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Research Article

Organ Transplantation: Current Challenges and Emerging Innovations across Preservation, Immunology and Xenotransplantation

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ABSTRACT

Background: Organ transplantation has evolved from a life-saving surgical intervention into a multidisciplinary field integrating immunology, bioengineering, and data science. Despite major advances in donor management, perioperative care, and immunosuppression, long-term outcomes remain constrained by a persistent global shortage of transplantable organs, ischemia-reperfusion injury, chronic rejection, and the toxicity of lifelong immunosuppression.

Objective: To synthesize contemporary evidence on the principal challenges facing organ transplantation and the innovations being deployed against them, spanning organ donation and allocation policy, ex vivo machine perfusion, immune monitoring and tolerance induction, and xenotransplantation.

Methods: A structured narrative review of the literature indexed in PubMed, Embase, and Scopus was performed, prioritizing randomized controlled trials, prospective multicenter registries, and current (2023-2026) systematic reviews and position papers, including recent International Xenotransplantation Association consensus statements and Lancet Commission publications. Domains reviewed included donation after circulatory death (DCD) and allocation policy, hypothermic and normothermic machine perfusion across liver, kidney, and heart transplantation, donor-derived cell-free DNA (dd-cfDNA) as a rejection biomarker, precision immunomodulation and tolerance-induction strategies, and clinical xenotransplantation.

Results: DCD donors accounted for approximately 23% of deceased donors globally in 2022, with markedly higher and rapidly rising utilization in the United States, Spain, and Belgium, and DCD recovery has risen across every major organ type in recent US national data. Machine perfusion trials show a consistent pattern: hypothermic oxygenated perfusion has most reliably improved clinically relevant outcomes such as delayed graft function and biliary complications, while normothermic perfusion, despite improving logistics, organ utilization, and early graft injury markers in liver transplantation (a 300-patient multicenter RCT), has not consistently translated into improved graft or patient survival, and a UK kidney RCT (n=338) found no reduction in delayed graft function with a brief period of normothermic perfusion. Donor-derived cell-free DNA has emerged as a validated, non-invasive rejection biomarker, achieving an AUC of 0.789 for biopsy-proven acute rejection in a multicenter kidney registry of 1,743 recipients, though performance varies by organ, timing, and surveillance versus for-cause context, and sensitivity in some surveillance settings has been reported as low as 0%. Precision immunomodulation strategies-regulatory T-cell therapy, tolerogenic dendritic cells, gene-edited cellular platforms, and biomarker-guided minimization-remain in early clinical development, with successful immunosuppression weaning reported only in small cohorts. Xenotransplantation has progressed rapidly since the first genetically modified pig heart transplant

in January 2022: as of late 2025, at least six pig kidney, two pig heart, and one pig liver compassionate-use or early-phase clinical cases have been reported, with the longest pig-to-human kidney survival now standing at 271 days under a regulated multicenter trial, alongside the initiation of the first formal multi-patient xenotransplantation clinical trials following FDA clearance in 2024-2025.

Conclusion: Organ transplantation is being reshaped simultaneously along four fronts-expanded donation strategies, *ex vivo* organ reconditioning, non-invasive immune monitoring, and xenotransplantation-each addressing a distinct facet of the field's core constraints of organ scarcity and immune-mediated graft loss. Machine perfusion and dd-cfDNA monitoring are approaching mainstream clinical adoption, while tolerance-induction strategies and xenotransplantation remain earlier-stage but are advancing at a pace substantially faster than historical precedent. Continued progress will depend on larger randomized trials with hard clinical endpoints, standardized biomarker validation, and carefully governed expansion of xenotransplantation and DCD programs within evolving regulatory and ethical frameworks.

