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Short Communication

The bioethics of ex vivo gene therapy in organ transplantation

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Abstract

Ex vivo gene therapy in organ transplantation represents a transformative convergence of molecular medicine, transplantation science, and bioethics. By genetically modifying donor organs or recipient immune cells, this approach seeks to reduce ischemia–reperfusion injury, improve graft survival, and mitigate immune rejection. Recent advances in gene editing, particularly the use of CRISPR-Cas9, and the successful development of bioengineered organs for xenotransplantation have brought *ex vivo* gene therapy to the threshold of first-in-human clinical trials. However, the promise of these technologies is tempered by profound ethical challenges. The lack of comprehensive long-term preclinical data complicates the scientific justification for first-in-human experimentation, creating challenges in determining when clinical trials can responsibly proceed. The question of *'Informed consent'* becomes invariably complex under conditions of uncertainty, necessitating an iterative, staged approach to communication that explicitly acknowledges both known and unknown risks. Broader questions of justice and equity arise concerning accessibility, affordability, availability, and cultural acceptability, predominantly in contexts where novel costly biotechnologies risk widening disparities in transplantation medicine. Medical ethics traditions ranging from principlism and deontology to communitarian and care ethics offer differing lenses, but no single framework fully addresses the pluralism of values involved in the realm of gene therapy in transplant practice. In conclusion, the integration of gene therapy into transplantation must be guided by transparent oversight, proportional risk–benefit assessment, and respect for participants who assume early research burdens. This perspective article stresses upon the need for sustained dialogue among clinicians, ethicists, regulators, and society to ensure that innovation in transplantation advances not only scientific frontiers but also ethical responsibility.

Keywords: Bioethics, Gene therapy, Organ transplantation, Transplantation ethics

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1. Introduction

Gene therapy is a biomedical approach that employs genetic material to treat, prevent, or potentially cure human diseases. It operates by introducing functional copies of defective genes or by replacing missing or mutated genes with healthy counterparts at the cellular level, through methods such as gene transfer or genome editing. This therapeutic strategy has been investigated in both inherited disorders, such as cystic fibrosis and Duchenne muscular dystrophy, and acquired diseases, such as certain forms of lymphoma and melanoma.[1]

While the idea of genome modification emerged soon after the discovery of DNA, the concept of gene therapy gained traction in the 1970s with advances in recombinant DNA technology, enabling the prospect of correcting genetic disorders at their molecular source. The first approved clinical trial was conducted in 1990, when a patient with adenosine deaminase deficiency–related severe combined immunodeficiency (ADA-SCID) received functional gene copies delivered via retroviral vectors. This early progress was hindered by significant safety setbacks, including vector-related hepatotoxicity and insertional mutagenesis observed in the late 1990s and early 2000s. Subsequent innovations in vector systems, particularly the development of adeno-associated viral (AAV) and lentiviral vectors, substantially improved safety and therapeutic efficacy of 'molecular surgery'. The emergence of genome-editing platforms such as zinc-finger nucleases, Transcription activator-like effector nuclease (TALENs), and especially Clustered regularly interspaced short palindromic repeats (CRISPR)-associated nuclease Cas9 further transformed the field by enabling precise gene editing. Today, gene therapy has advanced from

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preclinical studies to precision medicine reality, with regulatory approval of therapies such as Luxturna for inherited retinal dystrophy and Zolgensma for spinal muscular atrophy.[2]

The global burden of end-stage organ failure has intensified the reliance on transplantation, yet the persistent disparity between organ demand and availability remains a critical barrier. In addition, donor organs are frequently compromised by ischemia–reperfusion injury and other preservation-related insults, reducing their salvageability and long-term viability. Given the high cost, complexity, and risk associated with transplantation, there has been sustained interest in strategies that enhance graft tolerance and function. Beyond conventional immunosuppressive regimens, emerging modalities such as immunoisolation, targeted immunomodulation, and ex vivo genetic interventions like gene therapy are being strongly researched to mitigate acute rejection and improve overall graft outcomes.[3]

