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First Living Patient Received Pig Kidney Transplant

By Bridget M. Kuehn

When 62-year-old Richard "Rick" Slayman of Weymouth, MA, left Massachusetts General Hospital in Boston on April 3, 2023, to recover at home after receiving the first pig kidney transplant into a living human patient, it marked a major milestone in the field of xenotransplantation. "It's the starting line in a revolution in the way we potentially find organs for our patients," said Leonardo Riella, MD, PhD, FASN, medical director of kidney transplantation at Massachusetts General Hospital, in an interview with *Kidney News*.

Riella credited 30 years of xenotransplant research for enabling the transplant. The US Food and Drug Administration (FDA) allowed the transplant under its expanded access protocol, also called a compassionate use exemption. These exemptions allow patients who are seriously ill and lacking other therapeutic options to access experimental therapies. Riella and his colleagues will now carefully follow Slayman and submit their data to FDA to lay the groundwork for human clinical trials. If larger clinical trials are successful, genetically engineered pig kidneys could provide a valuable alternative to human kidney allografts to the nearly 100,000 people currently on the waitlist for a deceased donor organ (1).

"I applaud the courage of the patient taking part in this latest milestone in xenotransplantation, which is marching closer to becoming an alternative source of organs for the many thousands suffering from kidney failure," said Robert Montgomery, MD, DPhil, the H. Leon Pachter, MD, Professor and chair of the Department of Surgery at New York University (NYU) Langone Health and director of the NYU Langone Transplant Institute, in an emailed statement. "He is truly a hero and will be an inspiration to many. The Massachusetts General Hospital and eGenesis teams should be acknowledged for their enormous contribution to this important work to save lives."

Rapid advancements

Slayman's transplant was the latest in a string of recent developments in the field of xenotransplantation. Building on decades of research studying the transplantation of genetically modified pig kidneys into nonhuman primates, scientists from eGenesis (a company that maintains it is committed to ending the global transplant shortage and transforming the treatment of organ failure), Massachusetts General, and several other US academic centers recently published results

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New KDIGO CKD Guideline Focuses on Patient-Centered, Life-Cyle-Based Approach

By Bridget M. Kuehn

Nephrologists often encounter people with chronic kidney disease (CKD) who may present with different circumstances, such as an octogenarian with a high pill burden or a young adult making the transition from pediatric to adult care.

"One size does not fit all," said Adeera Levin, MD, professor of medicine and head of the Division of Nephrology at The University of British Columbia, Vancouver, Canada. "You have to take the individual into consideration."

With that in mind, a new CKD guideline from the Kidney Disease: Improving Global Outcomes (KDIGO) consortium aims to help nephrologists leverage the latest evidence, diagnostic tools, and medications to help them better personalize patient care (1). Levin, who cochaired the work group that created the guideline, noted that although some of the recommendations apply to all people with CKD, others acknowledge that the best patient care may sometimes depend on patient characteristics, such as life stage, gender, or the underlying cause of their condition.

New medications, developments in genetics and diagnostics, and research on subsets of patients have facilitated these more patient-centric recommendations. For example, the guideline recommends sodium-glucose cotransporter-2 inhibitors (SGLT2is) even for people with CKD who do not have diabetes to prevent CKD progression. It concurs with

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showing that genetically altered pig kidneys could last years in nonhuman primates despite some of the challenges of working in this animal model (2).

"We take for granted small things that we do to manage our patients, but in nonhuman primates, the availability of tools, technology, and treatment is much more limited," Riella explained. "So just seeing these kidneys, working in nonhuman primates for 2 to 3 years, has given us the confidence that it was scientifically justifiable to move the needle and move to patients."

The eGenesis team used organs from a miniature breed of pigs to avoid having organs that might outgrow their human or nonhuman primate recipients. The investigators used CRISPR [clustered regularly interspaced short palindromic repeats]-Cas9 [CRISPR-associated protein 9] gene editing to make 69 changes in the pig's genome. Three genes encoding pig proteins that can trigger an immune reaction in humans were removed to prevent rejection, Riella explained. Scientists added seven human genes to the pig's DNA to make the organs more compatible with the human immune system or to reduce the risk of clotting. The other 59 alterations inactivated porcine endogenous viruses hiding in the pig genome. Concern about pig viruses spreading to humans has been one barrier to xenotransplants in humans.

