transplantation

Kidney xenotransplantation at a clinical inflection point

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Refers to: Montgomery RA, Stern JM, Fathi F, et al. Physiology and immunology of a pig-to-human decedent kidney xenotransplant. *Nature.* 2026;650:218–229, and

Schmauch E, Piening BD, Dowdell AK, et al. Multi-omics analysis of a pig-to-human decedent kidney xenotransplant. Nature. 2026;650:205–217.

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Kidney transplantation remains the optimal treatment for patients with kidney failure, offering superior survival, quality of life, and cost-effectiveness compared with dialysis. Yet the persistent and widening gap between organ supply and demand continues to limit timely access to transplantation. As a result, many patients remain dependent on long-term dialysis, often with substantial morbidity and mortality. Xenotransplantation has long been envisioned as a potential solution to this shortage by enabling a more predictable and scalable source of transplantable organs.

Recent advances in gene editing, immunosuppressive strategies, and infectious risk mitigation have transformed xenotransplantation from a theoretical concept into a clinical reality,[1] culminating in the first pig-to-human kidney xenotransplantation performed in a living recipient in March 2024[2] (Figure 1). In this context, 2 recent Nature studies represent important milestones in the translational pathway toward human kidney xenotransplantation.[3,4] By leveraging the human decedent model, defined as transplantation of a kidney into a brain-dead donor maintained on physiologic support,[5,6] these investigations sought to assess whether gene-edited porcine kidneys could function in the human circulation without immediate rejection while permitting detailed evaluation of immunologic and physiologic responses.

What do the studies show?

The 2 Nature studies[3,4] use the human decedent model to interrogate complementary aspects of kidney xenotransplantation. Together, they provide a rare opportunity to examine early graft function, rejection phenotypes, and human anti-xeno immune responses under controlled conditions that are not feasible in living recipients.

The first study[3] reports the longest pig-to-human kidney xenotransplantation performed in a decedent. In this model, a gene-edited porcine kidney was transplanted into a 57-year-old brain-dead donor after bilateral native nephrectomies. The recipient had no intrinsic kidney disease or major comorbidities aside from stage IV glioblastoma. Immunosuppression combined lymphocyte depletion (antithymocyte globulin), costimulation blockade (belatacept), complement inhibition (eculizumab), and conventional maintenance therapy (tacrolimus, mycophenolate mofetil, and steroids). A notable feature of the experimental design was prior transplantation of a pig thymus under the donor kidney capsule several months earlier,[5] intended to promote immune tolerance.

The xenograft demonstrated robust early function, with a mean serum creatinine level of approximately 0.4 mg/dl during the first month and an estimated glomerular filtration rate exceeding that expected for a single human kidney. Despite this favorable initial performance, rejection episodes emerged over time. Antibody-mediated rejection occurred

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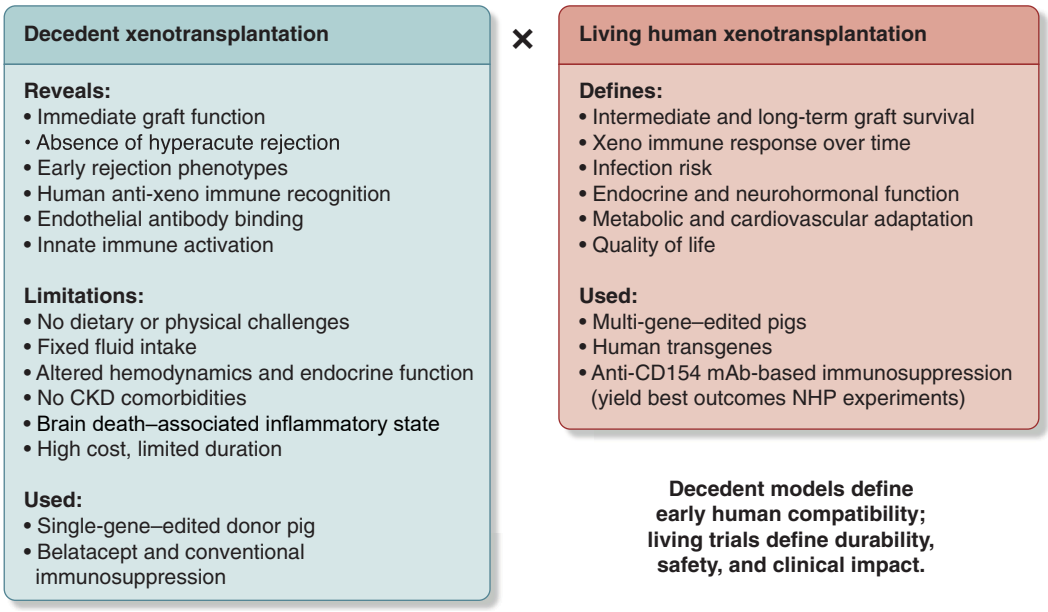

Figure 1 | Insights from decedent and living human kidney xenotransplantation. The human decedent xenotransplant model enables assessment of immediate graft function, early rejection phenotypes, human anti-xeno immune recognition, and endothelial antibody binding in a controlled setting, but is limited by brain death–associated inflammation, absence of physiologic stressors, unique physiologic abnormalities such as polyuria, and restricted study duration. In contrast, xenotransplantation in living human recipients, as demonstrated in recent clinical experience, permits longitudinal evaluation of immune control, physiologic homeostasis, infection risk, and quality of life, defining the parameters required for durable clinical success. CKD, chronic kidney disease; mAb, monoclonal antibody; NHP, nonhuman primates.

within the first month, accompanied by C4d, IgG, and IgA deposition on biopsy, followed by mixed antibody- and T cell–mediated rejection by day 49. Flow crossmatch testing revealed stronger IgM and IgG reactivity against porcine endothelial cells than against peripheral blood mononuclear cells, underscoring the importance of endothelial-specific antibody recognition in xenotransplantation.