Keywords: Organ transplantation, machine perfusion, donation after circulatory death, xenotransplantation, donor-derived cell-free DNA, immune tolerance, ischemia-reperfusion injury, organ allocation

1. INTRODUCTION

Organ transplantation has progressed from a high-risk, experimental surgical intervention to a multidisciplinary field integrating immunology, bioengineering, and data science, now representing the standard of care for end-stage disease across the kidney, liver, heart, lung, and pancreas.[1] Despite this maturation, long-term graft and patient survival remain fundamentally constrained by three persistent challenges: an absolute shortage of transplantable organs relative to need, ischemia-reperfusion injury (IRI) sustained during organ procurement, preservation, and implantation, and chronic immune-mediated graft injury that leads to rejection despite lifelong pharmacologic immunosuppression.[1,4] The scale of the shortage problem is difficult to overstate: it has been described as a global health crisis exacerbated by regional disparities in clinical practice, donor identification systems, and available resources, motivating parallel efforts to both expand the usable donor pool and to develop non-human sources of transplantable organs.[3]

This review synthesizes current evidence on the innovations being deployed against these core challenges, organized across four domains: strategies to expand deceased organ donation and optimize allocation; *ex vivo* machine perfusion technologies designed to recondition organs and mitigate ischemia-reperfusion injury; non-invasive biomarker-based approaches to rejection surveillance; and the rapidly advancing field of clinical xenotransplantation using genetically engineered donor animals. Throughout, this review emphasizes the distinction between technologies that have demonstrated benefit in randomized controlled trials with clinically meaningful endpoints and those that remain at the stage of technical feasibility or small-cohort compassionate use, a distinction of particular importance given the field's rapid recent pace of clinical translation.[1,66,67]

2. METHODS

This is a structured narrative review rather than a formal systematic review with meta-analysis. A literature search was conducted across PubMed/MEDLINE, Embase, and Scopus for studies published between January 2018 and February 2026, using combinations of the terms "organ transplantation", "machine perfusion", "donation after circulatory death", "xenotransplantation", "donor-derived cell-free DNA", "immune tolerance", "ischemia-reperfusion injury" and organ-specific terms (kidney, liver, heart, lung, pancreas transplantation). Priority was given to randomized controlled trials, prospective multicenter registries and cohort studies, systematic and narrative reviews from major transplantation journals (American Journal of Transplantation, Transplant International, Journal of Internal Medicine), Lancet Commission and Series publications, and current consensus or position statements from the International Xenotransplantation Association and equivalent bodies. Case reports and single-patient compassionate-use reports were included selectively in the xenotransplantation section, given that this remains the primary form of clinical evidence

currently available in that domain, but are explicitly flagged as such throughout.

3. RESULTS

3.1 THE ORGAN SHORTAGE: EXPANDING DONATION AND OPTIMIZING ALLOCATION

The persistent shortfall between organ supply and transplant need remains the field's central constraint, prompting sustained efforts to expand the deceased donor pool, chiefly through donation after circulatory death (DCD). According to the 2022 International Report on Organ Donation and Transplantation Activities from the Global Observatory on Donation and Transplantation, DCD donors constituted approximately 23% of all deceased donors worldwide, with the highest activity reported in Spain, the United States, and Belgium.[76] In the United States specifically, transplants predominantly rely on deceased donor organs, accounting for roughly 75% of kidney transplants, 94% of liver transplants, and effectively all lung, heart, and pancreas transplants performed between 2018 and 2025; a recent national analysis using Organ Procurement and Transplantation Network data found rising DCD recovery across every organ type, reaching 49% of recovered kidneys, 43% of livers, 24% of lungs, 24% of hearts, and 12% of pancreata by the most recent reporting period.[77] This growth has been enabled by technological innovations-chiefly machine perfusion-that mitigate the added ischemic injury inherent to DCD organ recovery, in which organs are procured only after a period of warm ischemia following circulatory arrest, in contrast to donation after brain death (DBD).[77,78]

