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Nephro-Economics 2025: Federal Cuts, Medicare Advantage Growth, Workforce Shortage, and Care Innovation Take Center Stage

By Bridget M. Kuehn

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Nephrology faces tremendous uncertainty in 2025 and 2026 with major policy and funding shifts underway, noted speakers at Nephro-Economics 2025: Advancing Kidney Care in a Changing Environment in late May. The event was hosted in collaboration with the Division of Nephrology at Columbia University Irving Medical Center. Speakers highlighted shifts in health coverage with reductions expected in Medicaid rolls and growth in Medicare Advantage enrollment, proposed funding cuts and reorganization of federal health research agencies, and the risk of future workforce shortages.

At the time of the meeting, the US House of Representatives had just passed a budget bill that would slash Medicaid funding, compromise student loan availability, and reconfigure Affordable Care Act coverage options. Policy changes like an executive order targeting diversity, equity, and inclusion efforts; elimination of some quality programs; uncertainty over tariffs; and changes in immigration policies that may affect international medical graduates (IMGs) also loomed large.

"We really don't know what is going to happen, the amount of uncertainty is tremendous, and it could be very impactful," said Daniel E. Weiner, MD, MS, FASN, an ASN councilor and professor at Tufts University in Boston, MA. "We're going to see huge changes in research funding. I don't think we are going to see huge overall cuts in federal research funding, but I think we are going to see changes."

But speakers also noted potential opportunities amidst the change, such as President Trump's 2019 Advancing Kidney Health Initiative, the potential for improved organization at the National Institutes of Health (NIH), and the chance to reshape kidney care by making it more patient-centered.

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Innovation Needed in Immunosuppressive Medications

By Karen Blum

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Kidney transplant recipient Conley Rohall-Andrade was in her college dormatory room one morning, packing her backpack and about to head to class for an examination, when she experienced a sudden loss of bowel control.

"She basically had it in the middle of the dorm room in her suite," said her mother and kidney donor, Anne Rohall-Andrade, JD, director of public policy at the American Kidney Fund and a member of ASN's Kidney Health Initiative (KHI) Patient and Family Partnership Council. "She was mortified that her suitemates saw it. She was horrified that she was going to be late for her exam. She changed as fast as she could, but she said it was just awful, and it really changed the relationship she had with her suitemates, especially as a freshman student," shared Rohall-Andrade on her daughter's behalf with permission.

Sudden diarrhea is just one of several side effects that can significantly impact quality of life for transplant recipients taking immunosuppression drugs, Rohall-Andrade said during a panel discussion at the Kidney Innovation Conference held in May in Washington, DC. Other side effects include tremors that make it difficult to hold a pen or to type, hair loss, headaches, insomnia, and joint pain, she said at the conference, which was sponsored by KHI, the Kidney Innovation Accelerator (KidneyX), and KidneyCure.

Many patients consider kidney transplant, thinking that post-transplant life will be significantly better, said

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Inside

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INDICATION

XPHOZAH (tenapanor) 30 mg BID is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

- Pediatric patients under 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

WARNINGS AND PRECAUTIONS

Diarrhea

Patients may experience severe diarrhea. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

MOST COMMON ADVERSE REACTIONS

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials.

Please see Brief Summary of full Prescribing Information on the following page.

Reference: XPHOZAH® (tenapanor) full Prescribing Information. Waltham, MA: Ardelyx, Inc.; 2023.

ardelyx®

XPHOZAH (tenapanor) tablets, for oral use
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

XPHOZAH is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

4 CONTRAINDICATIONS

XPHOZAH is contraindicated in patients under 6 years of age because of the risk of diarrhea and serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5)]*.

XPHOZAH is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea was the most common adverse reaction in XPHOZAH-treated patients with CKD on dialysis *[see Dosage and Administration (2) in the full Prescribing Information, Contraindications (4) and Adverse Reactions (6.1)]*. In clinical trials, diarrhea was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 754 adults with CKD on dialysis taking XPHOZAH in clinical trials as monotherapy and in combination with phosphate binders. Among the 754 patients, 258 patients were exposed to tenapanor for at least 26 weeks and 75 were exposed to tenapanor for at least one year. *[see Clinical Studies (14) in the full Prescribing Information]*.

Most Common Adverse Reaction

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in the XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with XPHOZAH. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with XPHOZAH (30 mg twice daily for five days), the peak exposure (Cmax) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by 50 to 65% compared to when enalapril was administered alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. However, the decrease in enalaprilat's exposure with XPHOZAH may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Therefore, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis is not required when enalapril is coadministered with XPHOZAH.

7.2 Sodium Polystyrene Sulfonate

Separate administration XPHOZAH and sodium polystyrene sulfonate (SPS) by at least 3 hours. SPS binds to many commonly prescribed oral medicines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Therefore, maternal use is not expected to result in fetal exposure to the drug.

The available data on XPHOZAH exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.2 times the maximum recommended human dose and in rabbits at doses up to 15 times the maximum recommended human dose (based on body surface area) *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

The estimated background risk of major birth defects and miscarriage for women with CKD on dialysis with hyperphosphatemia is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.2 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 15 times the maximum recommended human dose, based on body surface area). In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 16.5 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XPHOZAH and any potential adverse effects on the breastfed infant from XPHOZAH or from the underlying maternal condition.

8.4 Pediatric Use

Risk Summary

XPHOZAH is contraindicated in patients less than 6 years of age. In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week old rats; approximate human age-equivalent of less than 2 years of age) and in older juvenile rats (approximate human age-equivalent of 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

The safety and effectiveness of XPHOZAH in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups.

In juvenile rats administered tenapanor at 0.03, 0.1, or 0.3 mg/kg/day on PND 5 through PND 61, treatment-related mortalities were observed at 0.3 mg/kg/day. Lower mean body weight gains were noted in the 0.3 mg/kg/day group males and females compared to the control group primarily during PND 12–24 but continuing sporadically during the remainder of the dosing period; corresponding lower mean food consumption was noted in this group during PND 21–33. As a result, mean body weights were up to 15.8% and 16.8% lower in males and females, respectively, compared to the control group; the greatest difference was on PND 24 for males and PND 21 for females. Mean body weight in the 0.3 mg/kg/day group males was only 3.9% lower than the control group on PND 61. There were no tenapanor-related effects on mean body weights, body weight gains, or food consumption in the 0.03 and 0.1 mg/kg/day group males and females. A dosage level of 0.1 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for juvenile toxicity of tenapanor *[see Contraindications (4), Warnings and Precautions (5.1)]*.

In a 21-day oral dose range finding study in older (weaned) juvenile rats administered tenapanor at 0.1, 1, or 5 mg/kg/day on PND 21 through PND 41 (approximate human age-equivalent of 2 to 12 years of age), treatment-related mortalities or moribundities were observed during the first two days of the study in the 1 mg/kg/day males and the 5 mg/kg/day males and females. Watery feces, decreased food consumption, and lower mean body weight were also observed in the 1 and 5 mg/kg/day groups.

In weaned juvenile rats administered tenapanor at 0.1, 0.3, and 0.7 (males) or 1 (females) mg/kg/day on PND 21 through PND 80, no mortalities were observed. Significant decreases in mean body weights were observed in the 0.3 and 0.7 mg/kg/day males throughout the dosing period (up to 20.3% lower than control) and in the 1 mg/kg/day females between PND 23 to 35 (up to 16.7% lower than control), with food consumption notably decreased on PND 21 to 29. There were also reductions in tibia length between PND 76 and 80 in the 0.3 and 0.7 mg/kg/day males, and between PND 36 and 64 in the 0.7 mg/kg/day males, which were not observed during the 14-day recovery period. The NOAEL was considered to be 0.1 mg/kg/day for juvenile toxicity of tenapanor.

8.5 Geriatric Use

Of 1010 adult patients with CKD on dialysis randomized and treated in two randomized, double-blind, placebo-controlled randomized withdrawal clinical trials for XPHOZAH (TEN-02-201 and TEN-02-301) as well as a third randomized, double-blind, placebo-controlled trial (TEN-02-202) for XPHOZAH in combination with phosphate binders, 282 (28%) were 65 years of age and older. Clinical studies of XPHOZAH did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently than younger patients.

10 OVERDOSAGE

No data are available regarding overdosage of XPHOZAH in patients. Based on nonclinical data, overdose of XPHOZAH may result in gastrointestinal adverse effects such as diarrhea, as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

Instruct patients to contact their healthcare provider if they experience severe diarrhea *[see Warnings and Precautions (5.1)]*.

- Instruct patients not to use stool softeners or laxatives with XPHOZAH.

Administration and Handling Instructions

Instruct Patients:

- To take XPHOZAH just prior to the first and last meals of the day *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- Patients should be counseled not to take XPHOZAH right before a hemodialysis session, and to take XPHOZAH right before the next meal, as some patients may experience diarrhea after taking XPHOZAH.
- If a dose is missed, take the dose just before the next meal. Do not take 2 doses at the same time *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- To keep XPHOZAH in a dry place. Protect from moisture. Keep in the original bottle. Do not remove desiccant from the bottle. Keep bottles tightly closed *[see How Supplied/Storage and Handling (16) in the full Prescribing Information]*.

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Delays and downsizing

Some of the uncertainty stemmed from the fact that the Senate, at press time in June, had not yet passed its version of the reconciliation bill. Weiner suspected that the fiscal year 2026 appropriations process may not be completed by October 1. If that happens, he said, Congress would have to keep discretionary spending at 2025 levels for the start of 2026—or face a government shutdown.

He noted that a leaked version of the president's "skinny budget" proposal included a 40% cut in NIH funding, reducing spending to 2003 levels (1). The proposal also recommended cutting US Department of Health and Human Services funding by 26%. "That's daunting and intimidating," Weiner said.

But Weiner said that he did not think there would be sufficient votes in the Senate necessary to advance such dramatic cuts through the annual appropriations process. He noted that Republican Senators like Bill Cassidy (Louisiana), a physician, released a set of proposals in 2024 calling for ongoing support for NIH but an increased emphasis on efficiency (2). He also noted that former Republican Representative Cathy McMorris Rodgers (Washington) put out a plan to reorganize NIH in 2024, similar to some of the changes proposed in the leaked skinny budget (3). Weiner felt that reorganization was a more likely outcome than massive cuts. He said that reorganization that facilitates cross-disciplinary research could benefit kidney care, especially if Congress and the administration discuss the best reorganization approach with the kidney community. He added that ASN had also provided input to Senator Cassidy and other congressional leaders looking at NIH reorganization and would continue to actively engage with them.

