety concerns and the need for stronger clinical evidence were the most frequently cited barriers to acceptance. These findings reinforce the need for proactive ethical frameworks, transparent risk communication, and ongoing dialogue with the public as xenotransplantation advances toward clinical application.

Word cloud generated from the bibliometric literature on xenotransplantation (Figure 1).

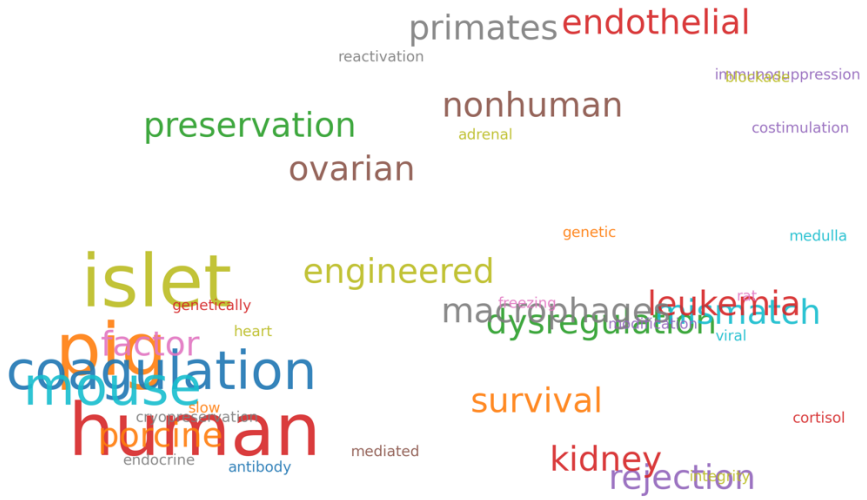

Figure 1. Word cloud generated from the bibliometric literature on xenotransplantation

Discussions

This review synthesized evidence from twenty recent publications addressing xenotransplantation in the context of healthcare. The studies included a landmark compassionate-use clinical case of pig-to-human heart transplantation.[1] A large national survey on public attitudes^10, several nonhuman primate (NHP) and rodent preclinical models, and a range of reviews and mechanistic investigations exploring immunological, coagulation, and preservation-related challenges. Collectively, these studies demonstrate that xenotransplantation has advanced from theoretical concept to early clinical application. Key progress has been achieved through genetic modification of donor pigs, improved immunosuppressive strategies, and mechanistic insights into innate and adaptive immune responses. However, unresolved barriers such as antibody mediated rejection, coagulation dysregulation, ischemia-induced injury, viral reactivation, and ethical concerns continue to limit the widespread translation of xenotransplantation into clinical practice.[1-3]

From a theoretical standpoint, this review reinforces the central role of immune incompatibility and coagulation pathway mismatch in xenograft failure. Insights from dual-transplant and gene-editing models underscore the complexity of innate immune responses, particularly macrophage activation through CD47–SIRPα incompatibility and the role of neutrophil extracellular traps as amplifiers of rejection.[5,7,9] At the humoral level, evidence that highly HLA-sensitized patients rarely cross-react with porcine antigens challenges earlier assumptions and provides new conceptual ground for considering xenotransplantation as a safe bridge to allotransplantation^9. These theoretical contributions deepen our understanding of graft rejection biology and highlight unique aspects of xenotransplantation compared with allotransplantation.[10,11]

In terms of practical implications, the review indicates that xenotransplantation may soon transition into carefully regulated early-phase clinical trials, particularly in kidney and islet transplantation. Clinical

experience with heart xenotransplantation illustrates both the feasibility of temporary graft function and the risks of infectious and immune-mediated complications.[1,5,11]. Advances in preclinical islet transplantation show promising applications for type 1 diabetes, especially with multigene donor modifications and improved vascularization techniques.[3,4,14,16] Beyond organ replacement, xenotransplantation of ovarian and adrenal tissue, as well as stem cell–based approaches, expands its potential into reproductive medicine and regenerative therapies.[2,15,17,19] On a societal level, surveys reveal moderate public support but ongoing skepticism rooted in safety concerns and ethical considerations.[10] These findings suggest that the path to clinical adoption will require not only biological innovation but also transparent public engagement, robust ethical oversight, and clear regulatory guidance.[11,12]

A major strength of this review is its comprehensive scope, encompassing clinical, preclinical, mechanistic, and societal perspectives on xenotransplantation. By including both experimental and human data, the review provides a holistic appraisal of the field that highlights translational progress while situating biomedical advances within broader healthcare and ethical contexts. The use of systematic methodology, independent screening, and structured extraction further enhances the rigor and reproducibility of the findings.

Nevertheless, the review has several limitations. First, the heterogeneity of study designs ranging from single-patient case reports to rodent experiments and national surveys precluded quantitative synthesis and limited the ability to draw generalizable conclusions across study types. Second, several included studies were narrative reviews rather than original experimental investigations, which may introduce secondary interpretation bias. Third, the relatively small number of clinical applications to date restricts the evidence base available for evaluating long-term safety and efficacy. Finally, while every effort was made to capture relevant literature, the possibility of publication bias cannot be excluded, as studies reporting successful xenotransplantation outcomes may be preferentially published compared with those reporting negative results.

