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Όρια μεταξύ ειδών και ανθρώπινα δικαιώματα: Νομικές και ηθικές σκέψεις για την ξενομεταμόσχευση

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Ανασκόπηση

Cross-Species Boundaries and Human Rights: Legal and Ethical Reflections on Xenotransplantation

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Abstract

Xenotransplantation, i.e. the transplantation of cells, tissues, or organs derived from animals into humans—stands at the forefront of biomedical innovation, offering a promising solution to the persistent shortage of human donor organs. As this field advances rapidly, it simultaneously raises complex scientific, ethical, and legal challenges that demand careful consideration. The responsibility to safeguard animal welfare while ensuring human health protection is paramount, particularly given the zoonotic risks inherent in xenotransplantation research. Preclinical studies must rigorously address the potential for transmission of infectious agents from animals to humans, requiring robust risk assessment and management strategies that protect not only individual patients but also public health at large. Balancing these concerns with the imperative to develop life-saving therapies underscores the vital role of scientific responsibility.

Ethical questions surrounding xenotransplantation go beyond traditional biomedical concerns, probing deeply into the boundaries between species and what it means to be human. The creation and use of chimeras and hybrids challenge established concepts of identity, raising questions about the moral status of these entities and the ethical limits of scientific intervention. Patient rights remain central in this discourse, especially regarding informed consent, compassionate use of experimental treatments, and the equitable distribution of scarce organs. These issues compel ongoing reflection on autonomy, justice, and societal values, highlighting the need for ethical frameworks that can guide clinical practice and research in this emerging field.

At the same time, xenotransplantation operates within a diverse and evolving global legal landscape. Regulatory frameworks vary considerably across countries, reflecting different cultural, ethical, and political priorities. International organizations such as the International Xenotransplantation Association (IXA) and the World Health Organization (WHO) play critical roles in shaping policies, offering guidance, and promoting harmonization to facilitate responsible development and safe clinical application. Navigating this complex regulatory environment is essential for researchers and clinicians, who must comply with multifaceted requirements to ensure the ethical conduct of clinical trials and patient safety.

This article integrates scientific, ethical, and legal perspectives to provide a comprehensive overview of the current state and future prospects of xenotransplantation. It emphasizes the importance of an interdisciplinary approach that promotes innovation while rigorously addressing risks and respecting both

animal welfare and human dignity. By fostering collaboration among scientists, ethicists, policymakers, and healthcare providers, the xenotransplantation field can advance responsibly, ultimately transforming the landscape of transplantation medicine and offering new hope to patients facing organ failure worldwide.

Keywords: xenotransplantation; organ shortage, regulation; clinical trials; animal welfare.

Όρια μεταξύ ειδών και ανθρώπινα δικαιώματα: Νομικές και ηθικές σκέψεις για την ξενομεταμόσχευση

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Περίληψη

Η ξενομεταμόσχευση—η μεταμόσχευση κυττάρων, ιστών ή οργάνων προερχόμενων από ζώα σε ανθρώπους—αποτελεί την αιχμή της βιοϊατρικής καινοτομίας, προσφέροντας μια πολλά υποσχόμενη λύση στην επίμονη έλλειψη ανθρώπινων μοσχευμάτων παγκοσμίως. Καθώς ο τομέας αυτός εξελίσσεται ραγδαία, προκύπτουν παράλληλα πολύπλοκες επιστημονικές, ηθικές και νομικές προκλήσεις που απαιτούν προσεκτική εξέταση. Η ευθύνη για την προστασία της ευζωίας των ζώων και την ασφάλεια της ανθρώπινης υγείας είναι υψίστης σημασίας, ιδίως λόγω των ζωονόσων που ενυπάρχουν στην έρευνα ξενομεταμόσχευσης. Οι προκλινικές μελέτες πρέπει να αντιμετωπίζουν αυστηρά τον κίνδυνο μετάδοσης λοιμωδών παραγόντων από τα ζώα στους ανθρώπους, εφαρμόζοντας αξιόπιστες στρατηγικές αξιολόγησης και διαχείρισης κινδύνου που προστατεύουν όχι μόνο τους μεμονωμένους ασθενείς αλλά και τη δημόσια υγεία συνολικά. Η ισορροπία ανάμεσα σε αυτούς τους προβληματισμούς και την ανάγκη ανάπτυξης σωτήριων θεραπειών υπογραμμίζει τον κρίσιμο ρόλο της επιστημονικής ευθύνης.

Τα ηθικά ζητήματα που σχετίζονται με την ξενομεταμόσχευση υπερβαίνουν τις παραδοσιακές βιοϊατρικές ανησυχίες, εξετάζοντας βαθιά τα όρια μεταξύ των ειδών και το τι σημαίνει να είσαι άνθρωπος. Η δημιουργία και χρήση χιμαιρών και υβριδίων προκαλεί αμφιβολίες σχετικά με την ηθική κατάσταση αυτών των οντοτήτων και τα όρια της επιστημονικής παρέμβασης. Τα δικαιώματα των ασθενών παραμένουν κεντρικά σε αυτόν τον διάλογο, ειδικά όσον αφορά τη γνώση και τη συγκατάθεση, τη χρήση πειραματικών θεραπειών με συμπόνια και τη δίκαιη κατανομή των σπάνιων οργάνων. Αυτά τα ζητήματα απαιτούν συνεχή προβληματισμό για την αυτονομία, τη δικαιοσύνη και τις κοινωνικές αξίες, υπογραμμίζοντας την ανάγκη ηθικών πλαισίων που καθοδηγούν την κλινική πρακτική και την έρευνα σε αυτόν τον αναδυόμενο τομέα.