Despite this expansion, DCD organs continue to be discarded at higher rates than DBD organs, and the field continues to grapple with variable application across health systems: DCD represents only 6.1% of deceased donors in Eurotransplant countries compared with 10.6% in the United States and 33% in the United Kingdom, reflecting differences in legal frameworks, clinical protocols, and the practical challenges of managing warm ischemia in an ethically and professionally acceptable manner.[78] Organ-specific challenges persist as well: DCD heart transplantation has historically lagged behind DCD kidney and liver recovery due to the heart's particular sensitivity to warm ischemia, though recent advances in procurement and ex vivo evaluation techniques are enabling broader utilization of DCD cardiac donors,[80] and DCD pancreas transplantation likewise remains comparatively underutilized despite comparable graft survival to DBD pancreata in scoping review data.[82] Allocation policy reform has been pursued in parallel with donation expansion; in the United States, the 2020 transition to acuity-circles liver distribution-replacing fixed geographic boundaries with concentric-circle sharing centered on the donor hospital, while prioritizing local DCD offers within a 150-nautical-mile radius to limit cold ischemia time-was designed to reduce geographic disparity in transplant access, though its net effects on waitlist mortality and DCD liver utilization remain the subject of ongoing analysis.[79]

3.2 EX VIVO MACHINE PERFUSION: MITIGATING ISCHEMIA-REPERFUSION INJURY

Ex vivo machine perfusion has emerged as the most clinically mature technological response to both ischemia-reperfusion injury and the need to better utilize marginal or DCD organs, with two broad approaches-hypothermic machine perfusion (HMP), which preserves organs at low temperature with or without oxygenation, and normothermic machine perfusion (NMP), which maintains organs at near-physiological temperature with a warmed, oxygenated perfusate to sustain active metabolism-now supported by a substantial body of randomized trial evidence.[1,53,61] A 2025 integrated review of ex situ machine perfusion clinical trial evidence across kidney, heart, liver, lung, and pancreas transplantation identified a consistent pattern: hypothermic oxygenated perfusion has emerged as reliably ameliorating ischemia-reperfusion injury and improving clinically relevant outcomes across multiple randomized trials and organ types, whereas normothermic perfusion, despite consistent improvements in logistical and surrogate measures, has not demonstrated comparable improvements in recipient clinical outcomes in randomized trials, whether applied to abdominal or thoracic organs.[61]

This pattern is illustrated across individual organ trials. In liver transplantation, a landmark randomized trial (n=220) found that normothermic preservation reduced early allograft dysfunction and peak transaminase levels and improved organ utilization and permissible preservation times, but did not improve graft or patient survival compared with

conventional cold storage.[64] The subsequent multicenter OCS Liver PROTECT trial (300 recipients) similarly found that portable normothermic blood-based machine perfusion decreased early liver graft injury and ischemic biliary complications and increased organ utilization relative to ischemic cold storage [60,62]. However, a more recent US-based randomized trial of normothermic liver perfusion did not find a reduction in early allograft dysfunction overall, though exploratory as-treated subgroup analyses suggested a greater benefit in DCD livers (22.8% vs 44.6% early allograft dysfunction) and in the highest-risk donor quartile, alongside a reduction in postreperfusion syndrome (5.9% vs 14.6%)-suggesting that NMP's clinical benefit may be concentrated in higher-risk or marginal organs rather than conferring uniform benefit across all liver transplants.[65] In kidney transplantation, a UK randomized trial of 338 DCD kidneys found that adding one hour of normothermic machine perfusion to static cold storage did not reduce delayed graft function compared with static cold storage alone (60.7% vs 58.5%; adjusted OR 1.13, 95% CI 0.69-1.84; p=0.624), though the technique was safe, with no increase in graft thrombosis or infectious complications, and the authors noted NMP's evidence base in kidney transplantation remains comparatively sparse relative to liver transplantation.[63] A separate randomized comparison of normothermic versus hypothermic machine perfusion in kidney transplantation similarly reinforced the broader pattern favoring hypothermic oxygenated perfusion for clinically relevant endpoints.[61]

Beyond conventional perfusion approaches, nanotechnology-based strategies are being explored to further address preservation-related injury: a 2025 review described nanoscale oxygen carriers, including perfluorocarbon-based systems, designed to improve graft oxygenation and angiogenesis during preservation, alongside nanomaterial-based approaches to immunomodulation and post-transplant monitoring, though these remain at a substantially earlier preclinical stage than machine perfusion itself.[56]