"There may be something that is gained by reorganization," he said. "Eliminating specific institutes within NIH is something that is going to be harder for the administration to accomplish and could have much more severe consequences than reorganization that may be more conducive to research that spans disciplines."

He expressed concern about the potential for reduced emphasis on health equity, for which ASN strongly advocates. He said it would be essential to distinguish health equity from the administration's current efforts to eliminate workforce diversity, equity, and inclusion efforts. He noted that framing health equity based on wealth and an urban versus rural setting may help. "We have to be advocates for our patients going forward," he said. "It's incumbent on us to ensure this is not the end of health equity."

Coverage shifts

The House budget reconciliation bill included substantial cuts to Medicaid of $60–$70 billion per year, along with work requirements for adults without disabilities up to aged 64 years, which could have serious impacts on people with chronic kidney disease, Weiner noted. He also noted that there may be fewer patients who are dual-eligible for Medicare and Medicaid. "Medicaid cuts are coming, and those are going to be impactful," Weiner said.

The current proposal could also slash the federal government's matching payments for insurance through Medicaid for states that provide coverage for undocumented immigrants. Some states may drop coverage for people who are undocumented or find alternative ways to offer them coverage through the private market, Weiner noted. The effects could be dramatic in Medicaid expansion states. Such changes would impact nephrology care, hospitals, and patients, particularly people with kidney diseases who are undocumented. "It is too soon to say what the effects will be state to state," he said.

Medicare Advantage has also become the primary payor for patients on dialysis. Starting in 2021, the 21st Century Cures Act gave people with kidney failure the option of selecting traditional fee-for-service Medicare or a Medicare Advantage plan offered through a private insurer, explained Eugene Lin, MD, MS, FASN, assistant professor of medicine, Division of Nephrology and Hypertension, at the Keck School of Medicine of the University of Southern California (USC) and a clinical and resident fellow at the USC Leonard D. Schaeffer Center for Health Policy & Economics, Los Angeles. By 2023, Medicare Advantage plan enrollment among people with kidney failure exceeded enrollment in traditional Medicare. Enrollment in Medicare Advantage plans in this population is expected to plateau at 60% by 2030, according to data from the Kaiser Family Foundation (4). Only 0.5% of people switch back to Medicare fee-for-service from a Medicare Advantage plan, but a higher percentage switch among Medicare Advantage plans, Lin noted.

"There isn't a whole lot of regret about choosing Medicare Advantage," he said. "We need to figure out whether Medicare Advantage is better than fee-for-service Medicare, and if it is not, what are the guardrails that we have to establish to ensure our patients are not shortchanged?"

The shift may also have effects on nephrologists and dialysis facilities. Medicare fee-for-service pays consistent rates for care across the board. However, Medicare Advantage plans receive a monthly payment from Medicare based on the risk profile of their patient pool and then administer the benefits themselves. Medicare Advantage plans negotiate rates with clinicians and dialysis facilities individually, which may be an advantage to larger systems that can negotiate better reimbursement for care. Lin noted that these plans also maintain narrow networks that exclude clinicians with the highest rates and steer patients toward the clinicians with the lowest rates.

Patients may choose these narrow network plans because they offer other perks that traditional Medicare does not. For example, the plans may offer vision coverage, hearing benefits, dental coverage, fitness plans, and telehealth perks that can be valuable for older people with kidney failure. Most Medicare Advantage plans also have lower out-of-pocket costs, Lin said. Traditional fee-for-service Medicare may have out-of-pocket costs as high as $12,000 a year for people with kidney failure, while Medicare Advantage Preferred Provider Organization plans may have an $8800 out-of-pocket limit, and Health Maintenance Organization versions may cap these costs at $4800, he explained. "[Patients] may be financially better off through lower premiums or a cap on out-of-pocket spending," he said. "In some cases, even more care coordination is offered through Medicare Advantage plans."

Lin said that prescription drug premiums and out-of-pocket costs may also be lower on Medicare Advantage plans. Generics in these plans may have zero copay. But Medicare Advantage plans may charge substantially more for expensive or branded specialty drugs. That's a concern, he said, because it could affect the availability of newer drugs like mineral corticoid receptor antagonists, sodium-glucose cotransporter-2 inhibitors, or glucagon-like peptide agonists that help reduce disease progression in people with kidney failure. Prior authorizations, he noted, can also limit access to medications in these plans. He said that reports have documented instances of inappropriate or blanket denials of preauthorization by some insurers (5, 6). Artificial intelligence technology may exacerbate authorization denials without clinician review, he continued. "They're using a sledgehammer for something that probably requires a fine needle, and they're relying on the professionalism and the integrity of physicians, physician assistants, and nurse practitioners to go and do the extra work of appealing these prior authorization denials to get [patients] the care that they need," he said.

Medicare Advantage may also limit dialysis network access. Lin explained that although larger chains are usually covered, smaller regional dialysis chains, independent facilities, or hospital-based dialysis facilities are often out-of-network. "The large dialysis organizations get the biggest markups [on reimbursement], followed by the regional chains, [and] the independent facilities, and then hospital-based facilities' [reimbursements] are at parity with fee-for-service Medicare," he said. "We should be worried about this phenomenon potentially worsening consolidation in the dialysis market."

Another system-level concern is that the federal government pays Medicare Advantage plans 20% more than it pays for traditional Medicare, which raises concerns about costs to the taxpayer, Lin noted. "We don't have a lot of data yet on whether Medicare Advantage is definitively better or worse than fee-for-service Medicare," he said. "There's likely a lot of heterogeneity in outcomes. There are winners and losers at every level of Medicare Advantage, and it is expensive to taxpayers and something that we should be thinking about."

Workforce challenges

Suzanne Boyle, MD, MS, a member of ASN's Workforce and Training Committee and chair of the ASN Data Subcommittee, noted that the Health Resources and Services Administration predicts a shortage of nephrologists by 2035.

She explained that the number of nephrologist training positions has increased by more than 100 over the past 15 years. According to ASN's Annual Nephrology Fellow Survey, almost 60% of trainees are IMGs (7). One-third of them are in the United States on visas, with 24% on J-1 visas. She noted that IMGs also make up most of the practicing nephrologist workforce. Over the next 5 to 10 years, a substantial proportion of the nephrology workforce aged over 65 years is expected to retire, she said.

Boyle noted that there is also a geographic mismatch where nephrologists practice and where there is a demand for care. Whereas metropolitan areas are often well-served, parts of Texas, the Midwest, and rural areas are underserved.

She said efforts to increase the supply of nephrologists and help increase access in underserved areas have focused on making nephrology more attractive, reducing barriers to entry for IMGs, and easing the interstate licensure process. Boyle believes that nephrology has lost potential recruits to the growing field of hospital medicine. She noted that new clinicians may be drawn to the lifestyle, salary, and reduced training requirements associated with hospital medicine. She said that there is a need to market nephrology during the second and third year of residency when many trainees select their specialties, highlighting ASN's Kidney STARS (Students and Residents) program (8).

She also shared that the fellows' survey consistently shows that fellows' top job concerns often focus on call frequency, overnight demands, location, and vacation time. "Early career nephrologists value lifestyle and value lifestyle more than compensation," she said. "As we try to sustain our profession, [it is important] that employers meet new early career nephrologists where they are and try to create positions they value."

Boyle noted that there is a perception that nephrologists are paid less than other specialties, which she said is a myth. However, she said it is vital to emphasize the potential for longer-term earnings associated with joint ventures and partnerships in nephrology. She also highlighted the availability of loan forgiveness programs. "Loan forgiveness programs come with a service component that could help get nephrologists in places in the country where we need them most," she noted.

Boyle said efforts to ease the pathways for IMGs are also needed. She noted that 11 states have passed alternative licensure legislation to make it easier for IMGs to practice in specialties that are underserved. But it is unclear if this legislation would increase the number of clinicians who choose nephrology or instead shift some toward primary care, which is the focus of some state programs. There is not yet a pathway to board certification for clinicians who complete these alternative licensure pathways. The American Board of Internal Medicine is also launching a pilot program for "exceptionally qualified" IMGs that would allow these individuals to be eligible for board certification after completing a nephrology fellowship, without having to complete a US residency. Numerous states have also entered interstate licensing agreements that can help increase physician mobility to fill gaps and make telehealth possible.

Easing the demand for nephrologists is also essential. Boyle said that advanced practice providers may help. She suggested using tools like artificial intelligence to provide risk-based triage of patients. She said that electronic medical record workflows that ensure that patients receive kidney health-preserving therapies may also help reduce the burden

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of chronic kidney disease and kidney failure and decrease the demand for nephrologists in the long term.

But a federal crackdown on immigration could throw a monkey wrench in some of these efforts. At press time, a pause on visa interviews had left some IMGs in limbo. It has raised concerns that some may not obtain visas in time to start residencies, which would disproportionately impact areas underserved by physicians who rely heavily on IMGs to fill residency slots (9). ASN also issued an alert advising noncitizen medical professionals, including permanent residents, to postpone any nonessential travel outside of the United States (10). The alert noted federal travel bans, changes to visa programs, and increased US Immigration and Customs Enforcement that may ensnare legal residents in the United States.

"In nephrology, we are very dependent on an international workforce," Weiner said. "There's a tremendous amount of uncertainty here; we just don't know what will come. But if people are not coming to this country, I don't know where we are going to find our transplant nephrology workforce. I don't know where we are going to find our dialysis nurses or our patient care technicians [or staff for nursing homes and hospitals]."

Other topics highlighted during Nephro-Economics 2025 included sessions on:

- the need for innovation in kidney care and new payment models;
- ongoing transplant reform efforts;
- the financial impact of living donation; and
- ASN's long-term policy goals. ■

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Innovation Needed in Immunosuppressive Medications

Continued from cover

Rohall-Andrade, who has been collecting patient stories. "Many of the patients I spoke to said that they would prefer to be on dialysis had they known that they were going to live a life with massive side effects. They said they felt better between dialysis treatments."