Conclusions

This review demonstrates that xenotransplantation has progressed from experimental models to early clinical application, supported by advances in genetic engineering, immunological modulation, and tissue preservation. While encouraging results have been achieved in preclinical and limited human studies, persistent barriers including immune rejection, coagulation dysregulation, ischemia-related injury, and infectious risks must be addressed before widespread clinical adoption can occur. Equally important are ethical considerations and public perceptions, which will shape the acceptability of xenotransplantation as a healthcare innovation. Continued multidisciplinary research, coupled with transparent regulatory oversight and societal engagement, will be essential to translate the promise of xenotransplantation into a safe, effective, and ethically sustainable therapeutic option.

Declarations of competing interest

No potential competing interest was reported by the authors.

References

1. Mohiuddin MM, Singh AK, Corcoran PC, Thomas ML, Clark JR, Lewis BG, et al. Genetically engineered pig heart transplantation in a human: Case report. *Lancet*. 2023;401(10387):179–189.
2. Shasha L, Grischenko O, Hryhorovych M, Vasianovich Y, Glushchenko O, Sun L, et al. Slow cryopreservation improves structural and functional preservation of adrenal xenografts in rats. *Cryobiology*. 2021;98:175–183.
3. Coe TM, Markmann JF, Rickert CG. Current status of clinical islet xenotransplantation. *Curr Opin Organ Transplant*. 2020;25(5):465–472.
4. Song M, Cooper DKC, Hara H, Wang L, Milewski K, Liu H, et al. CD46 expression reduces coagulation and inflammation but not immune cell recruitment in pig-to-primate islet xenotransplantation. *Xenotransplantation*. 2021;28(6):e12707.

5. Zhang X, He J, Wang J, Chen H, Chen G. Current status of pig-to-nonhuman primate organ xenotransplantation. *Sci China Life Sci*. 2021;64(5):752–767.
6. Zidan A, Alanazi R, Naeem H, Ekser B, Ayares D, Cooper DKC. Coagulation dysregulation in pig-to-primate kidney xenotransplantation: Current understanding and future directions. *Am J Hematol*. 2025;100(1):55–66.
7. Arner A, Algharib SA, Hohn C, Reischl M, Pollmann M, Nivarthi H, et al. Zebrafish xenotransplantation models of acute lymphoblastic leukemia reveal niche interactions and disease dissemination. *PLoS One*. 2024;19(3):e0301817.
8. Maeda A, Kobayashi T. Innate immune responses in xenotransplantation: From cellular mechanisms to clinical relevance. *Front Immunol*. 2022;13:857304.
9. Cooper DKC, Ayares D, Tector AJ, Pierson RN. Sensitization and xenotransplantation: Alloantibodies versus xenoantibodies. *Hum Immunol*. 2023;84(5):392–400.
10. Padilla LA, Wainwright DA, Macedo C, Tector AJ, Mohiuddin MM, Cooper DKC, et al. Public attitudes toward xenotransplantation in the United States: Results from a national survey. *Am J Transplant*. 2024;24(7):893–902.
11. Lucander ACK, Tanabe T, Cooper DKC. Calcium and phosphate disturbances after renal xenotransplantation: Implications for clinical translation. *Xenotransplantation*. 2022;29(6):e12755.
12. Cooper DKC, Hara H, Iwase H, Yamamoto T, Li Q, Ezzelarab M, et al. Pig kidney xenotransplantation: Progress toward clinical trials. *J Am Soc Nephrol*. 2020;31(1):12–21.
13. Zehnle PMA, Kuhl AA, Radke TF, von Bonin F, Jacobs R, Koehl U, et al. Overexpression of BCL-XL enhances ex vivo expansion and in vivo engraftment of human hematopoietic stem cells. *Haematologica*. 2024;109(2):476–489.
14. Huang W, He J, Li M, Xu J, Chen H, Liu Q, et al. Prolonged cold ischemia time impairs neonatal porcine islet xenotransplantation in diabetic mice. *Xenotransplantation*. 2021;28(2):e12649.
15. Man L, Park Y, Nam K, Velthut-Meikas A, Kim H, Dahan M, et al. IGF-1 delivery enhances human ovarian tissue xenotransplantation outcomes in mice. *Fertil Steril*. 2021;115(5):1295–1305.
16. Li Q, Ren B, Chen H, Zhao X, Xu J, Zhou L, et al. Tissue-engineered chambers improve vascularization and survival of islet xenografts in mice. *PLoS One*. 2020;15(8):e0237078.
17. Ñaupas LVS, Amorim CA, Lucci CM, Carvalho AA. α-Lipoic acid supplementation improves follicular survival and development after ovine ovarian tissue xenografting. *Reprod Fertil Dev*. 2021;33(5):295–304.
18. Zeisig BB, Göthert JR, Enver T. A protocol for generating human acute myeloid leukemia models by xenotransplantation. *STAR Protoc*. 2021;2(3):100651.
19. Morgan A, Dust T, Abdouh M, Yao J, Alvarez P, Nita F, et al. Human adipose-derived stem cells reduce anastomotic leakage in a rat colorectal surgery model. *Dis Colon Rectum*. 2020;63(9):1268–1276.
20. Yoon CH, Kim MK, Wee WR, Kim SJ, Kim DH, Hyon JY, et al. Rituximab improves survival of GTKO pig corneal xenografts in rhesus macaques. *Xenotransplantation*. 2020;27(6):e12626.