In parallel to successful studies in nonhuman primates, transplant teams across the country have developed a human preclinical model for pig kidney xenotransplants in human recipients, declared dead based on neurologic function, who were maintained on mechanical support for up to 2 months (3–6).

The genetically modified pig organs used in these decedent studies had fewer genetic modifications. Montgomery and his colleagues used a single gene edit to remove the gene encoding the alpha-gal protein that can trigger hyperacute rejection and standard immunosuppression. Locke and her colleagues (4) used pig kidneys with 10 genetic modifications—three to knock out three pig antigens that triggered hyper-rejection in nonhuman primate studies, a fourth modification removed a gene encoding a pig growth hormone to prevent the organ from outgrowing its human recipient, and the six human genes were inserted into the pig's genome to modulate the human immune response to the kidney. Locke also deployed immunosuppressive drugs routinely used for human kidney allograft recipients.

"It's thrilling to see the progress unfolding," Montgomery said in the statement. "While each transplant center studying this takes different approaches with the number of gene edits and medications, another big step will be when the FDA authorizes clinical trials so we may better understand what will work best for patients on our waiting lists."

Paient selection

While both decedent and nonhuman primate models have proved valuable, Riella noted that both have limitations. He explained that studies in human recipients declared dead based on neurologic function can only be conducted for a short time, limiting researchers' ability to assess longer-term outcomes like rejection or the risk of the pig organ transmitting infections to human recipients. The only option to determine those outcomes would be studies in human patients. A team at the University of Maryland School of Medicine transplanted two pig heart allografts into living human recipients under compassionate use exemptions (7). The first patient lived for 2 months posttransplant and the second for 6 weeks (8).

About 2 years ago, Riella and his colleagues began searching for a potential human recipient who was an appropriate candidate for a pig allograft. They selected Slayman, who has type 2 diabetes and hypertension and previously had a successful human kidney allograft that lasted for 5 years, but he had to return to dialysis after the allograft failed. He was struggling on dialysis and required two procedures each month to keep his vascular access open and was running out of options for vascular access locations, Riella said. Slayman faced a long wait time ahead on the deceased donor transplant list.

"He was very uncomfortable, and it was affecting his quality of life," Riella noted. After several discussions about the known and unknown risks of a pig kidney xenotransplant with his clinicians, Slayman opted to take the risk to become the first living human to receive a pig kidney transplant.

Riella and his colleagues used a combination of thymoglobulin, rituximab, steroids, and an experimental complement inhibitor ravulizumab for induction immunotherapy. For maintenance therapy, Slayman was started on tacrolimus, mycophenolate, and prednisone, which are commonly used after transplant of a human allograft. He also received an infusion of the experimental immunosuppressant tegoprubart, an anti-CD154 antibody costimulation blockade therapy that is currently in human clinical trials, Riella said. He noted that the drug was part of the "secret sauce" that improved survival in nonhuman primate pig kidney xenotransplantation studies.

So far, the gamble has paid off for Slayman. Riella noted that Slayman reported enjoying small things that many people may take for granted, like being pain-free and being able to shower after having his vascular access removed. "For patients like him, a transplant can be life-changing," Riella remarked. "His energy is very good."

Riella shared that he and his colleagues are carefully monitoring Slayman's health. He will have blood draws three times each week and clinic visits twice each week. Eventually, they hope to space out visits and follow the same monitoring regimens used for human allograft recipients.

In his statement, Slayman, who has been a patient at Massachusetts General for 11 years, said he had the utmost trust in his clinicians, felt well-informed about the potential risks, and wanted to help others. "I saw it not only as a way to help me but also as a way to provide hope for the thousands of people who need a transplant to survive," he reflected.

If the transplant is successful and leads to a successful clinical trial, it could change the paradigm for kidney care away from dialysis toward transplant for most patients, Riella said. He noted that human kidney allografts would remain the gold standard, but individuals who do not have the luxury of waiting for a deceased donor organ would have an alternative. Some patients, he noted, may still require dialysis because they may not be good candidates for transplant.

Already, Riella and his colleagues have received an overwhelming response from patients with kidney failure. "The number of messages that we've received after doing the xenotransplant from patients sharing their hopes and also their struggles and how they

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were seeing a light at the end of the tunnel was even more impactful than we could ever imagine," he said.