There was the patient who experienced diarrhea while riding on a Washington, DC, city bus and overheard the driver announcing that there was a biohazard needing cleanup; the person whose tremors made it impossible to walk from their kitchen to their living room without spilling coffee; a 19-year-old who said they felt alone in school because they have to run back to their dormatory in the middle of an activity to take medication; and others revealing that they cannot stand for long periods of time because of joint pain or that they struggle to sleep multiple nights in a row.

"We have fallen into this sort of false definition of success, which is, 'Are you alive?' 'Do you have a functioning organ at the end of 1 year?'" reflected Robert Montgomery, MD, DPhil, chair and professor of surgery at New York University (NYU) Langone Health and director of the NYU Langone Transplant Institute. That is what drives the financial aspects of transplant and is how quality is measured, he said. "I think we've done a really good job at hitting those targets, but from the patient's perspective, that is not nearly as meaningful as… quality of life and longevity." Lifestyle factors important to patients "really need to be amplified and studied, and those are areas where we need to innovate," Montgomery noted. "If you poll most transplant recipients, they'll say that they traded one disease for another," he added, noting that "in most cases, they traded up."

"I agree with you that most people trade up, but you'd be surprised how many patients might feel that they didn't," said Ogo Egbuna, MD, MSc, FASN, vice president of clinical development at Vertex Pharmaceuticals and a member of the KHI Board of Directors. There are tangible outcomes such as kidney function that can be readily identified "but lots of intangibles that are just as important," Egbuna noted.

Patients who receive a transplant can have "survivor guilt," Rohall-Andrade said, and therefore may feel that they do not have the right to complain about side effects or emotional challenges. "When you go to [medical] conferences, you'll hear a lot of scientific data and very complicated medical discussions, but the patient voice really has to be involved," she noted.

Beyond side effects, there are additional burdens placed on patients, continued Rohall-Andrade. They have to go for regular laboratory work and must take medications on a regimented schedule. Some patients may experience access issues getting their medications, especially if their doses were recently readjusted, and the pharmacy or an insurer denies the claim.

"It's like playing Whac-a-Mole," Rohall-Andrade said. "You've got a transplanted kidney, but you're really prone to infection, so you get these secondary infections that put you in and out of the hospital." Additionally, she said, immunosuppressant drugs that prevent graft failure put patients at higher risk of skin cancer and diabetes (ironically, the leading cause of kidney transplant). "You can see it's like a circular problem."

One recent study highlights the impact of kidney transplantation on health-related quality of life (HRQoL) in recipients aged ≥65 years (1). Overall, both mental and physical HRQoL were considered higher among kidney transplant recipients than among those on the waitlist. But in a separate analysis of 46 patients before and after transplantation, the number of patient-reported immunosuppressive, drug-related side effects was most strongly negatively associated with both mental and physical HRQoL. Side effects cited included erectile dysfunction (46% of males), bruises (36%), dry skin (26%), reduced interest in sex (25%), increased urge to urinate (22%), and lack of energy (23%).

The burden of medication compliance is another significant challenge for patients who need to take medications within 1 to 2 hours of a determined schedule or risk graft failure, Rohall-Andrade said. This can be amplified in patients with low health literacy.

"The meds have to be taken the same time every day, two to three times a day, and there are numerous reasons why patients miss that," she said. She has heard from one woman whose son was traveling in Europe and did not factor in the 6-hour time difference. He took his medications 6 hours late for 2 weeks and went into rejection. Another person she knows was taken to jail for a routine traffic issue and could not access his medications for 10 days. He, too, went into rejection.

The panel members discussed areas ripe for innovation. From a systemic perspective, if the health care system allowed more people to be transplanted quicker, "they would be in much better condition when they receive a transplant and wouldn't have the burden of all these comorbid conditions that accentuate and worsen the realities of the immunosuppression and other aspects of transplantation," Montgomery said.

Rohall-Andrade said patients who she talks to ask, "What's the next thing?" "We have birth control patches we can wear on our arm and injections for various conditions. Patients want to know why they have no choice," she said.

"It's been a while since we've seen some innovation in at least trials in clinical transplantation," Egbuna added.

The last immunosuppressant for transplant recipients was approved by the US Food and Drug Administration in 2012—before engaging patients and including their wishes was part of the drug development culture, said Mark Lim, PhD, vice president of Research, Discovery, and Innovation at ASN, in an interview with *Kidney News*. Now, times have changed.

During a breakout session, nephrologists, manufacturer representatives, and a patient advocate discussed a potential project on how to include new measures of safety and tolerability in clinical trials, said Lim, who oversees strategic priorities for KHI. This would include tolerability measures like uncontrolled diarrhea, which could result in compliance issues, as well as safety side effects like the increased risk for cancer.

From a drug development standpoint, people in the breakout group also touched on how they could measure improvements because "there's no yardstick for that," Lim said. For example, it may be scientifically achievable to reduce the number of uncontrolled incidents of diarrhea from 10 to 5 per month. "It isn't like you get rid of it, but at least it's better than the status quo." KHI representatives also tried to get a sense of whether they were headed in the right direction, said Lim: "We got a resounding yes." The next step is to host a more in-depth workshop on how to improve immunosuppressants, most likely in 2026, Lim shared. ■

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ASN Leads Kidney Community and Congressional Advocacy on Research and Innovation Funding Efforts

By Ryan Murray

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ASN partnered with the American Society of Pediatric Nephrology and the National Kidney Foundation to colead two kidney community sign-on letters to congressional leaders urging that they support the National Institutes of Health (NIH), in particular, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Kidney Innovation Accelerator (KidneyX), a public-private partnership between the Department of Health and Human Services (HHS) and ASN.

In one of the letters to congressional leaders on May 22 (1), nearly 30 kidney community organizations advocated that NIH receive at least $51.303 billion, including a $207 million increase for NIDDK in the fiscal year (FY) 2026 Labor, Health and Human Services, Education, and Related Agencies appropriations bill. Citing the urgent need to improve early diagnosis, treatment, and research into kidney diseases, the letter emphasized that kidney diseases are the ninth-leading cause of death in the United States yet remain chronically underfunded relative to their impact on public health and Medicare.

A second letter (2) urged Congress to provide $25 million in FY 2026 for KidneyX so that the program can continue to fund technological innovation in the prevention, diagnostics, and treatment of kidney diseases, including the development of artificial kidneys and xenotransplantation tools. Since its inception, KidneyX has supported 75 innovators in 23 states across 6 prize competitions and catalyzed over $400 million in investments from private and philanthropic sources. Increased federal investment is needed to ensure that these efforts continue and expand.

Congressional Kidney Caucus Cochairs Rep. Carol Miller (R-WV) and Rep. Suzan DelBene (D-WA), champions of kidney innovation and donor support, echoed these advocacy efforts through two bipartisan "Dear Colleague" letters (3, 4), for which ASN also helped build support among members of Congress.

The first (3), signed by 35 members of Congress, also supported $25 million for KidneyX in the FY 2026 bill. The letter highlighted stark statistics: More than 800,000 Americans live with kidney failure, Medicare spends over $150 billion annually on people living with kidney diseases, and 12 people die each day waiting for a kidney transplant. KidneyX, the letter argues, is a high-impact, underfunded initiative capable of transforming this landscape and urged HHS to continue advancing innovation through KidneyX.

The second letter (4) focused on supporting living organ donors, echoing a funding increase effort that ASN also led for the Health Resources and Services Administration's Living Organ Donation Reimbursement Program earlier this year, uniting more than 30 kidney patient and health professional organizations to urge $67 million in FY 2026 funding (5).

The Living Organ Donation Reimbursement Program helps donors defray out-of-pocket expenses such as travel and lost wages. Currently, reimbursement is capped at $6000, and income limits exclude many willing donors. The letter argues that expanding the program would remove disincentives to donation and improve transplant rates for the over 100,000 Americans waiting for lifesaving organs—most of whom need kidneys. It notes that living donation is not only the most effective treatment for kidney failure but also the most cost-efficient, saving approximately $100,000 per transplant over 10 years.

Yet meanwhile, the FY 2026 Presidential Budget, released by the Trump administration, outlines sweeping cuts to federal health funding that could reshape the future of kidney care and research. Chief among the concerns for the kidney community is a proposed $18 billion reduction to NIH, bringing the agency's funding to just $27 billion in FY 2026, a dramatic 39% decrease. If enacted, this would be one of the most substantial NIH funding rollbacks in its history.

The budget also proposes to reorganize NIH institutes and centers into an eight-institute structure and eliminate several institutes, most notably the National Institute on Minority Health and Health Disparities. Although NIDDK is not targeted for elimination under the reorganization plan, it would still be significantly affected by the broader restructuring effort. The proposed changes aim to consolidate NIH's mission around fewer, more "central" disease areas and reduce the number of institutes and centers. NIDDK would be consolidated with the National Heart, Lung, and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases into a new National Institute on Body Systems, funded at $4.152 billion. No further details are currently available about how funding would be reasonably allocated within the new institute.

However, it is essential to remember that congressional appropriations committees ultimately control funding levels—not the White House. Moreover, congressional authorizing committees ultimately control the NIH structure—the White House cannot unilaterally change statutorily-created institute centers. These realities underscore the essential nature of ASN's, and the broader kidney and transplant community's, advocacy efforts on Capitol Hill.

Taken together, these ASN-led kidney community and congressional appeals reveal a stark contrast between the priorities of the kidney community and those outlined in the FY 2026 Presidential Budget.

The call for increased NIH and NIDDK funding, sustained KidneyX investment, and expanded donor support will improve lives, advance equity, and ensure that the United States remains a global leader in biomedical innovation. At a time when kidney diseases are becoming more prevalent and expensive to treat, ASN believes that now is the time to accelerate investment rather than scale it back.

The FY 2026 proposed Presidential Budget's deep cuts to NIH would reverberate throughout the kidney community, impacting research, innovation, and patient care. However, the kidney community's advocacy efforts, led by ASN and a bipartisan coalition in Congress, show that there remains strong support for federal investment in kidney health.