Ex vivo gene therapy in transplantation includes genetic modification of donor organs using both viral (e.g., adenoviral, lentiviral, AAV) and non-viral vectors (e.g., lipid nanoparticles, electroporation, plasmid DNA) during machine perfusion to improve preservation and reduce rejection , engineering of recipient immune cells such as regulatory T cells (CAR Tregs) to induce tolerance , genome editing of xenogeneic organs (e.g., porcine) to eliminate antigenic epitopes and add human-compatible genes , and RNA-based approaches that deliver mRNA or siRNA ex vivo (often via lipid nanoparticles or electroporation) for transient protective effects . As of mid-2025, ex vivo gene therapy for solid organ transplantation is in early clinical stages with trials underway for kidneys and liver alongside strong preclinical readiness for lung.[4]

There are several schools of thought in medical ethics that guide decision-making in healthcare. Deontological ethics concentrates on duties and rules, judging actions right if they follow moral principles, while consequentialist (utilitarian) ethics gives importance to outcomes, aiming to maximize benefits for maximum stakeholders. Virtue ethics emphasizes the moral character of the healthcare professional, encouraging traits like compassion and honesty. The widely used principlism approach works on the four pillars of autonomy, beneficence, non-maleficence, and justice. Casuistry uses case-based reasoning, drawing parallels to established precedents, whereas care ethics emphasizes empathy, relationships, and the patient's lived experience. Finally, communitarian ethics prioritizes the well-being and values of the community over individual preferences. In practice, modern medical ethics often blends these schools to balance individual rights, professional integrity, and societal needs.[5]

Ex vivo gene therapy applied to organ transplantation represents one of the most ambitious frontiers of modern medicine, holding promise for addressing the global shortage of transplantable organs. However, the ethical challenges it raises extend far beyond laboratory science. They touch upon fundamental principles of autonomy, beneficence, non-maleficence, and justice, while also demanding careful consideration of accessibility, availability, affordability, and acceptability within diverse sociocultural contexts. Decisions in this field are rarely black-and-white; they exist in grey zones involving multiple stakeholders—patients, families, clinicians, researchers, funding bodies, policymakers, and society at large. Ethical pluralism reminds us that no single model (including principlism) fully captures the complexities at stake. To better understand these issues, framing them in a dialectical question-and-answer mode allows iterative exploration, where each inquiry may generate further questions rather than definitive answers.[6] It is important to clarify that the present discourse focuses solely on the ethical considerations surrounding the use of ex vivo gene therapy in organ transplantation, and does not engage with the scientific nuances or procedural aspects of the technique.

2. Framed Ethical Questions

2.1. Clinical and scientific justification

1. *Within current levels of scientific knowledge, is it ethically justified for a transplant surgeon to recommend transplantation with a bioengineered, ex vivo gene-edited organ even in the form of a clinical trial?*

The answer is in affirmative only if there's a defensible prospect of benefit, scientifically grounded rationale, and independent regulatory oversight. First-in-human (FIH) transplantation with bioengineered or gene-edited organs can be ethically offered only as research, under the institutional review board's (IRB) sanction, with transparency that it is experimental and death-causing complications are possible. The Miller–Truog analysis reminds us clearly that transplantation already sits on contested moral ground about causing death.[7]

Given the inherent complexity and relatively unpredictable success rates of even well-matched traditional organ transplantation procedures, the ethical calculus becomes more nuanced when introducing ex vivo gene therapy. In cases where long-term risks remain indeterminate and the transplant surgeon cannot reasonably anticipate all downstream complications, the question of whether such an intervention offers a net benefit to the altruistic clinical trial recipient as compared to conventional transplantation remains unresolved. At present, the authors acknowledges that the evidentiary threshold required to justify this added layer of intervention, particularly in the absence of robust longitudinal data, has not been met. However, as stated elsewhere in the manuscript, certain trials commenced in 2025, and the only fair characterization is that they represent 'an elegant experiment in uncertainty, equally capable of curing rejection or rejecting common sense'.