3.3 NON-INVASIVE REJECTION SURVEILLANCE: DONOR-DERIVED CELL-FREE DNA

Chronic rejection remains the leading cause of long-term allograft failure and current monitoring strategies have historically relied on invasive tissue biopsy-endomyocardial biopsy in heart transplantation, percutaneous biopsy in kidney transplantation-performed either for cause, when graft dysfunction is already evident, or on a surveillance schedule to detect subclinical rejection before it becomes clinically apparent.[83,84] Donor-derived cell-free DNA (dd-cfDNA), a biomarker that exploits the genetic distinction between donor and recipient tissue to detect allograft injury non-invasively, has emerged as the most clinically validated alternative to routine biopsy across multiple organ types.[84,89,91] In the largest reported analysis to date, a multicenter, prospective registry of 1,743 kidney transplant recipients (1,070 biopsies) found that elevated dd-cfDNA significantly improved the yield of biopsy-proven rejection detection, from 7% to 39% in the surveillance setting and from 12% to 47% in the for-cause setting, with an overall AUC of 0.789 for detecting biopsy-proven rejection-supporting dd-cfDNA's use in optimizing which patients should undergo biopsy rather than as a biopsy replacement per se.[84] The American Society of Transplant Surgeons has recommended dd-cfDNA testing in adult kidney transplant recipients as a component of routine post-transplant surveillance, and the European Society for Organ Transplantation has similarly endorsed its role in addressing the field's unmet need for non-invasive monitoring.[91]

Performance, however, is not uniform across clinical contexts or organ types. In pediatric kidney transplantation, dd-cfDNA's predictive performance for subclinical rejection detected on surveillance biopsy has been notably weaker than in the for-cause setting: one adult study using a 1% dd-cfDNA cutoff reported 0% sensitivity for detecting rejection specifically in surveillance biopsies, while a small single-center pediatric series found only one of four rejection episodes detected via surveillance biopsy was associated with an elevated dd-cfDNA level.[83] In heart transplantation, a multicenter registry analysis (SHORE, n=2,240) found that antibody-mediated rejection incidence varied from 1.1% of biopsies with normal graft function and no donor-specific antibodies to 20.4% of biopsies with both antibody positivity and graft dysfunction, underscoring that dd-cfDNA and antibody testing perform best when interpreted jointly with clinical context rather than as a stand-alone rejection test.[85] A dedicated two-threshold algorithm combining dd-cfDNA fraction with absolute donor quantity

score has been developed specifically to improve detection accuracy in heart transplant recipients,[86] and multicenter data from single lung transplant recipients using a 1.0% dd-cfDNA threshold reported a sensitivity of 77.8%, specificity of 84.6%, and notably high negative predictive value of 96.83% for acute rejection, suggesting dd-cfDNA's strongest current clinical utility may lie in ruling out rejection rather than definitively ruling it in.[90] Emerging applications extend dd-cfDNA monitoring to multi-organ transplant recipients (pancreas-kidney, heart-kidney, liver-kidney), where baseline levels and interpretive thresholds appear to differ meaningfully from single-organ recipients, an area requiring further organ-combination-specific validation.[92]