As the appropriations process unfolds, ASN will continue to press its case: that funding innovation, supporting donors, and sustaining vital research are essential to the health of millions of Americans—and to the fiscal health of the Medicare program. Whether these priorities will be reflected in the final FY 2026 budget remains to be seen, but the collective voice of the kidney community has never been clearer or more united. ■

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Acknowledgments: This article reflects information available as of June 5, 2025. For the latest policy developments, follow coverage in *Kidney News*, the ASN podcast feed, and visit ASN's new Kidney Health Advocacy webpage (https://www.asn-online.org/policy/kidney-health.aspx).

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ASN Advocacy Secures Key Win for IMGs as Visa Interview Pause Lifted

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Following swift advocacy by ASN and others in the kidney community, the US Department of State recently lifted the pause on new student and exchange visa interviews and will expedite interview scheduling for J-1 visas. This pause threatened the stability of the US health care workforce due to its impact on the ability of international medical graduates (IMGs) to procure visas in time to report to work following the spring National Resident Matching Program Match, particularly in nephrology. ASN President Prabir Roy-Chaudhury, MD, PhD, FASN, emphatically called on Secretary of State Marco Rubio to expedite interviews for IMGs with J-1 visas (1).

This pause would have jeopardized the timely arrival of thousands of IMGs who are scheduled to begin their residencies and fellowships by July 1, 2025, or shortly thereafter. ASN was especially alarmed about the potential impact on kidney care, as IMGs make up more than 50% of practicing nephrologists and nearly two-thirds of current nephrology fellows. Without ASN's rapid intervention, approximately 40% of incoming nephrology fellows—who care for over 37 million Americans with kidney diseases—may have been unable to begin their training on time.

ASN asserted that this policy shift would not just affect people living with kidney diseases. Nationwide, one in four physicians (and one in three internists) is an IMG, and many of these professionals serve in underserved and rural communities. Moreover, over 120,000 residents and fellows receive training in Department of Veterans Affairs Medical Centers. Delaying or denying these physicians' entry into the country would have threatened the care of countless veterans who rely on Veterans Affairs facilities.

In his letter, Dr. Roy-Chaudhury emphasized that although national security and thorough vetting of visa applicants are vital, physicians are among the most heavily vetted professionals entering the United States. ASN called on the Department of State to extend the same exemption for IMGs that had already been granted to participants in the upcoming 2026 World Cup and 2028 Olympic Games—two events that underscore the feasibility of granting timely entry under strict protocols.

To amplify this message, ASN worked together with the broader medical community to lift the pause, including the American College of Physicians and Intealth, which oversees the Educational Commission for Foreign Medical Graduates. ASN had launched an open petition urging Secretary Rubio and the Department of State to immediately exempt IMG J-1 visa applicants from the pause and to expedite their visa processing.

This key win for IMGs benefits the broader nephrology and medical community, and continues ASN's broader efforts to protect access to care for millions of Americans. ■

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CREATIVE CORTEX

The Inferno Within

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This artwork powerfully embodies the slow, relentless burn of chronic kidney disease—a silent, smoldering battle within the body. The inflamed glomeruli, once pristine filters of life, now twist and writhe in fiery distortion, their structure unraveling in waves of deterioration. The deep reds and molten golds echo both inflammation and resilience, reflecting a struggle between decay and adaptation. It is a haunting yet mesmerizing portrayal of persistence, loss, and the fragile balance of survival. ■

Artwork by AnilzArt. Anil Saxena, MD, FASN, is a digital artist based in Dubai, United Arab Emirates. His abstract artwork blends trained medical expertise with vibrant color palettes, creating visually captivating landscapes of human identity and transformation. Saxena's work has been exhibited internationally and featured on the covers of medical journals.

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A SPOTLIGHT ON GENETIC KIDNEY DISEASES

By Suman Behera and Itunu Owoyemi

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Welcome to this special section of *Kidney News*, dedicated entirely to the rapidly evolving landscape of genetic kidney diseases. As coeditors, we are thrilled to bring you a collection of articles that illuminates the profound impact of genetics on kidney health, from rare monogenic disorders to the more complex genetic predispositions contributing to both common and rare kidney diseases.

The advancements in genetic research, next-generation sequencing, and kidney maps are revolutionizing our ability to diagnose, understand, and treat these conditions.

While many cases of chronic kidney disease (CKD) are linked to conditions like diabetes and hypertension, genetic factors play a significant role. Genetic variants can explain a considerable proportion of CKD cases, with estimates of observational heritability of CKD ranging from 25% to 44% (1).

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disorder due to pathologic variants in two genes, PKD1 (in approximately 78% of cases) or PKD2 (in approximately 15% of cases), occurring in 4%–8% of people living with CKD (2).

Inherited kidney diseases are among the leading causes of early-onset CKD and are responsible for at least 10%–15% of cases of kidney replacement therapy in adults and most pediatric patients on kidney replacement therapy (3).

This section features experts' views on genetic kidney diseases like ADPKD, Alport syndrome, congenital anomalies of the kidneys and urinary tract, primary hyperoxaluria, Fabry disease, and *APOL1*-related CKD and on genetic testing of transplant recipients and donors. We conclude the section by sharing patient stories and viewpoints, aiming to break the stereotype that genetic diseases are tied to sex, race, or ethnicity.

We believe these contributions will serve as an invaluable resource for nephrologists, geneticists, and researchers to improve outcomes for people living with genetic kidney diseases. We give our sincere thanks to the authors for their dedication to advancing this crucial field and improving understanding of genetic kidney diseases. ■

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The authors and section coeditors report no conflicts of interest.

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Clinical Practice Guidelines for Genetic Testing in ADPKD

By Neera K. Dahl, Pranav S. Garimella, and Fouad T. Chebib

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The 2025 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines (1) introduced practice points and recommendations regarding the role and clinical utility of genetic testing in autosomal dominant polycystic kidney disease (ADPKD). ADPKD remains primarily a clinical diagnosis based on imaging. However, genetic testing is increasingly recognized as an important adjunct in diagnosis, prognosis, and family planning.

For individuals with a known family history of ADPKD, ultrasound-based diagnostic criteria are highly predictive. For a 35-year-old with at least four cysts (total from both kidneys), the positive predictive value for ADPKD is 100%, with 96% sensitivity across *PKD1* and *PKD2* genotypes (2). In patients without a known family history, diagnostic clues indicating ADPKD include enlarged kidneys with bilateral cysts, liver cysts, and impaired kidney function at an older age. Conversely, features such as liver fibrosis should raise suspicion for an alternative diagnosis (1).

Common indications for genetic testing include the absence of family history, a pretransplantation genetic diagnosis, potential kidney donor evaluation in individuals under 40 years of age with affected family members, and cases with early-onset or atypical presentations (Figure, A) (3). Recent guidelines recommend broader use of genetic testing in situations such as noticeable differences in disease severity within a family, discrepancies between imaging findings and clinical progression, a low glomerular filtration rate (GFR) despite a small number of cysts, unusual imaging characteristics, or the presence of extrarenal features suggestive of a syndromic cystic condition other than ADPKD, such as tuberous sclerosis (Figure, A and B).

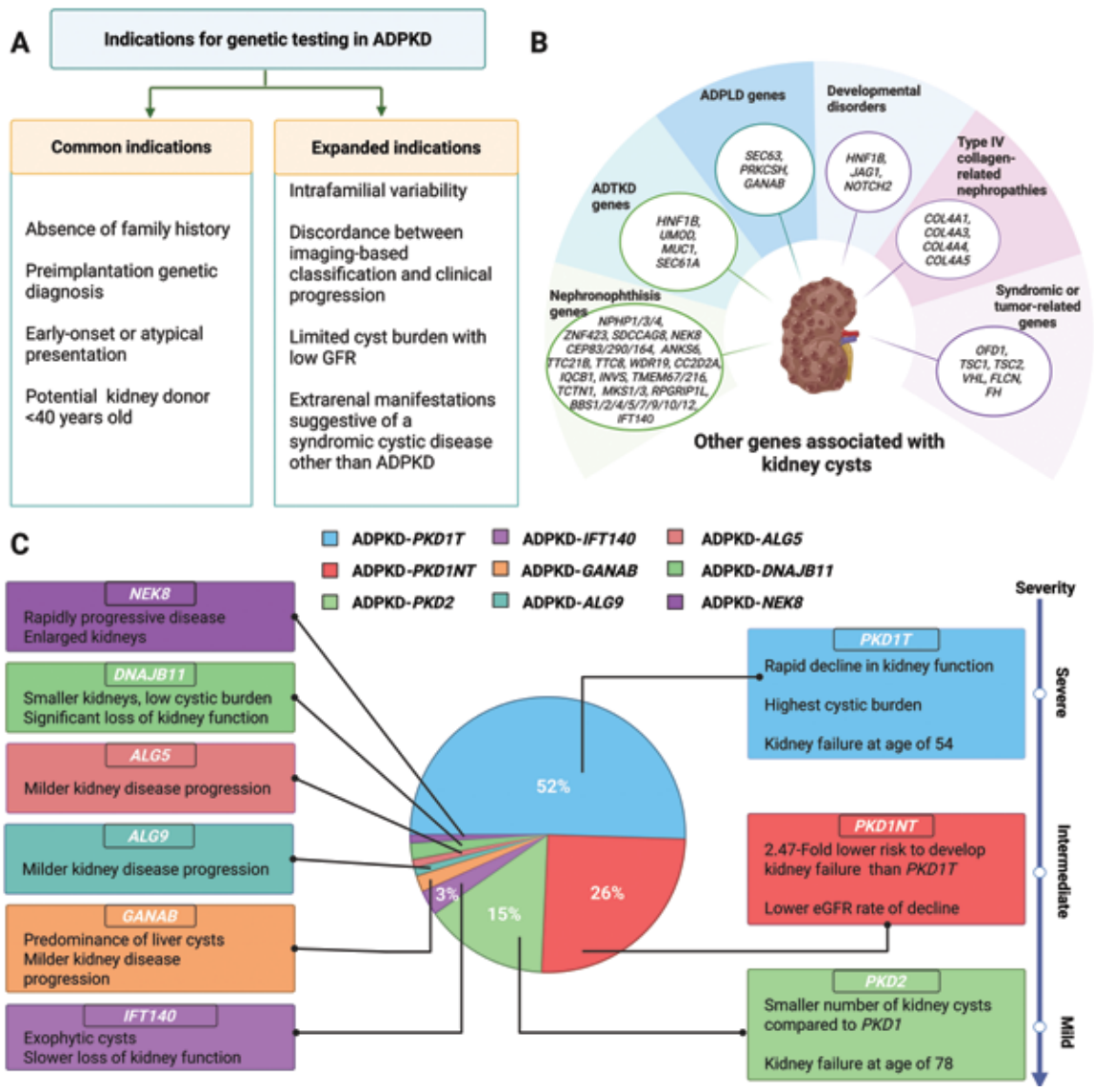
The genetic landscape of ADPKD has broadened, with eight genes (including two variants for *PKD1*) now associated with the phenotype of bilaterally enlarged cystic kidneys. *PKD1* and *PKD2* remain the most common, accounting for 78% and 15% of cases, respectively. These genes are highly penetrant, with pathogenic or likely pathogenic variants typically manifesting as a clinically apparent disease. Among the less common genes, *IFT140* is the third-most frequently implicated, often associated with exophytic large cysts and relatively preserved kidney function (4). Other genes include *GANAB, ALG5*, and *ALG9*, typically associated with milder kidney disease progression. *GANAB* may occasionally present with predominant hepatic cysts. *NEK8* is linked to rapidly progressive disease with enlarged kidneys, whereas *DNAJB11* is associated with smaller kidneys and significant kidney function decline at an older age (Figure, C).