2. *Should first-in-human studies proceed when risks are uncertain, or must alternative models (animal, in vitro, AI simulations) be exhausted first?*

While the precautionary principle may advocate for strict restraint, contemporary ethical frameworks offer a more calibrated approach. Under current standards, it is sufficient to demonstrate to an Institutional Review Board (IRB) that the risks are reasonable in relation to the anticipated benefits, and that human exposure is scientifically justified. Ethical guidance for first-in-human (FIH) trials permits initiation when preclinical evidence is robust, alternative methodologies have been reasonably exhausted; including a critical stance against the *'framing of gene manipulation as a universal solution'*, and when clear protocols for monitoring, adverse event reporting, and trial termination are in place. Ethics does not demand indefinite reliance on animal, in vitro, or AI-based testing; rather, it requires a reasonable prospect of benefit and a minimization of foreseeable risk prior to human exposure. This approach is consistent with foundational principles articulated in the Declaration of Helsinki and other international standards governing human research ethics.[8]

3. Informed Consent

1. *To what extent must a donor or their proxy be informed about the genetic engineering of the organ to be transplanted, and does incomplete knowledge undermine valid consent?*

   All material features must be explained in plain language like the fact of editing, target genes, uncertainties (graft behavior, malignancy risk, off-target effects), and data-sharing/surveillance plans. Consent is valid only if the *material* facts and uncertainties are disclosed even when mechanistic knowledge is incomplete as per the accepted global standard of a 'true informed consent'.

2. *How can truly informed consent be obtained from recipients if even the medical team lacks complete knowledge of long-term complications?*

   Yes, by foregrounding uncertainty as a core element of disclosure, the consent process must explicitly delineate the spectrum of knowns and unknowns; ideally progressing from known knowns to known unknowns, and finally to unknown unknowns. This includes transparent communication about anticipated risks, data use, and the burdens of monitoring. In this context, consent functions as an authorization under uncertainty, not an act of omniscience. It acknowledges that participants are making informed decisions within the limits of current scientific understanding. Moreover, the consent process in such scenarios should not be treated as a singular event, but rather as a dynamic continuum.[9] It must evolve over time through IRB-vetted language, with provisions for staged re-consent as new evidence emerges and risk–benefit profiles shift. This approach aligns with ethically sound practices in translational research and reinforces participant autonomy in the face of evolving knowledge.

3. *Is it necessary to disclose all known complications from prior gene therapy trials (including catastrophic failures), or only those deemed "material" to current decision-making?*

   It would be prudent to disclose prior *material* harms and near-misses, especially sentinel events (e.g., leukaemia after using retroviral vectors; the Gelsinger clinical trial death case) and connect them to how today's protocol mitigates analogous risks. It ensures that materiality is met and respects autonomy of the participant.

4. *Should the principle of "therapeutic misconception" and "therapeutic drift" be addressed explicitly, ensuring that patients understand participation as experimental rather than curative?*

   It has to be made clear to the recipient that the trial's primary aim is to generate knowledge, not guaranteed cure; this is a known pitfall in clinical research ethics and must be corrected during consent. At the same time, on the side of investigators, there should be no scope for therapeutic drift in the trial to prevent ethically permissible innovation into unacceptable risk.

4. Risk, Benefit, and Uncertainty

1. *If early recipients face unforeseeable complications or death, does 'beneficence' justify such risks for the sake of scientific progress and future patients?*

   Early deaths/serious harms can only be justified if they are proportional to the humanitarian importance of the problem and only after risk minimization. This mirrors classic research ethics: degree of risk must not exceed the problem's importance and must be independently reviewed. One has to stop or redesign trials if emerging harms outweigh value. Miller–Truog argue that life-saving tech often coexists with physician-caused death; ethical legitimacy demands forthrightness plus safeguards but not an outright denial.