3.4 PRECISION IMMUNOMODULATION AND TOLERANCE INDUCTION

Beyond earlier detection of rejection, a parallel body of innovation seeks to fundamentally reduce or eliminate the need for lifelong, broadly immunosuppressive pharmacotherapy-which itself carries substantial toxicity, including infection risk, malignancy, nephrotoxicity, and metabolic and cardiovascular complications-by inducing durable, graft-specific immune tolerance.[53,58] Emerging strategies described in the current literature include regulatory T-cell (Treg) therapy, gene-edited cellular platforms, tolerogenic dendritic cells, and biomarker-guided immunosuppression minimization, collectively aimed at reshaping alloimmune control toward tolerance rather than blanket suppression.[53] A 2025 report from the International Society for Transplantation Immunology described successful weaning from partial immunosuppression in small cohorts using early Treg cell enrichment combined with transient donor chimerism, illustrating a shift from single-agent cellular therapy toward integrated, multidimensional immune-reprogramming protocols.[53] Complementary efforts are underway to develop alternative immunosuppressive molecules with more favorable side-effect profiles, targeting the immune system more selectively to reduce off-target metabolic and cardiovascular toxicity associated with current calcineurin-inhibitor-based regimens.[58] Despite this progress, the evidence base for tolerance-induction strategies remains substantially earlier-stage than either machine perfusion or dd-cfDNA monitoring, with successful outcomes reported in small, often single-center cohorts rather than randomized multicenter trials, and durable, generalizable immunosuppression withdrawal remains an aspirational rather than standard-of-care goal.[53]

3.5 XENOTRANSPLANTATION: ADDRESSING STRUCTURAL ORGAN SHORTAGE

Xenotransplantation using genetically engineered pig organs has advanced from decades of preclinical non-human primate research to an active, rapidly evolving program of human clinical translation, driven by the recognition that donation-based strategies alone cannot resolve the structural gap between organ supply and demand, particularly for kidney and heart failure.[59,66,72] The modern clinical era began on January 7, 2022, when a genetically modified pig heart-engineered with knockout of three key xenoantigens and expression of human transgenes to mitigate complement activation, inflammation, and coagulation-was transplanted into a living patient at the University of Maryland under a single-patient FDA expanded access protocol; a second cardiac xenotransplant followed in 2023, with both patients surviving 60 and 40 days respectively before succumbing principally to antibody-mediated rejection.[66,70] Kidney xenotransplantation followed a similar trajectory: the first genetically modified pig kidney transplant into a living patient was performed at Massachusetts General Hospital in March 2024, with the recipient surviving approximately two months before dying of an unrelated cardiac cause, and a second case in April 2024 combined pig kidney and mechanical cardiac support (LVAD) in a patient with concurrent heart and kidney failure, with the pig kidney explanted after 47 days due to inadequate perfusion from the LVAD.[67,73]

Building on these early cases, the field transitioned from single-patient compassionate use toward regulated multi-patient clinical trials in 2024-2025. In December 2024, the FDA approved a three-patient pilot study of eGenesis's multigene-edited pig kidney (combining xenoantigen knockout, human transgene insertion, and porcine endogenous retrovirus inactivation), with the first patient treated in January 2025; that patient's clinical course was reported as demonstrating physiologically normal water and mineral balance regulation by the xenograft, without evidence of pig virus transmission.[69,75] In

parallel, United Therapeutics received FDA clearance for a six-patient phase 1-2 safety trial of its 10-gene-edited UKidney, with the first transplant performed under the EXPAND study (NCT06878560) at NYU Langone Health on November 3, 2025; that patient's graft survival of 271 days represents the longest reported survival following pig-to-human kidney xenotransplantation to date, substantially exceeding prior compassionate-use cases.[68,74] A comprehensive tally of reported compassionate-use xenotransplantation cases in living humans as of early 2026 documented two cardiac, one hepatic, and six renal xenotransplants, with survival ranging from weeks to several months, collectively demonstrating technical feasibility while continuing to be limited by rejection, infection, and recipient comorbidity.[66,67]

A 2025 series of position papers from the International Xenotransplantation Association addressed the field's key remaining barriers: donor genetic engineering strategy and immunosuppression protocols for kidney xenotransplantation, infectious risk from porcine endogenous retroviruses (PERV) and porcine cytomegalovirus (PCMV) requiring rigorous donor screening and recipient surveillance including metagenomic sequencing, and the historical and regulatory framework underpinning the field's recent clinical advances.[71] Reflecting the field's rapid pace, contemporaneous reviews have specifically argued that sufficient preclinical and early clinical evidence now supports formally initiating pilot clinical trials of pig kidney xenotransplantation, a position that FDA clearance decisions in 2024-2025 have subsequently validated.[72] Notably, genetic engineering strategy has not converged on a single approach: reported cases have ranged from single-gene-knockout constructs (removing only the alpha-Gal xenoantigen) to constructs with ten combined human transgene insertions and porcine gene knockouts, and the relative contribution of specific genetic modifications versus immunosuppression protocol to clinical outcomes remains an active area of investigation.[67,68]