Given these genotype–phenotype correlations, KDIGO now suggests incorporating the gene name into disease nomenclature (e.g., ADPKD-*PKD1*, ADPKD-*PKD2*). *PKD1* pathogenic variants are commonly truncating (*PKD1T*), which result in the absence of full-length polycystin-1 (5), and are associated with faster progression to kidney failure than nontruncating variants (*PKD1NT*). In addition to providing a diagnosis, genetic test results can be used in the PROPKD (Predicting Renal Outcome in Polycystic Kidney Disease) score, incorporating genotype (*PKD1T*, *PKD1NT*, or *PKD2*), age, sex, and early-onset hypertension or urologic events, to aid in risk stratification (6).

Beyond the two major (*PKD1* and *PKD2*) and six minor (*IFT140*, *ALG5*, *ALG9*, *NEK8*, *DNAJB11*, and *GANAB*) PKD genes, a growing number of additional genetic mutations can present with a phenotype that includes cystic kidneys. These include developmental disorders (*JAG1*, *NOTCH2*, and *HNF1B*), type IV collagen-related genes (*COL4A1*, *COL4A3*, *COL4A4*, and *COL4A5*), autosomal dominant tubulointerstitial kidney disease (ADTKD) genes (*HNF1B*, *MUC1*, *UMOD*, and *SEC61A*), syndromic or tumor-related genes (*OFD1*, *TSC1*, *TSC2*, *FLCN*, *VHL*, and *FH*), nephronophthisis genes (*NPHP1*, *NPHP3*, *CEP164*, *ZNF423*, *SDCCAG8*, *IFT140*, *TTC21B*, *CEP83*, *CEP290*, *ANKS6*, *NEK8*, *TTC8*, *WDR19*, *CC2D2A*, *IQCB1*, *TMEM67*, *RPGRIP1L*, *TCTN1*, *TMEM216*, *NPHP4*, *INVS*, *BBS1*, *BBS2*, *BBS4*, *BBS5*, *BBS7*, *BBS9*, *BBS10*, *BBS12*, *MKS1*, and *MKS3*), and autosomal dominant polycystic liver disease (ADPLD) genes (*PRKCSH*, *SEC63*, and *GANAB*) (Figure, C). In our clinical practice, variants in *HNF1B*, *UMOD*, and *COL4A* genes, as well as heterozygous *PKHD1*, are among the most frequently identified alternative diagnoses in patients initially suspected of experiencing ADPKD. Although heterozygous mutations in *PKHD1* may occasionally be associated with cystic kidney disease in adults, autosomal recessive PKD remains the most common and well-established clinical manifestation of *PKHD1* mutations. Therefore, comprehensive cystic kidney disease panels should include both the eight core ADPKD genes and this broader list of mimics.

As genotype-specific therapies are being developed, and clinical trials expand, genetic testing is expected to become an integral part of routine ADPKD management. Identifying the underlying gene will be essential, not only for diagnosis and family counseling but also for informing prognosis and guiding precision therapies. ■

Figure. Genetic testing indications and genotype–phenotype correlations in ADPKD



(A) Clinical indications for genetic testing in ADPKD. (B) Broader differential diagnosis of cystic kidney disease highlighting genes that can present with kidney cysts and possibly mimic ADPKD. (C) Genotype–phenotype associations among the eight ADPKD-related genes (including *PKD1T* and *PKD1NT* variants for *PKD1*). A pie chart shows their relative prevalence. eGFR, estimated GFR.

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From Basement Membrane Thinning to Alport Syndrome: An Array of Presentations Caused by *COL4A3/A4/A5* Gene Variants

By Jeffrey H. Miner

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Alport syndrome is classically described as a hereditary disorder with a triad of features: 1) progressive kidney disease that results in kidney failure in adolescence or early adulthood, 2) sensorineural deafness, and 3) anterior lenticonus accompanied by retinal defects (1). The first sign of Alport syndrome is usually hematuria. Affected individuals eventually develop proteinuria, followed by glomerulosclerosis and tubulointerstitial fibrosis, progressive reduction in the glomerular filtration rate, and kidney failure. Although the renin-angiotensin system blockade can significantly delay proteinuria and kidney failure (2), there is no cure for Alport syndrome.

Alport syndrome is caused by pathogenic variants in the type IV collagen *COL4A3*, *COL4A4*, and *COL4A5* genes, each of which encodes the respective α chain of the collagen α3α4α5(IV) heterotrimer (1). These heterotrimers form extracellular networks that are abundant in the kidney glomerular basement membrane (GBM), in cochlear basement membranes, and in various eye basement membranes (1). The Alport GBM exhibits characteristic ultrastructural features that include thinning, thickening, and splitting (1), which can have a basket-weave appearance.

The kidney disease aspect of Alport syndrome is usually most severe when one of the α chains is completely missing due to null variants (e.g., nonsense, splice site, or frameshift variants), because without all three chains present, the trimer can neither form nor be secreted into the GBM (3). In contrast, missense variants that impact the structure and/or function of the collagen α3α4α5(IV) heterotrimer but do not prevent its accumulation in the GBM usually result in delayed kidney failure (3).

The *COL4A3* and *COL4A4* genes are present in a linked head-to-head orientation on chromosome 2, and both copies of one of them must be mutated to cause the autosomal recessive version of Alport syndrome (ARAS) (1). Because the *COL4A5* gene is on the X chromosome, affected hemizygous males have a disease presentation that is similar to ARAS, whereas heterozygous females, who carry one unaffected copy of *COL4A5*, typically show less-severe and highly variable features of Alport syndrome due to the complex and variable effects of random X chromosome inactivation (1).

Although the existence of autosomal dominant Alport syndrome (ADAS) was recognized decades ago and considered rare (4), the last approximately 15 years of expanded DNA sequencing efforts by academic and commercial laboratories to identify genetic causes of kidney diseases revealed that many individuals with chronic kidney disease (CKD) carry heterozygous pathogenic variants in *COL4A3* and *COL4A4*, although they were not previously diagnosed as having Alport syndrome (5). A standout group of these patients had focal segmental glomerulosclerosis (FSGS) lesions and thin GBMs—the latter being a common feature of Alport syndrome—but no hearing or eye defects (6, 7).

Surprisingly, sequence data from healthy individuals in the general population have revealed that 1 in 106, or about 1% of the population, carries a heterozygous pathogenic variant in *COL4A3* or *COL4A4*, which was suggested to slightly increase kidney disease risk as compared with the general population (8). The great majority will not develop kidney diseases, but most will likely have thin GBMs due to the impaired collagen α3α4α5(IV) network, along with occasional or persistent microscopic hematuria, neither of which may ever be detected. However, for reasons that remain understudied, a small fraction will develop CKD, usually later in life as compared with Alport syndrome, and will develop the FSGS lesions described above. Many of these will require renal replacement therapy.

Although most patients who carry a *COL4A3* or *COL4A4* pathogenic variant and develop CKD lack the hearing defects, the eye defects, and the early kidney failure that are typical of "classic" Alport syndrome, the clear genetic relationship to Alport syndrome has stimulated many discussions among patients, geneticists, clinicians, and researchers about how to classify these individuals within the array of Alport gene-related kidney disease presentations. This is especially sensitive for those who are unexpectedly diagnosed with ADAS using genetic testing, such as prospective or expecting parents with either family planning or prenatal screening. Relatives of patients with ARAS who are tested and found to be hematuric and/or to carry a monoallelic variant also have an increased risk for

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From genes to presentation: Understanding the *COL4A3/A4/A5* variants

Alport syndrome is caused by pathogenic variants in the *COL4A3*, *COL4A4*, or *COL4A5* genes (the Alport genes).

These genes encode the α3, α4, and α5 chains of type IV collagen (COL4), which form a critical structural "Alport COL4" network in the glomerular basement membrane (GBM).

Variants of different severities that affect this network lead to GBM defects and a spectrum of clinical presentations.

Mode of inheritance	Genetic variant type	Genes affected	Impact on GBM	Phenotypic presentation
X-Linked males; autosomal recessive males and females	Null variant (nonsense, splice site, frameshift)	*COL4A3/A4/A5*	Absent Alport COL4 network	Classic severe Alport syndrome: hearing loss, ocular defects, early kidney failure
X-Linked males; autosomal recessive males and females	Missense variant	*COL4A3/A4/A5*	Alport COL4 network may be present at lower levels and/or with abnormal structure and function.	Classic severe Alport syndrome: hearing loss, ocular defects, slight-to-moderate delay in kidney failure
X-Linked females	Any pathogenic variant	*COL4A5* (heterozygous)	Patchy GBM involvement due to X inactivation	Highly variable: from hematuria to mild or moderate CKD, with or without hearing and ocular defects
Autosomal dominant	Any pathogenic variant	*COL4A3/A4* (one allele affected)	Thin GBM due to partial network disruption	Often microscopic hematuria; a small fraction develops late-onset CKD ± FSGS; hearing and ocular defects are rare

Key implications

- **Annual monitoring**: Recommended for anyone with a *COL4A3* or *COL4A4* pathogenic variant and hematuria
- **Genetic testing**: Essential for proper classification and risk assessment
- **Renin-angiotensin system blockade:** Can delay proteinuria and kidney failure progression
- **Family implications:** Important for screening relatives of patients with ARAS

Visual graphic by Jia Ng, MD, MSCE

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CKD. It has been recommended that all individuals who carry a *COL4A3* or *COL4A4* pathogenic variant and have hematuria should be monitored annually because of the increased risk (9).