References

1. United Network for Organ Sharing (UNOS). The kidney transplant waitlist. Accessed April 10, 2024. https://transplantliving.org/kidney/the-kidney-transplant-waitlist/
2. Anand RP, et al. Design and testing of a humanized porcine donor for xenotransplantation. *Nature* 2023; 622:393–401. doi: 10.1038/s41586-023-06594-4
3. Kuehn BM. Pig-to-human xenotransplants take another step forward. *Kidney News*, October/November 2023; 15(10/11):1, 7–8. www.kidneynews.org/view/journals/kidney-news/15/10/11/article-p1_1.xml
4. Locke JE, et al. Normal graft function after pig-to-human kidney xenotransplant. *JAMA Surg* 2023; 158:1106–1108. doi: 10.1001/jamasurg.2023.2774
5. Porrett PM, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. *Am J Transplant* 2022; 22:1037–1053. doi: 10.1111/ajt.16930
6. Montgomery RA, et al. Results of two cases of pig-to-human kidney xenotransplantation. *N Engl J Med* 2022; 386:1889–1898. doi: 10.1056/NEJMoa2120238
7. Neergaard L. Surgeons perform second pig heart transplant, trying to save a dying man. *Associated Press*. September 22, 2023. Accessed April 10, 2024. https://apnews.com/article/pig-heart-transplant-d894f6ce27b7db71ecb0ec393cac3e86
8. University of Maryland School of Medicine. In Memoriam: Lawrence Faucette. October 31, 2023. Accessed April 10, 2024. https://www.medschool.umaryland.edu/news/2023/in-memoriam-lawrence-faucette.html

New KDIGO CKD Guideline

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recommendations from a previous KDIGO guideline recommending SGLT2is for people with CKD and diabetes.

"Everyone is very excited; we now have drugs that we can recommend to modify kidney disease progression that also have other benefits," Levin said. "This is the first time we've had strong evidence-based recommendations for the treatment of chronic kidney disease at all stages."

The breadth of new recommendations in the guideline is the result of major progress in the field, according to a statement from the cochairs of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), Sankar Navaneethan, MD, MS, MPH, FASN, Garabed Eknoyan, MD, Endowed Professor in Nephrology at Baylor College of Medicine in Houston, TX, and Jeffrey William, MD, assistant professor of medicine in nephrology at Harvard Medical School and internal medicine–nephrology physician at the Beth Israel Deaconess Medical Center in Boston, MA: "This is a testament to the broader effort by the nephrology scientific community and the funding agencies that have focused on improving early diagnosis, development of risk prediction tools, and generation of high-quality clinical trial evidence for various therapeutic options for CKD, a common, progressive, and expensive clinical condition."

Diagnostic tools

Levin noted that an accurate evaluation of kidney function using all of the diagnostic tools available is the first step to providing good CKD care. The guideline recommends estimating glomerular filtration rates (GFRs) using creatinine and, when available, adding cystatin C. The evidence of the advantages of this approach has been accumulating over the past 10 years, but in the last 2 to 3 years, there has been a groundswell of support for making the change.

"We all know that [the] eGFR [estimated GFR] is still not perfect, but in some instances, we need the most accurate approach that we can get," said workgroup member Rasheeda Hall, MD, MS, MBA, FASN, a nephrologist and associate professor of medicine at Duke University School of Medicine and staff physician at the Durham Veterans Affairs Health Care System in Durham, NC. "We felt like [the recommendation] was the best way to move everyone forward."

The guideline also recommends using race-free equations to estimate GFR. Many countries already use race-free equations, but race-adjusted kidney function estimation has been common in the United States until recently. Based on evidence showing that race-corrected eGFRs disadvantaged Black individuals and delayed kidney care, the National Kidney Foundation-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases in 2021 recommended dropping race-based formulas and using creatinine or, ideally, creatinine plus cystatin C for kidney function (2). The task force recommendation has led to rapid uptake of the change at many hospitals and prompted many laboratories to add in-house cystatin C. Hall noted that the guideline recommendation may help support policy changes needed to get more hospitals and laboratories on board.

The guideline also emphasizes the importance of identifying the cause of CKD in an individual based on their clinical evaluation, medical and family history, social and environmental factors, medications, and genetic or pathologic testing. "More and more we have targeted therapies for specific conditions, so it behooves us to know what the cause of kidney disease is [in an individual person] so that we can target the right therapy and even use the right prediction equation," Levin said.