2. *Do altruistic recipients who volunteer regardless of outcome provide sufficient ethical grounds for experimentation, or does societal responsibility extend further?*

   Altruism helps but isn't sufficient. Participant willingness doesn't erase institutional duties; society (via IRBs/regulators) must still ensure fair risk–benefit, scientific merit, and special protections against undue influence.

5. *Should oversight bodies establish mandatory "risk thresholds" below which human trials cannot ethically begin?*

Yes. Oversight bodies should specify entry criteria (preclinical efficacy/toxicology vs safety profile), risk ceilings (e.g., projected mortality/malignancy above which FIH cannot start), and explicit early-stopping boundaries reviewed by an independent Data Monitoring and Safety Board (DSMB).

5. Justice, Equity, and the 4 A's[10]

1. *How can **accessibility** be ensured so that trials are not limited to elite research hospitals in high-income countries?*

   To ensure such organ transplantation trials are accessible, multi-centric designs with capacity-building, transparent referral criteria, and publicly funded travel/support are required so that access is not limited to those with financial means or proximity to major centre. Allocation ethics in transplantation already presses for fair access.

2. *Will such therapies ever reach **availability** at scale, or are they destined to remain experimental for decades?*

   As of now the availability at scale is uncertain and there is a need to plan for staged diffusion. An ethical way of dealing things in this domain requires realistic promises, investment in manufacturability, and prospective access plans, not a mere hype surrounding it. Allocation frameworks from transplantation ethics can guide staged roll-out.

3. *If costs remain prohibitively high, how can **affordability** be addressed without deepening inequities in transplant medicine?*

   Affordability standards can be met by building value-based pricing, public funding, and coverage with evidence development. All efforts must be made to avoid mechanisms that entrench disparities in already scarce transplant domains.

4. *How can **acceptability** be assessed in societies with cultural, religious, or ethical objections to genetic manipulation and xenotransplantation?*

   It would be wise to engage communities well in advance; include cultural/religious advisors in protocol design; offer alternatives without penalty; and measure acceptability as an endpoint (decline reasons, perception surveys) before broad rollout of the project. The acceptability of xenotransplantation or bio-engineered organs may find greater cultural resonance in Eastern societies, where mythology includes examples of divine bodily transformations such as Narasimha, a deity with a lion's head and human body, or Lord Ganesha with an elephant's head. Western traditions also contain parallels, from classical myths of centaurs, mermaids, and the Minotaur to Christian notions of bodily renewal and resurrection, suggesting that both cultural spheres possess symbolic precedents for hybrid or altered bodies, though expressed in different ways.

5. *Do early trials risk exploiting socioeconomically vulnerable patients who lack access to conventional transplantation pathways?*

   The process should include measures to mitigate "no-option" desperation bias as the *sole* inclusion driver, providing independent patient advocates, and ensuring standard-of-care options are not withheld to increase enrolment.

6. Societal and Public Health Concerns

1. *Should recipients of gene-edited xenografts/allografts be subject to lifelong surveillance to monitor for zoonotic/genetic risks, and how does this balance with autonomy and privacy?*

   Yes, lifelong surveillance is an inevitable reality in this scenario and is ethically permissible if it is proportionate, scientifically justified, and consented to upfront. This includes clear disclosure of what is monitored, for how long, with whom data are shared, and the consequences of opting out. Given the potential risks of zoonosis and genetic complications, the establishment of durable registries is justified, provided they are governed by robust oversight mechanisms and adhere to principles of data minimization.

2. *Is it ethical to impose lifestyle restrictions (e.g., reproduction, travel, or disclosure duties) to safeguard public health?*

   Lifestyle limits (e.g., travel, reproduction, disclosure) require strong justification and least-restrictive means. They have to be imposed only when necessary to mitigate credible public-health risks, with time-limits and appeal pathways. e.g., targeted travel advisories or partner disclosure duties only when risk evidence supports them. These issues crop up in xenotransplantation scenarios and typically not in an ex vivo gene therapy case.