In summary, the revolution in the use of genetics for kidney disease research and diagnosis has revealed a complex array of pathogenic variants in *COL4A* genes and a continuum of disease presentations, from hematuria, to nonsyndromic late-onset kidney disease with FSGS lesions, to classic Alport syndrome with variable rates of progression to kidney failure. Myriad genetic and clinical data from around the world have provided the basis for genotype–phenotype correlations that have been mechanistically refined by decades of basic research into collagen IV biochemistry (10). ■

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Advances in Understanding the Genetics of Pediatric Kidney Diseases

By Caroline M. Kolvenbach and Friedhelm Hildebrandt

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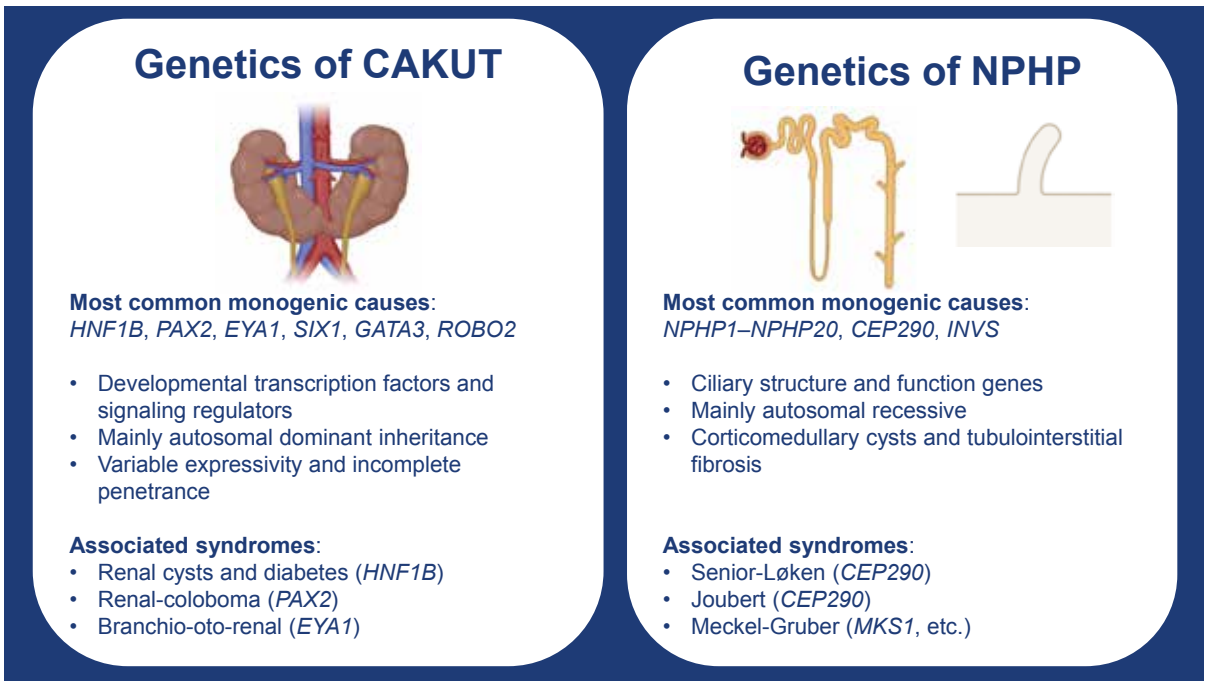
Congenital anomalies of the kidneys and urinary tract (CAKUT) and nephronophthisis (NPHP) are two major causes for chronic kidney disease in children and adolescents. While clinically distinct, genetic factors play a substantial role in both of their etiologies. Advances in sequencing technologies led to the identification of numerous causative genes. Understanding the genetics and pathogeneses of CAKUT and NPHP is essential for a precise molecular diagnosis, risk assessment, and the potential development of targeted therapies in the future.

Genetics of CAKUT

CAKUT comprises a large variety of anomalies that arise from defective kidney or urinary tract development, including renal agenesis, renal hypodysplasia, ureteropelvic junction obstruction, and vesicoureteral reflux (1). The majority of cases with CAKUT are detected early during routine prenatal ultrasonography. CAKUT occurs with a frequency of approximately 3–6 out of 1000 live births and accounts for almost 50% of chronic kidney disease (1, 2). Most CAKUT presents in isolation with no extrarenal features but may also be part of a multiorgan syndrome. There is evidence that a considerable fraction of CAKUT is genetic in origin, yet the genetic basis of CAKUT is highly heterogeneous. To date, approximately 50 genes have been identified as causative monogenic disease genes, accounting for about 10%–20% of cases (1). These gene products are often key regulators of transcription and signaling pathways, which are critical during kidney and urinary tract development (Figure). The following two genes have been shown to be the most common monogenic causes for CAKUT, if mutated. Disease-causing variants in *HNF1B* cause renal cysts and diabetes syndrome, which includes various CAKUT phenotypes (1, 2). *PAX2* is a transcription factor involved in the development of the kidneys and eyes. Pathogenic variants have been shown to result in renal anomalies and optic nerve colobomas, collectively referred to as renal-coloboma syndrome (2). Copy number variants have also been shown to be implicated in CAKUT. They account for approximately 5%–10% of CAKUT cases, the most frequent being the 17q12 deletion (including the *HNF1B* locus), followed by 22q11 deletion (including the *CRKL* locus; DiGeorge syndrome) (1, 3). Collectively, a molecular diagnosis can be obtained for a notable percentage of cases.

Figure. Genetic causes of CAKUT and NPHP and associated syndromes



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Genetics of NPHP

NPHP is an autosomal recessive cystic kidney disease for which approximately 20 genes have been identified to date (Figure) (4). These genes encode proteins that localize to the primary cilia, basal bodies, and centrosomes—structures

that are present in most cell types and imperative for epithelial cell signaling and polarity (4, 5). Consequently, pathogenic variants in NPHP genes result in compromised ciliary function, thereby classifying NPHP as a ciliopathy. In NPHP, a history of polyuria, polydipsia, anemia, and growth retardation is common. The histologic hallmarks of NPHP include tubulointerstitial fibrosis, tubular basement membrane disruption, and corticomedullary cyst formation. In 15%–20% of cases, NPHP can be associated with extrarenal organ involvement (6). For example, retinal degeneration with NPHP in Senior-Løken syndrome and cerebellar vermis aplasia and coloboma of the eye in Joubert syndrome have been associated with *CEP290* variants (4, 5). Genetic testing enables molecular genetic diagnosis for NPHP disorders in approximately 60% of cases (5). The most commonly mutated gene in juvenile NPHP is *NPHP1*. Biallelic deletions of the *NPHP1* gene account for approximately 20% of all NPHP cases (5).

Clinical implications of genetic testing

The complexity of genetic kidney diseases is exemplified by CAKUT and NPHP. Numerous signal transduction pathways, several of which overlap, have been implicated in the pathogeneses and highly variable phenotypic expressivity of both forms. As sequencing technologies improve and become increasingly available, the expansion of our understanding and management of these genetic disorders are expected to further advance. Emerging research on novel candidate or modifier genes; environmental or oligo- or polygenic factor gene-environment interactions; and various RNA transcripts may elucidate the underlying causes for both diseases.

A precise molecular genetic diagnosis facilitates improved multidisciplinary clinical management and prognoses and allows for screening of at-risk relatives. Genetic information enables informed reproductive decisions for future family planning. It also allows for distinguishing between cystic forms of CAKUT and ciliopathies or in the case of NPHP, from other cystic kidney diseases. Ultimately, knowledge of the molecular pathways involved may eventually lead to the development of personalized therapeutic strategies in the future. Promising current gene therapy approaches include adeno-associated virus-mediated gene therapy aiming to replace the missing gene product or clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) gene editing to correct disease-causing alleles (1, 7–9). Modulating signaling pathway activity with promising drug candidates may also attenuate disease progression (10).

Conclusion

Advances in genetics have elucidated many genes and pathways implicated in CAKUT and NPHP; however, a significant number of cases remain unexplained due to the complexity of both diseases. Nevertheless, genetic counseling and testing have become indispensable components of clinical practice, playing pivotal roles in the clinical management of the disease, prognosis, and possible development of personalized medicine. ■

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Evaluation and Management of Primary Hyperoxaluria

By Nicholas W. Salupo and Juan Calle

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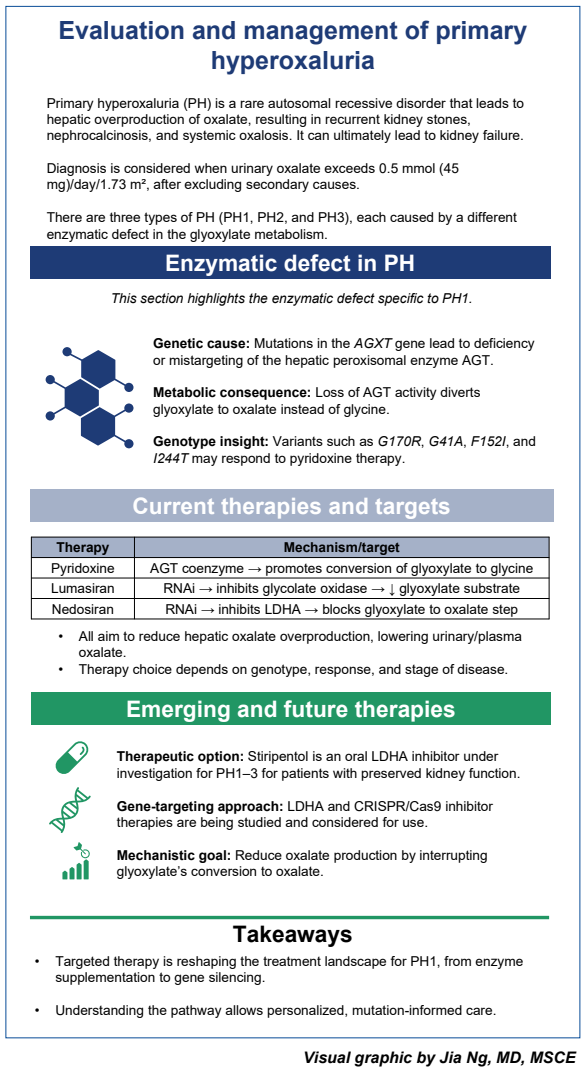
Oxalate is an organic anion produced in the liver and also found in foods such as spinach, rhubarb, tree nuts, and chocolate (1). Hyperoxaluria, an abnormally high urinary excretion of oxalate, can result from excess dietary intake; increased oxalate absorption due to gastrointestinal abnormalities; or primary hyperoxaluria (PH), a group of autosomal recessive errors of the glyoxylate metabolism that lead to hepatic overproduction of oxalate (2). The increased concentration of urinary oxalate (Uox) can induce calcium oxalate crystallization, which can lead to recurrent nephrolithiasis, nephrocalcinosis, and oxalosis of extrarenal organs such as the heart, bones, retina, thyroid, skin, gastrointestinal tract, and blood (2, 3).