Reinforcing the guideline's benefits, another member of the workgroup, Lesley Inker, MD, director of the Kidney and Blood Pressure Center and the Kidney Function and Evaluation Center at Tufts Medical Center, Burlington, MA, explained that some kidney diseases, such as polycystic kidney disease or immunoglobulin A nephropathy, have specific therapies, and for other kidney diseases, there may be ongoing clinical trials in which patients may want to participate. Levin predicted that even more targeted therapies are on the horizon as nephrologists identify and learn more about the genetic causes of CKD.

LaVarne A. Burton, president and chief executive officer of the American Kidney Fund, in a statement in March applauded the new guideline's focus on both patient-centered care and its emphasis on finding undiagnosed causes for kidney diseases (3). She noted that 5% to 15% of people with kidney diseases do not know the cause of their condition. The American Kidney Fund launched its Unknown Causes of Kidney Disease Project in 2020 to research the impact of undiagnosed or misdiagnosed kidney diseases on patient care and outcomes.

Life-cycle approach

The CKD guideline also emphasizes a life-cycle-based approach that balances goal-directed therapy with the patient's needs, age, gender, use of gender-affirming therapies, and other circumstances. "People at different phases of life [experience] different kinds of kidney disease. Understanding the disease-specific and person-specific issues will help nephrologists make the best treatment plan for every individual," Inker said.

Inker noted that treatment plans and treatment goals also must evolve over time as people age or their condition changes. Given the large number of older adults with CKD, Hall said, it was important for the guideline to emphasize the complexity of care for this subpopulation. She noted that in addition to frailty and loss of muscle mass with advanced age, these individuals are likely to be on multiple medications and have multiple prescribers. They may also have cognitive impairments that make medication changes and other instructions difficult to remember or follow.

The guideline also highlights the need for frequent medication reviews, dose adjustments, and collaborative care with pharmacists and other specialists to manage patients taking multiple medications. Levin stated that it is essential to check for known or unexpected drug interactions regularly and to make sure the medications that patients are taking are evidence informed. "The totality of patients' medications needs to be looked at, again, in the context of the individual," she said.

The guideline also encourages nephrologists to deploy a full spectrum of interventions to preserve kidney function, including nutrition and exercise, and provides information on managing patients' symptoms. Additionally, it outlines steps for the management of co-occurring cardiovascular disease with medications such as statins in individuals with elevated cholesterol or SGLT2is in people with CKD and heart failure.

"Cardiac disease is the most common complication in chronic kidney disease," Inker said. She noted a growing convergence of treatments for CKD, cardiovascular disease, and metabolic diseases like diabetes and obesity, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs), which are also discussed in the guideline. Inker anticipates that convergence will grow.

Navaneethan and William noted that the medication recommendations reflect the results of recent large clinical trials. "Despite slow uptake, nephrologists are now getting more comfortable in using [SGLT2is], and we believe they should continue to focus on adapting their practice to incorporate goal-directed medical therapy, which includes the use of [renin-angiotensin-aldosterone system inhibitors] as well," they wrote. "As evidence for other drugs such as GLP-1RA and ns-MRA [nonsteroidal mineralocorticoid receptor antagonist] emerges, sequential or combination therapy, especially for those with diabetic kidney disease, is also being recommended."

They also highlight the guideline's emphasis on personalizing care, which they note is an increasing focus across medical specialties. "With several new therapeutic options becoming available (such as GLP-1RA and ns-MRA) and CKD being more common in the geriatric population, the KDIGO guideline provides a framework for adoption of these agents by considering various elements such as age, comorbid conditions, and access to medication."

Navaneethan and William also applauded the guideline's emphasis on multidisciplinary, team-based care to achieve care personalization, reduce barriers to adherence, and match care to patients' values.

"Nephrology is a team sport, and it's very hard to do all of these things and manage the complexity of the patient journey as a solo practitioner," Levin said. She hopes the KDIGO guideline will help more institutions and countries embrace team-based care models.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024 105:S117–S314. doi: 10.1016/j.kint.2023.10.018
2. Delgado C, et al. A unifying approach for GFR estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *J Am Soc Nephrol* 2021; 32:2994–3015. doi: 10.1681/ASN.2021070988
3. American Kidney Fund. American Kidney Fund applauds new KDIGO 2024 Chronic Kidney Disease Guideline. March 14, 2024. Accessed April 12, 2024. https://www.kidneyfund.org/article/american-kidney-fund-applauds-new-kdigo-2024-chronic-kidney-disease-guideline