Immune repertoire analysis demonstrated marked clonal expansion of T cells after transplantation, with a small number of clones increasing from a minor fraction of the baseline repertoire to dominance within weeks. Histologic and ultrastructural analyses revealed progressive tubular injury, while unexpected IgA deposition highlighted immune patterns that diverge from conventional human allotransplant experience. The decedent model also exposed physiologic differences that complicate interpretation, including profound polyuria due to diabetes insipidus (exceeding 20 l/d and requiring vasopressin), severe electrolyte wasting, hyperphosphatemia, substantial transfusion requirements (>24 units of packed red blood cells), and absence of detectable porcine erythropoietin or renin production. Notably, cotransplantation of thymic tissue failed to induce donor-specific hyporesponsiveness, as recipient T cells reacted similarly to donor and third-party pig antigens.

The second study[4] extends these observations by applying multi-omic approaches to define the molecular and cellular immune responses underlying human anti-xeno rejection. Integrated transcriptomic, immune repertoire, and pathway analyses identified coordinated activation of innate and adaptive immune programs, including endothelial stress responses, interferon signaling, and expansion of specific T- and B-cell clones. These data provide a mechanistic context for the histologic and serologic findings observed in the prolonged decedent model and reveal immune signatures that may not be fully captured by conventional pathology alone. Collectively, the 2 studies illustrate how the decedent xenotransplant model can serve as both a physiologic testing platform and a mechanistic window into human immune recognition of gene-edited porcine kidneys.

Why are these studies important?

These studies represent an important translational milestone in kidney xenotransplantation

by providing a detailed assessment of human compatibility with gene-edited porcine kidneys. The decedent model occupies a unique and complementary niche in xenotransplantation research, enabling direct evaluation of graft function, immune activation, and rejection mechanisms in the human circulation without exposing living recipients to undue risk. By combining longitudinal physiologic monitoring with detailed immunologic and molecular analyses, these investigations offer critical insights into early rejection pathways, cross-species immune recognition, and endothelial responses that cannot be fully modeled in nonhuman systems.

Beyond physiologic readouts, a key contribution of these studies is the consistent identification of innate immune activation as a dominant feature of the early human anti-xeno response. Decedent xenotransplantation revealed activation of myeloid and interferon-driven pathways, endothelial stress responses, and macrophage enrichment within the graft. Importantly, recent experience in a living human xenotransplant recipient similarly demonstrated persistent activation of innate immune programs and macrophage expansion, despite preserved graft function and absence of overt antibody-mediated rejection[7] This convergence across models suggests that innate immune activation is not merely an artifact of brain death physiology, but rather a fundamental component of the human response to xenogeneic organs.

These observations have important implications for the design of future immunosuppressive strategies. Current regimens, largely adapted from allotransplantation, are optimized to control adaptive immune responses but may be insufficient to fully modulate innate immune pathways, including macrophage activation, endothelial injury, and interferon signaling. The persistence of innate immune activation in both decedent and living human xenotransplantation highlights the need to incorporate targeted approaches that more directly address innate immunity, while balancing the risks of over-immunosuppression and infection. Such insights provide a mechanistic rationale for refining immunosuppressive regimens alongside continued advances in donor genetic engineering.

At the same time, several observations from the decedent xenotransplant model differed substantially from those reported in a living human recipient, complicating direct extrapolation to clinical trial design.[2,7,8] In contrast to the marked electrolyte instability and extreme polyuria observed in decedent settings,[3,6,9] physiologic studies in a living human recipient demonstrated preserved urine concentration, effective electrolyte regulation, physiologically appropriate urine output, and maintenance of blood pressure despite reduced activation of the renin-angiotensin-aldosterone system.[8] These differences underscore the importance of intact neurohormonal regulation, nutritional intake, and hemodynamic variability in interpreting xenograft performance.

Importantly, the porcine kidney used in the decedent study carried only a single galactose knockout and lacked the additional human transgenes and carbohydrate deletions incorporated into organs currently used clinically. Prior nonhuman primate studies have demonstrated that kidneys with limited genetic modification are associated with substantially shorter graft survival, whereas multi-gene–edited organs can support prolonged function beyond 2 years.[1] The use of less extensively edited pigs may also necessitate more intensive immunosuppression, highlighting the importance of advancing clinical trials with more comprehensively engineered donor organs paired with immunosuppressive strategies that balance immune control and infectious risk.

Looking ahead, forthcoming regulatory-approved clinical trials from leading xenotransplantation programs, including Revivicor and eGenesis, will represent a critical next step for the field. These studies will deploy porcine organs incorporating both multiple genetic deletions and human transgenes, more closely reflecting the biologic platforms intended for clinical use. As such, they are better positioned to address the remaining immunologic, physiologic, and infectious challenges that cannot be fully resolved in decedent models. Importantly, xenotransplantation has reached a moment of cautious but genuine hope. Patients with kidney failure have been remarkably vocal, engaged, and willing to participate in these early studies, motivated by the possibility of expanding access to transplantation and improving long-term outcomes. With continued scientific rigor, ethical oversight, and patient partnership, xenotransplantation has the potential to evolve into a true alternative to long-term dialysis. The ultimate aspiration is that dialysis will no longer represent the default lifelong therapy

for most patients with kidney failure, but rather a bridge to more definitive and durable kidney replacement strategies.

DISCLOSURE

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