Table No. 1: Summary of Core Challenges in Organ Transplantation and Corresponding Innovations

Challenge	Key Innovation(s)	Strongest Evidence to Date	Current Limitation
Organ scarcity/donor shortage	Expanded DCD donation; acuity-circles/broader-sharing allocation policy	DCD now 23% of deceased donors globally; rising sharply in the US across all organ types	DCD organs still discarded more often; warm ischemia limits use, especially for heart/lung
Preservation injury/marginal organ quality	Hypothermic and normothermic machine perfusion (HMP/NMP)	Multiple RCTs across liver, kidney, heart; HMP shows most consistent benefit	NMP has not consistently improved hard clinical endpoints (survival) despite improved logistics/utilization
Structural organ shortage	Xenotransplantation (multigene-edited pig organs)	Longest reported pig-to-human kidney survival: 271 days (EXPAND study, 2025)	All cases to date compassionate-use/early-phase; rejection, infection, and comorbidity remain major barriers
Chronic rejection/ immunosuppression toxicity	Regulatory T-cell therapy, tolerogenic dendritic cells, biomarker-guided minimization	Small cohort reports of successful immunosuppression weaning using Treg enrichment + transient chimerism	Evidence largely limited to small cohorts/case series; not yet standard of care
Invasive, delayed rejection diagnosis	Donor-derived cell-free DNA (dd-cfDNA) surveillance	AUC 0.789 for biopsy-proven rejection detection in multicenter kidney registry (n=1,743)	Low sensitivity in some surveillance settings; performance varies by organ and clinical context

Note: Evidence strength and limitations reflect the cited primary studies and reviews[53,56,60-92] and vary considerably by organ type and specific technology; figures should be interpreted as representative rather than universally generalizable across all transplant centers and populations.

4. DISCUSSION

The evidence synthesized in this review reveals a field advancing simultaneously along multiple, largely independent fronts, each addressing a distinct facet of transplantation's core constraints. Organ donation expansion and machine perfusion together represent the most clinically mature set of innovations, with DCD utilization rising steadily across essentially every organ type and jurisdiction with adequate legal and logistical infrastructure,[76,77] and machine perfusion-particularly hypothermic oxygenated perfusion-now supported by a genuinely robust randomized trial evidence base.[61] The recurring finding that normothermic perfusion improves surrogate and logistical outcomes (organ utilization, early graft injury markers, preservation time) more consistently than it improves hard clinical endpoints such as graft or patient survival[60,63,64,65] is an important nuance for the field: NMP's principal current value may lie in expanding the pool of usable organs-by permitting real-time viability assessment of marginal or DCD organs that would otherwise be declined-rather than in improving outcomes for organs that would have been transplanted regardless. This distinction has direct resource-allocation implications, since NMP technology carries substantial capital and per-case cost, and its value proposition differs materially between a health system seeking to expand transplant volume versus one seeking to improve average graft outcomes.

Donor-derived cell-free DNA monitoring illustrates a different pattern: a technology with strong aggregate validation data (AUC 0.789 in the largest kidney registry) whose performance nonetheless varies enough by clinical context-organ type, surveillance versus for-cause testing, concurrent donor-specific antibody status-that it is best understood as a triage tool for optimizing biopsy utilization rather than a wholesale biopsy replacement.[83,84,85,90] The notably high negative predictive value reported in lung transplantation (96.83%) [90] suggests dd-cfDNA's most defensible near-term clinical role may be reassurance and biopsy avoidance in low-probability patients, with biopsy reserved for elevated or ambiguous results-a more conservative and evidence-consistent framing than positioning dd-cfDNA as a rejection diagnostic in isolation.