Παράλληλα, η ξενομεταμόσχευση λειτουργεί εντός ενός διαφοροποιημένου και εξελισσόμενου παγκόσμιου νομικού πλαισίου. Τα ρυθμιστικά πλαίσια ποικίλλουν σημαντικά ανάλογα με τη χώρα, αντανακλώντας διαφορετικές πολιτισμικές, ηθικές και πολιτικές προτεραιότητες. Διεθνείς οργανισμοί όπως η Διεθνής Ένωση Ξενομεταμόσχευσης και ο Παγκόσμιος Οργανισμός Υγείας (ΠΟΥ) διαδραματίζουν κρίσιμο ρόλο στη διαμόρφωση πολιτικών, την παροχή καθοδήγησης και την προώθηση της εναρμόνισης των προτύπων για την υπεύθυνη ανάπτυξη και ασφαλή κλινική εφαρμογή. Η πλοήγηση σε αυτό το σύνθετο ρυθμιστικό περιβάλλον είναι απαραίτητη για τους ερευνητές και τους κλινικούς ιατρούς, που πρέπει να συμμορφώνονται με πολυδιάστατες απαιτήσεις για να διασφαλίσουν την ηθική διεξαγωγή των κλινικών δοκιμών και την ασφάλεια των ασθενών.

Το άρθρο αυτό συνδυάζει επιστημονικές, ηθικές και νομικές προσεγγίσεις, προσφέροντας μια ολοκληρωμένη επισκόπηση της τρέχουσας κατάστασης και των μελλοντικών προοπτικών της ξενομεταμόσχευσης. Τονίζει τη σημασία μιας διεπιστημονικής προσέγγισης που προωθεί την καινοτομία, ενώ ταυτόχρονα αντιμετωπίζει με αυστηρότητα τους κινδύνους και σέβεται τόσο την ευζωία των ζώων όσο και την ανθρώπινη αξιοπρέπεια. Με την προώθηση της συνεργασίας μεταξύ επιστημόνων, ηθικολόγων, νομοθετών και επαγγελματιών υγείας, ο τομέας της ξενομεταμόσχευσης μπορεί να εξελιχθεί

υπεύθυνα, προσφέροντας τελικά νέες ελπίδες σε ασθενείς που αντιμετωπίζουν ανεπάρκεια οργάνων παγκοσμίως.

Λέξεις κλειδιά: ξενομεταμόσχευση; έλλειψη οργάνων; κανονισμοί; κλινικές δοκιμές; ευζωία ζώων.

Introduction

Xenotransplantation: Concepts and Latest Advancements

Advancements in transplantation procedures are paving the way for allowing medical professionals to perform xenotransplantation. This identifies the transplantation of an organ or tissue within two individuals belonging to different species, where the transplanted body part is called a xenograft. The Food & Drug Administration (FDA) defines xenotransplantation as "any procedure that involves the transplantation, implantation or infusion into a human recipient of either a) living cells, tissues or organs from a non-human animal source or b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs".1 Xenotransplantation encompasses both animal-to-animal and animal-to-human procedures. Although it remains a relatively recent area of interest compared to the most known allotransplantation, xenotransplantation—particularly animal-to-human procedures—has already yielded promising early results.

Within the scientific community, pigs are widely regarded as the most suitable donors for genetically modified organs, primarily due to the anatomical compatibility of their organs with those of humans, as well as their rapid reproductive cycles and ability to produce multiple offspring per pregnancy. At present, the organs most commonly considered for xenografting are kidneys, hearts, and the thymus gland, which is often transplanted together with the kidney to support immune compatibility.

In terms of heart transplantation, a landmark procedure was performed in January 2022, when the first gene-edited pig heart was transplanted into a human patient.[2] Unfortunately, the patient died two months later due to a porcine virus infecting the graft.[3] The following year, in 2023, a second similar transplant was attempted, but the graft was ultimately rejected, and the recipient passed away.[4]

Kidney xenotransplantation has shown more stable outcomes so far. In 2023, a genetically modified pig kidney was transplanted into a brain-dead man and later safely removed, marking a significant step forward in testing feasibility and safety.5 In 2024, the first living recipient of a modified pig kidney was reported; although the patient later passed away, the cause of death was unrelated to the transplant itself.6 Around the same period, a gene-edited pig kidney and thymus gland were transplanted into a living woman who was also supported by a mechanical heart pump. The graft remained viable and performed effectively for forty-seven days before being removed due to complications arising from the patient's pre-existing cardiovascular condition. She later died from said unrelated health issues.7 Most recently, on January 25th, 2025, a gene-edited pig kidney was transplanted into a human as part of a three-

1 U.S. Food and Drug Administration, *Xenotransplantation.*

2 The Guardian, *Maryland man receives pig's heart in world-first transplant.*
3 The Guardian, *Man who had landmark pig heart transplant dies after pig virus infection.*
4 CNN, *Lawrence Faucette, second person to receive pig heart transplant, dies.*
5 CNN, *Pig kidney successfully functions in human for over a month.*
6 CNN, *Pig kidney transplant patient discharged and recovering at home.*
7 CNN, *Woman is back on dialysis after doctors remove transplanted pig kidney.*

person clinical study, further advancing clinical research in this emerging field.8

These experimental procedures demonstrate not only scientific progress but also the increasing feasibility of xenotransplantation as a therapeutic option. However, they also underscore the importance of continued monitoring, refinement of genetic modifications, and rigorous ethical and clinical oversight to ensure long-term safety and effectiveness.