3. *How should communication with the public be managed to avoid hype, misinformation, or therapeutic misconception about "miracle cures"?*

   All communications must remain sober, transparent, and grounded in research. Any use of "miracle cure" language undermines the integrity and purpose of scientific discourse. Public communication should clearly articulate the specific elements of uncertainty, available alternatives, and the aims of the trial. Miscommunication in science can be as ethically damaging as unethical human experimentation.[11]

7. Animal and Environmental Ethics in the context of xenotransplantation

1. *To what extent is it ethical to genetically modify and use animals as organ sources, and how should their welfare be safeguarded?*

   The strongest argument in favour is its potential to save human lives, particularly by addressing deaths caused by critical shortages of donor organs. Conversely, critics caution that such practices risk commodifying sentient animals, drawing ethical parallels to factory farming—except here the stakes are higher, as the justification is explicitly tied to human survival.[12]

2. *Do gene-edited animal organ sources risk ecological consequences (e.g., genetic escape, zoonoses), and who bears responsibility for such risks?*

   Yes, there are ecological and zoonotic concerns in this arena. It is of utmost importance to assign clear responsibility, which requires biosecurity, containment, surveillance, and liability/response plans for genetic escape or zoonoses. At the same time, oversight bodies should define who bears post-trial obligations.[13]

8. Governance and Oversight[14]

1. *What independent oversight mechanisms—ethics boards, registries, or global treaties—are required to ensure transparency and accountability?*

   Independent, layered oversight is required which includes an IRB review, data safety monitoring, adverse-event registries, and public reporting. Transparency and accountability are core to contemporary human-subjects governance.

2. *Should international guidelines (e.g., WHO, IXA, Nuffield Council) be binding before clinical adoption proceeds?*

   International guidance should strongly inform practice; binding status depends on jurisdiction. In absence of binding treaties, the trial protocols should be in line with WHO/Helsinki declaration-style norms and specialty bodies; institutions should treat them as de facto requirements for ethical acceptability.

3. *Who should ultimately decide when the balance of risk and benefit justifies first-in-human trials: regulators, clinicians, patients, or society at large?*

Decision authority is shared between all the stakeholders. Regulators set floors; IRBs vet protocols; clinicians ensure clinical integrity; informed patients decide about participation; and society (via public policy) frames acceptable risk for first-in-human trials. This plural-governance model reflects modern research ethics.

The ethical permissibility of *ex vivo* gene therapy in organ transplantation can be rigorously assessed through the framework proposed by Emanuel, Wendler, and Grady, namely?:[15] value, scientific validity, fair subject selection, a favourable risk–benefit ratio, independent review, informed consent, and respect for enrolled subjects. Collectively, these requirements underscore that the pursuit of scientific innovation must be tethered to demonstrable clinical relevance, methodological robustness, equitable participation, proportionate risk management, and transparent oversight. Within this framework, informed consent and ongoing respect for participants remain indispensable, ensuring that those who assume the risks of early-phase research are neither misled nor marginalized.

Nevertheless, the distinct features of gene therapy necessitate heightened vigilance against recurring ethical vulnerabilities. The risk of therapeutic misconception, where participants mistakenly construe experimental interventions as established therapies, must be explicitly addressed through careful communication. Equally, therapeutic drift, in which investigational practices gradually blur into clinical norms without sufficient evidence, threatens both scientific validity and patient protection. Moreover, the danger of generating therapeutic orphans, populations systematically excluded from access to novel therapies due to socioeconomic, geographic, or cultural barriers, raises serious questions of justice and equity. A research agenda attentive to these concerns can ensure that *ex vivo* gene therapy in organ transplantation advances not only as a scientific milestone but also as an ethically sound contribution to the future of transplantation medicine.

9. Conflict of Interest

None to declare.

10. Financial Support

None.

11. Ethics Committee Approval

None.

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