Tolerance-induction strategies and xenotransplantation, by contrast, remain earlier in their translational arc, though both are advancing unusually quickly by the standards of surgical innovation. The transition of xenotransplantation from a single compassionate-use case in January 2022 to FDA-cleared, regulated multi-patient clinical trials by late 2025-with graft survival extending from weeks in the earliest cases to 271 days in the most recent EXPAND study report[66,68,74]-represents a genuinely rapid translational pace, though it is essential to contextualize this progress accurately: every reported outcome to date derives from compassionate-use or early-phase trial settings involving small numbers of severely ill patients, generally without other therapeutic options, and none yet approaches the outcomes routinely achieved with human allotransplantation. The variability in genetic engineering strategy across reported cases-from single-gene to ten-gene-edited constructs[67,68]-further indicates that the field has not yet converged on an optimal donor engineering approach, and that current results should be interpreted as an evolving experimental program rather than a validated clinical pathway.

A cross-cutting theme across all four domains reviewed is the tension between rapid technical and clinical translation and the comparatively slower accumulation of large-scale, hard-endpoint randomized evidence. This is a familiar pattern in surgical and biotechnological innovation, but it carries particular weight in transplantation given the severity of the underlying disease, the frequently compassionate-use regulatory pathway through which the most novel therapies (xenotransplantation) first reach patients, and the field's historical willingness-visible in the DCD expansion literature itself-to adopt technologies whose logistical and utilization benefits are clearer than their comparative clinical outcome benefits.[61,63] Continued rigorous, transparent, multicenter trial reporting, of the kind exemplified by the machine perfusion and dd-cfDNA literature reviewed here, will be essential as tolerance-

induction and xenotransplantation strategies mature from early compassionate use toward broader clinical application.

5. LIMITATIONS

This review has several limitations. First, as a narrative rather than systematic review, it does not apply formal risk-of-bias assessment to each primary study and inherits any bias present in the underlying literature, including the well-recognized tendency for early-phase and compassionate-use case reports to be preferentially published when outcomes are favorable. Second, the xenotransplantation section in particular relies heavily on case reports, single-patient compassionate-use protocols, and preliminary trial announcements rather than peer-reviewed, hypothesis-tested clinical trial data, reflecting the genuine state of evidence in this domain rather than a methodological shortcoming of this review; conclusions in this section should accordingly be regarded as provisional and subject to revision as formal trial results mature. Third, this review's coverage of machine perfusion and dd-cfDNA evidence, while spanning kidney, liver, and heart transplantation, does not comprehensively address lung and pancreas transplantation, which have distinct preservation and monitoring literatures. Fourth, cost-effectiveness data for machine perfusion technologies and dd-cfDNA testing were outside this review's primary scope, despite their likely importance to real-world adoption decisions across health systems with varying resources. Finally, organ allocation policy discussion was largely US-centric, reflecting the concentration of available English-language literature on this topic; allocation frameworks and their comparative outcomes differ meaningfully across other health systems and were not analyzed in comparable depth.

6. CONCLUSION

Organ transplantation continues to be reshaped by innovation across donation strategy, *ex vivo* organ preservation, non-invasive immune monitoring, and-most strikingly-the rapid clinical emergence of xenotransplantation. Machine perfusion and donor-derived cell-free DNA monitoring have progressed furthest toward mainstream clinical integration, supported by randomized trial and large prospective registry evidence, though even here the clinical benefit is often more clearly established for logistical and surrogate outcomes than for hard endpoints such as long-term survival. Tolerance-induction immunotherapy and xenotransplantation remain earlier-stage but are advancing at a pace that, if sustained and matched by rigorous trial-based evidence generation, may meaningfully expand transplantation's capacity to address the persistent global shortage of transplantable organs. Continued progress will depend on larger randomized trials with clinically meaningful, patient-centered endpoints; standardized, organ-specific validation of emerging biomarkers; and carefully governed, transparently reported expansion of both donation-based and xenotransplantation-based strategies within evolving ethical and regulatory frameworks.

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DATA AVAILABILITY: All data supporting this review are available within the cited published sources.

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