1. Animal Welfare, Zoonotic Risk, and Human Health: A Scientific Responsibility

Preclinical Research and Animal Welfare

Initially, preclinical xenotransplantation studies were carried out primarily between non-human species, serving as essential models for advancing scientific understanding while avoiding the ethical complexities of human trials. Today, these studies are governed by strict international regulations designed to ensure that scientific progress does not come at the expense of animal welfare. In Europe, this balance is articulated through Directive 2010/63/EU, which sets a comprehensive ethical framework for the use of animals in scientific research.

Central to this directive are the principles of replacement, reduction, and refinement—the "3Rs"—which guide researchers toward minimizing animal use and suffering. Scientific justification is now a prerequisite for any study involving animals, and approval must be obtained from competent authorities before experiments can begin. Rather than allowing open-ended or excessive animal use, researchers are required to carefully design their studies to involve only the minimum number of animals necessary to achieve reliable results. Moreover, the directive emphasizes not just the quantity but the quality of animal care. It mandates that any potential pain or distress be reduced to the lowest possible level through refined procedures and humane practices. Animals must be housed in environments tailored to their species-specific needs, with adequate space, enrichment, and opportunities for social interaction—all of which are critical to their well-being and to the reliability of scientific data. Importantly, the directive recognizes that ethical research also depends on the professionals conducting it. For this reason, it requires that all personnel involved be properly trained in both scientific techniques and animal welfare. Veterinary care must always be available, and clear humane endpoints must be set to prevent unnecessary animal suffering. These requirements reflect a commitment to advancing science responsibly and with respect for animal life.

In the United States (US), preclinical xenotransplantation research is primarily overseen by the U.S. FDA, operating under the authority of the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. Xenotransplantation products are classified as biological products, meaning they must undergo the FDA's Investigational New Drug (IND) application process before entering clinical trials. This regulatory framework is designed not only to ensure rigorous safety evaluations but also to uphold strong ethical standards throughout the research process.

Central to the FDA's oversight are its xenotransplantation guidelines, which mandate that animal testing be scientifically justified, ethically reviewed, and supported by thorough risk assessments. These guidelines emphasize the selection of the least sentient animal species capable of yielding valid data, in line with broader ethical considerations. Additionally, researchers must provide detailed documentation regarding animal housing, nutrition, and care, ensure regular veterinary supervision, and define humane endpoints to minimize suffering. The guidelines also extend beyond animal welfare to include biosafety, requiring evaluation of potential zoonotic risks and the implementation of

8 CNN, *Pig kidney transplant patient discharged and recovering at home.*

environmental safety measures. As the research advances toward human trials, informed consent procedures must be comprehensive and transparent, particularly concerning the animal origin of the treatment and any associated risks.[9]

Beyond these foundational requirements, recent shifts in U.S. regulatory policy signal a broader transformation in the approach to preclinical research. In 2025, the FDA announced a phased transition toward New Approach Methodologies (NAMs)—innovative alternatives such as computational modeling and lab-grown human tissues. These emerging tools aim to reduce reliance on animal models while enhancing scientific precision and aligning with international efforts to adopt more humane, sustainable research practices.[10] Together, these regulatory measures and evolving policies demonstrate a commitment not only to ensuring the safety and efficacy of xenotransplantation but also to advancing a more ethical approaches for biomedical research.

These preliminary studies serve to test basic feasibility, immune responses, and organ compatibility in xenotransplantation. As the research progresses, subsequent phases typically involve non-human primates as recipients because their physiological and immunological systems closely resemble those of humans. This step is crucial as it allows researchers to more accurately predict potential outcomes and identify safety concerns that may arise in future human clinical trials, thereby improving the likelihood of success and patient safety.

Safety: Managing Infectious Risk for Human Health

Managing infectious risks in xenotransplantation is a critical and multifaceted challenge that requires stringent oversight and constant innovation.11 One major concern involves the health status of recipients: patients with multiple comorbidities are at increased risk of complications post-transplant, whereas those with isolated organ failure tend to have higher survival rates.12 A key risk in this context is xenozoonosis—the transmission of infectious agents, particularly retroviruses, from animals to humans. Although advances in genetic engineering have enabled the breeding of pathogen-free source animals, the threat persists, especially when pathogens remain undetectable during pre-transplant screening.13 Consequently, recipients

9 U.S. Food and Drug Administration, *Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans; Guidance for Industry*, CBER, 13.12.2016; U.S. Department of Health and Human Services, *PHS Guideline on Infectious Disease Issues in Xenotransplantation*, 19.1.2001 (updated 23.6.2022).

10 FDA, Roadmap to Reducing Animal Testing in Preclinical Safety Studies; Reuters, *US FDA to phase out animal testing in drug development.*

11 Public Health Service PHS Guideline on Infectious Disease Issues in Xenotransplantation, 19.1.2001, updated 23.6.2022;

12 Sorror MA, et al. Influence of comorbidities on outcome in 1102 patients with acute myeloid leukemia undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2024, 59: 115–123;

13 Denner J, Tönjes RR. Infection barriers to successful xenotransplantation focusing on porcine endogenous retroviruses. Clin Microbiol Rev 2012, 25: 318-343; Meije Y, Tönjes RR, Fishman JA. Retroviral restriction factors and infectious risk in xenotransplantation. Am J Transplant 2010, 10: 1240-1247.

must consent to lifelong monitoring and may face restrictions on movement, which can extend to family members and close contacts. To guide prevention and management strategies, expert recommendations—such as those from the Infectious Disease Community of Practice of the American Society of Transplantation—provide protocols for identifying, assessing, and mitigating infectious disease risks, particularly in trials involving swine-derived grafts.14

Effective risk management also depends on robust regulatory and procedural frameworks. The FDA outlines specific criteria for the selection and maintenance of source animals, including breeding in closed colonies, microbiological screening to exclude pathogens dangerous to humans or immunocompromised individuals, environmental surveillance, and the storage of biological samples for future testing. Of particular concern are pathogens with long incubation periods that may go undetected at the time of transplantation.