There should be strong clinical suspicion of PH in individuals with recurrent calcium stones, pure calcium oxalate monohydrate stones, or nephrocalcinosis. A PH diagnosis can be considered when Uox is greater than 0.5 mmol (45 mg)/day/1.73 m^2 in the absence of secondary etiologies. Given the challenges presented by accurate pediatric urine collections, random Uox-to-creatinine ratios are often used. Age-specific normal Uox ranges should be referenced (2).



Visual graphic by Jia Ng, MD, MSCE

PH is classified into three subcategories. PH type 1 (PH1) is the most common manifestation and most likely to progress to kidney failure. It occurs due to a defect in the pyridoxine-dependent hepatic peroxisomal enzyme, alanine-glyoxylate aminotransferase (AGT). This defect is most commonly the result of a mistargeting mutation in the *AGXT* gene (4). The age of presentation is variable, but the median age at diagnosis is 5 to 5.5 years old (5).

PH2 presents as a milder disease than PH1 and the risk of kidney failure is lower. It occurs due to a homozygous or compound heterozygous mutation in the glyoxylate reductase/hydroxypyruvate reductase *GRHPR* gene. PH2 is usually a less aggressive form of PH (6).

PH3 is caused by a homozygous or compound heterozygous mutation in the *HOGA1* gene (7). PH3 can cause hematuria, recurrent nephrolithiasis, acute kidney injury, and chronic kidney disease, but at least one case of kidney failure has been reported (8).

Early diagnosis is critical to limiting disease progression to kidney failure. Uox measurements may be falsely low due to chronic kidney disease. An increased plasma oxalate measurement may support a PH diagnosis. Differentiating PH1, PH2, and PH3 is difficult, due to the shared presence of elevated Uox excretion. Increased urinary glycolate may support PH1, serum L-glyceric acid may be increased in PH2, and PH3 may increase urinary excretion of hydroxy-oxo-glutarate (5, 9). A definitive diagnosis is made by molecular testing for variants in the three known causative genes for PH (*AGXT*, *GRHPR*, and *HOGA1*) (2, 3).

The goal of management is reducing urinary calcium oxalate saturation and oxalate production. All forms of PH should be managed with fluid intake targeting 3 L/day/1.73 m^2 of urine output and urinary alkalinization. Dietary oxalate restriction may still be used in those with high dietary oxalate (1, 2). Intensive dialysis is often unable to keep up with daily oxalate production in PH, which can reach 315 mg/L to 675 mg/L in PH1. Despite standard maintenance hemodialysis or peritoneal dialysis, plasma oxalate is likely to remain above the supersaturation threshold (10). The majority of oxalate clearance occurs during the first 1–2 hours of hemodialysis; thus, more frequent hemodialysis is recommended instead of longer treatments (3). While the possibility exists that health insurers may subsidize intensive dialysis for PH, this may be dependent on individual patient circumstances and the specific insurance plan (10, 11). The nephrology team caring for the patient should make every effort to provide more frequent hemodialysis for these patients.

Pyridoxine, an AGT coenzyme, promotes glyoxylate conversion to glycine rather than oxalate in patients with PH1 with *G170R*, *G41A*, *F152I*, and *I244T* mutations (2). If Uox is reduced by 30% or more, then pyridoxine should be continued until transplantation (2). Liver transplantation, the only curative intervention for PH1, corrects the underlying enzymatic defect due to the *AGXT* mutation, but the optimal transplant strategy is unclear. Patients with fully pyridoxine-responsive PH1 should be considered for liver–kidney transplant (LKT) or KT alone with RNA interference (RNAi) therapy (12). Current RNAi use with KT-only data is limited, but increasing adoption will clarify long-term efficacy. In patients with an incomplete pyridoxine response, LKT is recommended over isolated KT due to a six-times higher rate of allograft survival at 5 and 15 years after transplant (2). Patients with PH2 with severe disease or systemic oxalosis may benefit from LKT (2).

RNAi agents lumasiran and nedosiran have been shown to reduce hepatic oxalate production and may change our approach to transplantation in PH1 (12). Lumasiran silences the gene that encodes glycolate oxidase, and nedosiran inhibits L-lactate dehydrogenase A (LDHA) production, an essential factor in cytosolic conversion of glyoxylate to oxalate. RNAi agents have not yet shown efficacy in PH2 (2).

There are reports of stiripentol, an oral LDHA-targeted medication, reducing Uox in patients with PH1 with a pyridoxine-responsive mutation. A trial is currently underway to determine the efficacy of stiripentol monotherapy in patients aged 6 months or older with PH1–3 and an estimated glomerular filtration rate more than 45 mL/min/1.73 m^2 (2). Future therapies for PH1 and PH2 may include LDHA inhibitors and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) inhibition of glycolate oxidase and LDHA. (13, 14). ■

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Fabry Disease: Are We Looking Hard Enough?

By Anjay Rastogi

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Anderson-Fabry disease, also known as Fabry disease, is a rare X-linked genetic disorder of the glycosphingolipid metabolism. It belongs to a group of lysosomal storage disorders and is the second-most common after Gaucher disease. Kidney diseases impact individuals with Fabry disease quite frequently, and it is likely that a person with Fabry disease will cross paths with a nephrologist along their journey. Key questions to ask are: Will the nephrologist be able to correctly identify and diagnose this patient? Why is it important that we identify these individuals? And what is the clinical utility of a Fabry disease diagnosis?

Fabry disease is considered to be a rare disease, but it is not rare if you have it. Fabry disease is associated with significant morbidity, mortality, cost, and poor quality of life. Furthermore, for every person diagnosed with Fabry disease, they have, on average, five family members who also have the disease (1). The prevalence of classic Fabry disease is reported anywhere between 1 in 8454 to 1 in 117,000 individuals, with the true prevalence likely being much higher than that (2, 3). Screening programs—including newborn screening, that do not rely on clinical manifestations for diagnosis—report a much higher prevalence, with classical disease present in 1 in 22,000 to 1 in 40,000 males and atypical or late onset in approximately 1 in 1000 to 1 in 3000 males and 1 in 6000 to 1 in 40,000 females (4). No ethnic or racial predilection has been noticed to date.

So, how can we explain this apparent discrepancy in the known and true prevalence, and what can we do to improve the diagnostic capabilities?

There are many challenges in diagnosing Fabry disease, including but not limited to its rarity and myriad presentations that tend to evolve over time (5). Kidney care professionals should know about this diagnosis and need to keep a healthy level of suspicion of Fabry disease. Ongoing education on Fabry disease is vital, including in the form of live, interactive presentations; webinars; continuing medical education events; and social media. Collaboration with other subspecialties is also important. Not infrequently, the diagnosis is made by other subspecialists including dermatologists, ophthalmologists, optometrists, neurologists, and cardiologists. At times, the diagnosis is made on a kidney biopsy by the pathologist. However, in these cases, the biopsy was most likely ordered not with Fabry disease in mind; a kidney biopsy is highly suggestive but not diagnostic of Fabry disease. A positive biopsy will need to be followed up by more confirmatory testing including genetic testing and enzyme activity.

Genetic testing is the gold standard for diagnosing Fabry disease and is required before initiating Fabry disease-specific therapy. In a classic male, enzyme activity of 1% to 5% should also help in confirming the diagnosis. Kidney genetic testing has evolved quite rapidly over the last several years, and broad-panel kidney genetic testing has significantly improved diagnostic capabilities. Availability, affordability, accessibility, easy interpretation, and access to genetic counselors are key to widespread application of these useful tests.

Early diagnosis is of paramount importance to slow the progression of disease by implementing guideline-directed therapies and management. The average delay in diagnosis ranges from between 15 and 20 years (6). This is vital time that is lost, as early diagnosis and intervention are key if we, as nephrologists, are going to improve long-term outcomes.

Historically, females have been underdiagnosed, undermanaged, and considered carriers for X-linked diseases, but we now know that is not the case. In adult females, one of the two X chromosomes is inactivated. This process is thought to be random. Depending on the luck of the draw, a female patient can have the entire spectrum of Fabry disease manifestations from none to full-blown (7, 8). It is important to not call females carriers but heterozygotes for X-linked disorders.

Many patients with Fabry disease are misdiagnosed with other conditions including multiple sclerosis and irritable bowel syndrome. When errors like this occur, in addition to not treating the primary disease, we may also be treating a condition that the patient does not have, with therapies that could lead to inadvertent therapy-associated adverse events.

How do we increase the diagnostic yield?

- Implementing broad-panel kidney genetic testing
- Screening newborns and initiating other similar programs that do not depend on clinical manifestations for testing
- Screening at-risk family members
- Screening patients on dialysis, especially patients with early onset with no identifiable cause
- Screening transplant recipients and donors, especially if related
- Screening enriched populations, including those with unexplained left ventricular hypertrophy or cryptogenic stroke
- Collaborating among specialties and institutions
- Engaging with local and regional referral centers
- Initiating support groups, not just in providing support to patients with a diagnosis but also for patients who might have Fabry disease but are waiting for a confirmatory diagnosis

So, are we looking hard enough for Fabry disease? Unfortunately not, and we can and must do better. Nephrologists have a central role in the journey of the patient with Fabry disease in collaboration with other specialties. With significantly more focus and emphasis placed on rare kidney diseases, including those with genetic causes, the future looks promising.