In parallel, pharmacovigilance must be integrated from the preclinical phase onward, following its core components: detection, assessment, understanding, and prevention of adverse effects. Implementing these systems early allows for timely identification and response to risks affecting both animal models and potential human recipients, thereby preserving the integrity of xenotransplantation trials. Oversight of these trials must be carried out by institutional review boards and research ethics committees, which—though not necessarily state-run—must be independent, publicly recognized bodies with the authority to evaluate protocols comprehensively. Their responsibilities include preemptive scientific and ethical assessments, continuous monitoring, and ensuring compliance with established timelines and standards. Benchmarking their evaluations against internationally accepted best practices helps ensure that xenotransplantation research proceeds safely, ethically, and transparently, with a clear commitment to protecting individual and public health.

In early 2025, a biotech company called United Therapeutics announced that it had received the green light from the FDA for its gene-edited pig kidneys trial, with plans to perform six transplants by the summer and with the ambicious intent of reaching the number of fifty patients.[15]

2. The Ethics of Crossing Boundaries: Animal Use, Human Identity, and Patient Rights

Ethical Issues in Animal-Based Trials

Beyond assessing clinical efficacy, both preclinical and clinical xenotransplantation trials must be firmly grounded in comprehensive ethical evaluation. This ethical scrutiny extends beyond the scientific justification for using animal models, encompassing the standards of care, housing, and overall welfare provided to research animals. Ensuring humane treatment involves routine

14 Mehta SA, Saharia KK, Nellore A, Blumberg EA, Fishman JA. Infection and clinical xenotransplantation: Guidance from the Infectious Disease Community of Practice of the American Society of Transplantation. *Am J Transplant* 2023, 23(3): 309–315.

15 United Therapeutics Corporation. *FDA clearance of Investigational New Drug application for UKidney™ clinical trial*. 3.2.2025; Healey N. *World-first pig kidney trials mark turning point for xenotransplantation*. Nature Medicine, 18.3.2025; *We need this*: Pig-to-human kidney transplants enter clinical trials, Healio, 27.6.2025; Successful pig-to-human xenotransplant paves the way for clinical trials. Kidney News, 27.6.2025.

environmental monitoring, appropriate living conditions for laboratory herds, individualized risk assessments, and attention to the broader public health implications of such research. These considerations reflect the complex nature of ethics in xenotransplantation.

Philosopher Bernard Rollin's concept of minimal moral standing is particularly relevant in this context. According to this principle, animals bred specifically for research purposes—such as those used in xenotransplantation—are entitled to a basic level of moral consideration. This implies a duty to minimize their suffering, promote their welfare, and treat them humanely, even within the constraints of scientific investigation. It also involves the use of enriched environments, the least invasive procedures possible, and a broader respect for the sentience of these animals.[16]

However, this raises a deeper ethical tension: while animals do not possess legal rights and are protected primarily through welfare standards rather than rights-based frameworks, we often apply human-centered concepts of "humane treatment" to their care. It is therefore questionable whether it is truly appropriate or sufficient to impose standards derived from human ethics onto beings that lack legal personhood. Moreover, in the context of xenotransplantation, many animals are bred and kept alive explicitly for utilitarian purposes. As such, animals are utilized as subordinated beings relative to humans, precisely because of their instrumental role in clinical trials. The notion of treating these animals "humanely" often reflects a minimal ethical concession that does not fully address the fundamental moral conflicts inherent in their use.

Ethically, it cannot be overlooked that animals intrinsically may have the potential to be recognized as rights holders, and not merely subjects of welfare considerations. This perspective invites reflection on whether it is conceivable to envision a future in which animals are granted legal rights that would exclude their use in clinical trials. Such a shift could encourage the development and preferential use of laboratory-created beings with utilitarian purposes, potentially redefining the ethical landscape of biomedical research.

Ethical and Societal Perspectives on Chimeras and Hybrids

Expanding on ethical concerns about using animals in trials, the creation of hybrids and chimeras presents a complex alternative that challenges traditional boundaries and sparks new debates in ethics, law, and science. Being a combination of human and non-human DNA, hybrids and chimeras are among the most controversial topics in bioethics, raising questions about the boundaries of human identity. Although definitions remain debated, both terms have recognizable features: a hybrid typically results from combining a human cell nucleus with an animal egg, while a chimera involves the coexistence of human and animal cells within the same organism, often from early embryonic fusion. This definitional ambiguity complicates regulatory frameworks and ethical interpretation.[17] The EU-funded CHIMBRIDS project extends the definition further, suggesting that simply hosting cells from two organisms in one body qualifies as a

16 Rollin B, *Animal Rights and Human Morality*, 1st ed, Prometheus Books, Buffalo, New York.

17 Bokota S. *Defining human-animal chimeras and hybrids: A comparison of legal systems and natural sciences*, Ethics & Bioethics (in Central Europe) 2021, 11(1–2): 101–114.

chimera—raising regulatory concerns if, for instance, heterograft recipients are included.[18]

A related development is human embryoids, created from pluripotent stem cells to model embryo-like growth.[19] Though promising for research, they intensify the need for regulatory standardization. The EU allows in vitro research with no intent of implantation,[20] while in vivo development is largely prohibited due to risks to human dignity. Implanting such embryos—whether into an animal or human womb—is the most controversial aspect, with artificial wombs potentially offering a less ethically problematic alternative. Hybrids and chimeras could provide a limitless source of cells and tissues for transplantation and regenerative therapies. Genetic engineering allows scientists to create these organisms in vitro and derive embryonic stem cells, useful for studying mutations, developing therapies for diseases such as neurodegenerative diseases, and advancing personalized medicine. Still, ethical concerns persist, especially regarding the potential of therapeutic human cloning, with most arguments currently weighing against it.

While in vitro development with no implantation may not violate human dignity, the in vivo transfer raises questions of both human and animal welfare. Given that hybrids and chimeras contain human genetic material, their moral status is debated. Even if not violating human dignity directly, their creation could challenge the integrity and protection of animals. Though "animal dignity" is not a legally recognized concept, it is increasingly discussed through the lens of animal welfare.

If such beings were born, their legal and moral classification would present new ethical challenges. It would be necessary to consider whether they should be recognized as persons or if a new legal and moral status should be created for them. Central to this debate are questions of language, identity, cognitive ability, and appearance. The choice of pronouns—using “he” or “she” instead of “it”—reflects a broader societal discussion on how value and identity are attributed. The ability to self-determine might serve as one possible standard for personhood; however, many humans, such as those with severe physical or mental disabilities, are fully recognized members of society despite lacking self-determination. Applying this criterion exclusively to hybrids would therefore be discriminatory. Appearance further complicates the matter, since a being that looks more human may be more socially accepted, even with limited autonomy, while a being with greater cognitive capacities but more animal-like features might not receive the same recognition. Assigning legal and moral status to hybrids and chimeras challenges current ethical frameworks, which may need to be rethought based on multiple values—including appearance, genetic proximity, and cognition—rather than a single criterion. The underlying issue involves not only how these beings would exist biologically, but also how they would be perceived socially and legally in a world centered on humans.

Consent, Compassionate Use, and Organ Distribution: Ethical Reflections on Patient Autonomy

Informed consent, the right to withdraw, moral dissent, and the balance between individual autonomy and collective welfare are central concerns. Although organ allocation is primarily governed by law, ethical and psychosocial

18 Cordis, *EU funds project on chimera and hybrid research*. 19.6.2007.

19 Iltis AS, Koster G, Reeves E, Matthews KRW. Ethical, legal, regulatory, and policy issues concerning embryoids: a systematic review of the literature. *Stem Cell Research & Therapy* 2022, 13(1): 1–13; Nicolas P, Etoc F, Brivanlou AH. The ethics of human-embryoids model: a call for consistency. *Journal of Molecular Medicine* 2021, 99(4): 569–579.

20 European Parliament, Council of Europe, Use of human embryos and foetuses in scientific research, Recommendation 1100 (1989); Council of the European Union. *Council adopts new rules on substances of human origin*. 27.5.2024.

evaluations play a crucial role in determining eligibility, aiming to prioritize not only those without alternatives but also those likely to benefit significantly in terms of quality of life.

In standard allotransplantation procedures, organ distribution is grounded in three foundational principles: justice, medical utility, and respect for persons.[21] The principle of justice relates to fairness in both the distribution of organs and the evaluation of candidates. Key factors include medical urgency, time on the waiting list, compatibility likelihood, age, and geographical proximity to the donor hospital. In addition, whether the patient is undergoing a first or repeat transplant is also ethically relevant. The principle of medical utility encompasses both objective and subjective dimensions. Objectively, it seeks to maximize the total number of successful transplants performed. Subjectively, it evaluates the recipient's post-transplant life expectancy, integrating considerations of quality and length of life. This principle intersects with concepts from health economics, particularly cost-utility analysis, which incorporates both the *beneficence* of prolonging life and the *non-maleficence* of avoiding harm. It also aligns with utilitarian ethics, which prioritize outcomes and aim to maximize overall benefit.[22] The third principle, respect for persons, reflects the obligation to treat individuals as ends in themselves. This includes upholding their autonomy, valuing their informed preferences, and enabling meaningful self-determination in medical decision-making. These ethical principles are already embedded in allotransplantation systems and should be extended to guide xenotransplantation practices. However, new ethical tensions may emerge, raising the question of whether additional or modified principles are needed.

For instance, when a xenograft represents the only medically viable option for a given patient, its use may be ethically justified under principles of beneficence and medical necessity. This scenario opens to broader ethical considerations surrounding the compassionate use of medical treatments that are still experimental or under clinical trial. While it may offer hope to patients in critical conditions, it also raises complex questions about risk-benefit assessment, informed consent, regulatory oversight, and equity of access. In the case of xenotransplantation, its potential use under compassionate grounds requires careful ethical scrutiny, particularly given the uncertainties surrounding safety, efficacy, and long-term outcomes. Equally important is the psychological and emotional condition of the patient. Facing a life-threatening illness, an individual might feel compelled to accept a highly experimental and invasive procedure out of desperation, even when the expected benefits are marginal. In such cases, it becomes necessary to question whether the patient's consent is truly autonomous or merely the product of fear and limited options. This calls for the careful involvement of ethics committees and

21 OPTN Ethics Committee. Ethical Principles in the Allocation of Human Organs. IntechOpen, 2019: 3-10; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 1979.

22 National Institute for Health and Care Excellence (NICE). *Glossary: Utility*.; Organ Procurement and Transplantation Network (OPTN), *Ethical Principles in the Allocation of Human Organs.*

the implementation of psychological assessments tailored to the patient's situation.

The issue of consent becomes even more complex when considering the use of brain-dead individuals in early xenotransplantation procedures. A brain-dead individual cannot, by definition, provide contemporaneous informed consent. Therefore, the process must rely on prior expressions of will. The most formal mechanism is the use of advance directives, which—depending on the jurisdiction—may or may not be legally binding. Even where such directives exist, healthcare providers are not necessarily obligated to follow them if the procedure is deemed non-beneficial. In such cases, the legal representative is tasked with acting in the patient's best interest. It is ethically preferable that consent for such an intervention be obtained from a fully competent and alert patient, capable of making an informed decision based on clear medical advice. Yet, when the prospect of survival is extremely limited, patients or their families may accept high-risk procedures in hopes of even brief life extension. Ethical, psychological, and medical evaluations are therefore essential to ensure that decisions are made responsibly and without coercion. In some situations, patients may have informally expressed their willingness to participate in experimental treatments. While ethically relevant, such informal statements are often not legally binding. As a result, healthcare providers and legal representatives may hesitate to act on them, especially in high-risk contexts. When no preferences are known, proceeding with experimental xenotransplantation in a brain-dead individual raises serious ethical and legal challenges. In jurisdictions where diminished autonomy still carries legal protections, such interventions could be seen as involuntary medical treatment, violating both ethical and human rights standards. There is, however, one scenario in which the use of xenografts in brain-dead patients may be ethically defensible: when used to sustain organ function temporarily for the purpose of allograft donation. In these cases, a xenograft could preserve the viability of transplantable organs until they are retrieved for recipients. If the deceased had previously consented to organ donation and to extraordinary measures to support that intention, the temporary use of xenografts could be considered consistent with their wishes. This approach mirrors current practices in allotransplantation, where life-support is maintained post-mortem until the donation process is complete.

The possibility of choosing between an allograft and a xenograft raises further ethical considerations, particularly in relation to patient perception and preference. While xenografts—especially those derived from genetically modified animals—may be clinically equivalent to human allografts, their animal origin could carry significant psychological, cultural, or ethical implications for some patients. This potential reluctance raises the question of whether it might be ethically permissible—or even advisable—to introduce forms of incentive or compensation to encourage acceptance of xenografts. Such a strategy should be designed to guarantee patient autonomy, avoiding undue inducement.

Throughout the selection process, additional factors may influence eligibility. These include the patient’s behavioral reliability, such as the absence of a history of recklessness or negligence that could compromise adherence to clinical protocols. Infact, beyond initial consent, the right to withdraw consent before or after the procedure warrants careful evaluation. Patients must be thoroughly informed by physicians about all potential outcomes and necessary steps to maintain control over the treatment process. It is important to clarify the boundary between patient autonomy and the physician’s responsibility. While patients cannot be forced to undergo the procedure without consent, withdrawing consent after implantation of the xenograft raises complex questions about which medical acts are being refused. If a patient demands graft removal, medical, psychological, and ethical evaluations are essential to navigate potential controversies. Moreover, the patient and their family must be willing to engage in continuous consultation before, during, and after the procedure, demonstrating a clear commitment to follow safety protocols and long-term treatment plans.

In allotransplantation, recipients are already required to adopt strict lifestyle modifications to protect both their health and the graft. Xenotransplantation introduces an additional layer of complexity: the potential risk to public health.

This elevates the ethical stakes, requiring even stricter adherence to safety protocols and raising the controversial possibility of using background checks to assess a patient's likely compliance. While such evaluations might seem justified by the need to prevent harm, they raise serious ethical concerns. They risk infringing on human dignity by relying on assumptions that past behavior determines future conduct, which could unfairly exclude individuals from accessing potentially life-saving treatment. Such exclusions may ultimately amount to discrimination, undermining the principle of equal access to care.

3. *Xenotransplantation and Legal Diversity: Navigating Global Regulatory Landscapes*

The Role of IXA and WHO in Shaping Xenotransplantation Governance

State's regulations on the topic of xenotransplantation have been particularly fragmented and haven't addressed every side of the issue in an holistic way. Undoubtedly, WHO has played a crucial role on the development of the topic of xenotransplantation, together with other international entities such as the IXA and the Transplantation Society. Their combined contribution has been considered the common ground on which state's regulations have been standing. However, standardization is a priority that is now taking nearly two decades to develop. Legally speaking, the topic is addressed both directly and indirectly by soft law sources, as well as guidelines and regulations. It is interesting to assess how IXA and WHO contribution intersected troughout the years and also trace the key milestones that have shaped the discourse on xenotransplantation over the years.

In 2003, IXA's Ethics Committee published a contribution aimed to point out requirements of adequate preclinical data, as well as proper oversight by competent authorities and approval by specific institutional bodies in charge of ethical overseeing over human research and animal welfare.[23]

In 2001 and 2004, the WHO called on the international community to address the risks associated with xenotransplantation by publishing the *Guidance on Xenogenic Infection/Disease Surveillance and Response*.[24] This document aimed to promote debate and foster coordination and cooperation on a global scale. It emphasized the need for regulation to prevent zoonotic infections and highlighted the importance of surveillance through data collection, registries, and effective communication within a multi-level international network. Notably, the annexes include a glossary, sample forms and reports, and indicators for evaluating the network. While the Guidance sought to promote harmonized regulation, a global standardization of practices remains urgently needed to ensure safety, ethical consistency, and legal clarity.[25]

23 Sykes M, d'Apice A, Sandrin M; IXA Ethics Committee. Position paper of the Ethics Committee of the International Xenotransplantation Association. Xenotransplantation 2003, 10: 194-203; Menell J, Allison M, Wolf L. Regulatory aspects of clinical xenotransplantation. *Xenotransplantation* 2015, 22:?205-13.

24 World Health Organization, *Guidance on Xenogeneic Infection/Disease Surveillance and Response: a strategy for international cooperation and coordination*, WHO, Geneva, 2001.

25 WHO. Guidance on Xenogeneic Infection/Disease Surveillance and Response: A

In 2008, the WHO, together with the IXA, the Chinese Ministry of Health, and the University of South China, launched a global consultation on clinical xenotransplantation. This collaboration produced three key documents (2008, 2011, 2018) shaping international ethical and regulatory guidelines. The 2008 consultation outlined general principles and specific recommendations for WHO, Member States, and researchers.[26] It recognized xenotransplantation as a potential solution to organ shortages but emphasized strict controls, thorough scientific and ethical review, public engagement, lifelong patient monitoring, and international data sharing. WHO was urged to coordinate global efforts and infectious risk management. Member States were encouraged to regulate and inform the public, banning unsafe practices if necessary. Investigators had to ensure biosafety, provide solid trial justifications, and plan long-term follow-up. Patient selection required no alternative treatments and fully informed, compliant candidates.

The 2011 consultation had three primary objectives: to review the current state of science and clinical practice in xenotransplantation, to assess the need for revisions to existing guidance, and to refine strategies for the surveillance, prevention, and management of infectious risks.[27] A key concern was the persistence of unregulated trials, some of which had disregarded previous recommendations. While the principles laid out in 2008 were reaffirmed as sufficient to protect public health, this second consultation reinforced the urgency for the WHO to promote ongoing international collaboration, transparency, and periodic reassessment of practices. It also recommended that Member States, sponsors, and investigators pursue greater consistency with best available standards, address misinformation, and rely on independent, experienced laboratories to ensure quality and credibility. Overall, this second phase maintained continuity with the initial framework, while encouraging improvements in clinical trial design and promoting a more integrated, globally coordinated approach to xenotransplantation.

The 2018 consultation marked the third and most technical iteration of this global process.[28] Its primary goal was to revisit the scientific and regulatory status of xenotransplantation and to update consensus-based recommendations for infectious disease control in preparation for upcoming trials. The 2018 consultation was organized into expert panels and six specialized working groups, which revised and expanded the "Principles and Recommendations" of the original Consultation. These groups covered a wide range of topics, including xenozoonosis, regulatory frameworks, biorepositories, genetically modified pig facilities, biomaterials, and immunosuppression strategies. Key discussions addressed emerging issues such as new technologies in gene editing, donor animal herd management, legal developments across jurisdictions, and practical

Strategy for International Cooperation and Coordination.

26 World Health Organization, *First WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, China, 19–21 November?2008: the Changsha Communiqué*, WHO, Geneva, 2008.

27 World Health Organization, *Second WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials*, Geneva, 2011.

28 World Health Organization, Third *WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials*, Geneva, 2018.

aspects of trial applications. Particular attention was given to developing protocols for xenotransplantation of islet cells, corneas, and kidneys. During the consultation, progress in cell and tissue xenotransplantation was discussed, highlighting the move toward early-phase clinical trials and emphasizing core ethical standards such as respect for persons, beneficence, justice, lack of alternative treatments, justified immunosuppression, strong preclinical evidence, community safety, and rigorous donor animal biosecurity. The infrastructure and microbiological controls for genetically modified pigs were reviewed, showcasing facilities in several countries. Regulatory frameworks were clarified, including definitions of xenotransplantation products and oversight pathways that vary based on product type and development stage, with particular attention to the risks of genetically modified donor animals. Public health emergency reporting, disease surveillance, and recipient monitoring systems were also covered, along with discussion of specific viral infections and the introduction of Prevymis, a novel antiviral drug in development at that time.

Overall, these three consultations laid a foundation for the ethical and legal governance of xenotransplantation at the global level. While the 2008 consultation provided a conceptual and regulatory baseline, the 2011 and 2018 meetings progressively expanded the technical depth and scope of guidance, reflecting the evolving scientific landscape and reinforcing the need for coordinated international standards to ensure both patient safety and ethical integrity.

Regulatory Sources Overview

In the US, the main regulatory bodies overseeing xenotransplantation are the FDA and the Centers for Medicare and Medicaid Services. The FDA offers various online resources related to xenotransplantation, including two key Guidance documents from the Center for Biologics Evaluation and Research (CBER).[29] CBER's jurisdiction covers allergenics, blood and blood products, cellular and gene therapies, tissue-based products, vaccines, and xenotransplantation products. Notably, the FDA issued the Public Health Service Guidance "Infectious Disease Issues in Xenotransplantation" (2001) and the "Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans" Guidance for Industry (2016). Additionally, in 2009, the FDA released a Guidance for Industry titled "Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach." The FDA also runs the Expanded Access Program, often called compassionate use, which allows patients with life-threatening conditions to access investigational medical products. Another important body is the Cellular, Tissue, and Gene Therapies Advisory Committee, which evaluates data on the safety, effectiveness, and appropriate use of human cells, tissues, gene therapies, and xenotransplantation products intended for transplantation, implantation, infusion, or gene transfer in disease treatment as well as tissue repair and reconstruction. FDA guidance on xenotransplantation regulates from initial considerations related to animal welfare and surveillance, to development to production of xenograft in the States, and also regulates related

29 Hawthorne WJ. Ethical and legislative advances in xenotransplantation for clinical translation: focusing on cardiac, kidney and islet cell xenotransplantation. *Front Immunol* 2024.

clinical investigations in the Country. On the other hand, the institutions like the Institutional Animal Care and Use Committee, on the other hand, regulate the side that has to do with animal welfare, from the selection, the housing in specialized facilities and the constant monitoring in order to prevent the spread of diseases and to guarantee the positive results of all phases of the procedure. Even sample storage holds its own differences throughout the Countries, since the US requires fifty years, whereas the UK requires thirty years.

Within the European Union, the European Medicines Agency (EMA) classifies xenogeneic cell therapy products as Advanced Therapy Medicinal Products (ATMP).[30] ATMPs are the focus of two Guidances, one on Gene Therapy medicinal products, the other one on Cell-therapy and tissue engineering. These fall under Regulation 1394/2007, which covers their authorization, supervision, pharmacovigilance, risk management, and addresses combination products. On the whole, clinical trials in the EU are regulated by Regulation No. 536/2014. In addition, several directives are relevant in this context: Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms; Directive 2001/83/EC on the Community code for medicinal products for human use; Directive 2001/20/EC on good clinical practice in the field of ATMPs; and Directive 2009/41/EC on the contained use of genetically modified microorganisms. Also applicable are Directive 2005/28/EC, concerning good clinical practice for investigational products and manufacturing/import authorization, and Directive 2006/86/EC, which implements Directive 2004/23/EC with respect to traceability requirements, notification of serious adverse reactions and events, and technical specifications for the coding, processing, preservation, storage, and distribution of human tissues and cells.

On the other hand, the Council of Europe's 2003 report on the state of the art in this field led to Recommendation (2003)10 which set out strict ethical and regulatory guidelines for xenotransplantation, urging a precautionary approach due to unknown infectious risks. It emphasized long-term recipient monitoring, animal welfare, and international cooperation. The text also reinforced the importance of informed consent and public health protection. Equally significant are the Declaration of Istanbul on Organ Trafficking and Transplant Tourism (2018), and the Convention on Human Rights and Biomedicine (Oviedo Convention, 1997), which addresses the protection of human rights and dignity in the application of biology and medicine.

In Switzerland, the Federal Law on the Transplantation of Organs, Tissues and Cells (2004), known as the Transplantation Act, explicitly includes grafts of animal origin in its definition of transplant products.[31] These are described as "products manufactured from human or animal organs, tissue or cells that can be standardized or whose manufacturing process can be standardized," and require authorization from the competent regulatory authority.

In China, the regulatory body responsible is the Chinese FDA. Organ donations saw a sharp decline after the World Medical Association (WMA) urged China to end the widespread practice of procuring

30 European Medicines Agency. *Advanced Therapy Medicinal Products: Overview*. EMA, London, 2025.

31 Swiss Confederation. Federal Act on the Transplantation of Organs, Tissues and Cells (Transplantation Act). Fedlex, 810.21, 1.7.2007.

organs from executed prisoners without consent—a practice that had long been the country's primary organ source. Its discontinuation significantly reduced the availability of organs for allotransplantation. Nevertheless, the Chinese public responded positively to the shortage, with the Red Cross Society of China reporting a notable rise in registered donors. At the same time, the People's Republic of China continues to explore xenotransplantation as a potential solution to its organ shortage.[32]

Conclusions

The advancements in xenotransplantation represent a significant breakthrough in addressing the critical shortage of human donor organs. Xenografts offer a promising solution by utilizing animals bred specifically for transplantation, providing a more abundant and readily available source of organs due to their rapid reproduction rates and biological similarities to humans. Genetic modifications, empowered by precise gene-editing tools such as CRISPR, are revolutionizing the transplant paradigm—shifting the focus from suppressing the recipient's immune system toward tailoring donor organs to improve compatibility, reduce rejection, and minimize risks such as retroviral infections.

These scientific achievements have already translated into notable clinical milestones, despite ongoing challenges like immune rejection and zoonotic risks. Furthermore, xenotransplantation may alleviate logistical hurdles in organ donation by maintaining essential bodily functions in recipients through xenografts, thereby increasing flexibility in organ procurement and potentially enhancing transplant success rates.

However, the promise of xenotransplantation also brings complex ethical and regulatory concerns. While expanding legal organ availability could reduce dependence on illicit organ markets and transplant tourism, there is a risk that unregulated xenotransplant clinics, particularly in regions with weaker oversight, could foster new forms of medical tourism linked to health risks and ethical violations. Thus, comprehensive and coordinated international regulatory frameworks are essential. Such frameworks should include rigorous monitoring of donor animal health, transparent eligibility criteria for recipients, and global governance mechanisms designed to safeguard patient safety, ensure equitable access, and prevent exploitation.

Moving forward, xenotransplantation requires continued interdisciplinary collaboration across genetic engineering, immunology, infectious disease control, ethics, and law. By integrating robust scientific innovation with ethical responsibility and regulatory vigilance, xenotransplantation has the potential not only to save countless lives but also to redefine the future of transplantation medicine and global health.

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