Increased accessibility to broad-panel kidney genetic testing has been a huge step forward and is already having a significant impact on how we diagnose and manage genetic causes of kidney diseases. The upcoming Kidney Disease: Improving Global Outcomes (KDIGO) Genetics in Kidney Health Summit this September will continue furthering this cause. ■

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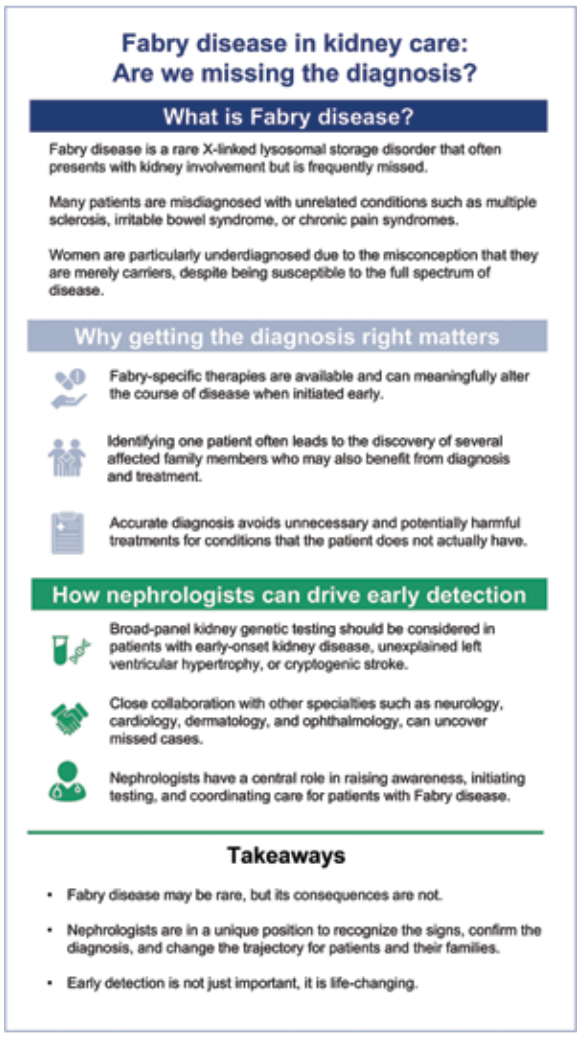

Visual graphic by Jia Ng, MD, MSCE

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Advancing *APOL1* Epidemiology and Chronic Kidney Disease: Lessons From Sub-Saharan Africa

By Titilayo O. Ilori and Rulan S. Parekh

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African Americans have four times higher incidence of advanced stage kidney disease and develop kidney failure 10 years earlier compared with European Americans (1). In 2008, the chromosome 22 locus was identified and associated with higher odds of kidney failure among African Americans, explaining about 70% of the higher burden (2). In 2010, using the 1000 Genomes Project, variants in the *APOL1* gene were associated with higher odds of focal segmental glomerulosclerosis (FSGS) and chronic kidney disease (CKD) among African Americans (3). There is an accelerated form of kidney disease progression among those carriers of risk variants of *APOL1*. Variants underwent selection due to trypanosomal infection, leading to sleeping sickness, and carriers were protected (4, 5).

Alteration of the amino acid sequence of the protein by *APOL1* coding variants (two haplotypes called G1 and G2) leads to proteinuria in animal models (6). Earlier studies determined that individuals with one copy (G1 or G2) had no risk of CKD compared with those with two risk alleles. Studies report higher odds (range, 7–29) associated with CKD depending on sample size and type of kidney disease (7). *APOL1* high-risk carriers have a two- to three-times higher rate of CKD progression (8). The prevalence of individuals with two risk alleles is approximately 10%–15%, and single risk alleles are approximately 50% in the United States (9).

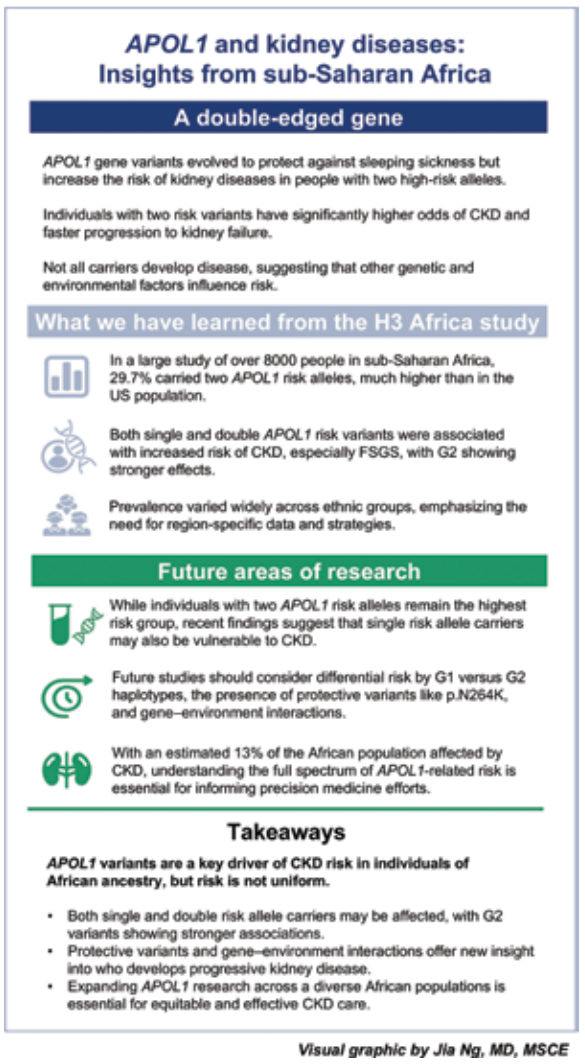
Not all individuals with the high-risk *APOL1* variants develop CKD or progress to kidney failure. Although the prevalence of individuals with two high-risk *APOL1* alleles is approximately 10%–15%, the lifetime probability of developing kidney failure for individuals with a high-risk *APOL1* genotype is estimated to be 15%–30% (10, 11). This suggests likely gene–gene or gene–environment interactions leading to progressive kidney disease. Recently reported is the *APOL1* p.N264K missense variant, which is coinherited with the G2 *APOL1* haplotype and has a protective CKD effect (12). Similarly, in vitro studies demonstrate that this variant reduces toxicity of the high-risk *APOL1* alleles (13).

So, what do we know about *APOL1* in sub-Saharan Africa? In a case-control study of over 8000 participants from the Human Heredity and Health (H3) in Africa Kidney Disease Research Network, the prevalence of individuals with two *APOL1* high-risk alleles was 29.7%, and in those with one risk allele, the prevalence was 43% (14). The prevalence of two risk alleles varied widely among Ghanaian and Nigerian participants, with pockets as low as 11.4% among the Hausa people and as high as 50.1% among the Ibo people (14).

Several findings in the H3 Africa study are unique, given our understanding to date. Apart from the high prevalence of two risk alleles in some regions, there was also a significant association of *APOL1* single risk alleles with CKD. There was a graded response, with a higher CKD risk from zero to two risk alleles, which was evident due to the large study population. An *APOL1* single risk allele was associated with 18% higher odds of CKD and 61% higher odds of FSGS, whereas two *APOL1* risk alleles were associated with 25% higher odds of CKD and 84% higher odds of FSGS (14). Additionally, there was a differential risk by alleles, with higher odds associated with the G2 compound haplotype compared with G1, especially for FSGS.

What does this mean for ongoing studies? The focus on *APOL1* high-risk carriers with two risk alleles remains the highest risk group for CKD progression. Future studies should consider differential risk by the G2 versus G1 haplotype, the carrier status of the protective variant, and the risk for carrying a single risk *APOL1* allele. The burden of CKD is substantial in Africa, with approximately 13% of the population with CKD (15). The association with CKD is significant but qualitatively lower than reports in the United States, suggesting that there may be other risk factors in Africa.

The genetics of *APOL1* are evolving as we continue to learn about this unique genetic risk factor, which disproportionately affects individuals of West African ancestry. ■



Visual graphic by Jia Ng, MD, MSCE

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Genetic Testing in Kidney Transplant Recipients and Donor Candidates

By Mireille El Ters

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Significant advances have occurred in our understanding of the genetic basis for kidney diseases in general and specific pathological entities such as focal segmental glomerulosclerosis (FSGS) (1, 2). This knowledge translated into the incorporation of genetic testing in nephrology practice (3) and in the kidney transplant evaluation (4, 5). An important task of the transplant nephrologist is to understand the etiology of kidney diseases to better estimate the risk of recurrence, as well as to help with screening of biologically related donors.

Of particular importance are conditions such as primary FSGS, in which recurrence has been reported in at least 30% of cases and is associated with poor prognoses (6). Despite promising new advances (7), there is currently no pathognomonic laboratory or pathological finding to differentiate primary from secondary forms of FSGS. In that context, genetic testing may help identify secondary FSGS, which is at low risk of recurrence with notable exception of biallelic *NPHS1* (nephrin) variants that have been associated with recurrence related to development of an anti-nephrin antibody post-transplant (8). In carefully selected cohorts of adult patients with FSGS, the rate of positive genetic findings is about 40% (5, 9). On the contrary, genetic abnormalities in the complement system associate with higher risk of recurrence in atypical hemolytic uremic syndrome (aHUS) (10) and warrant prophylaxis with complement blockade (11). Genetic testing has also been helpful to determine the need for combined liver–kidney transplant in rare conditions such as primary hyperoxaluria as well as rare forms of amyloidosis, such as fibrinogen A alpha-chain amyloidosis and hereditary transthyretin amyloidosis (12, 13). Finally, in unknown kidney disease, pursuing genetic testing may be beneficial to uncover diseases at high risk for recurrence and help with screening biologically related donors. Younger age of onset, presence of extrarenal manifestations, as well as family history of kidney diseases increase the yield for genetic diagnosis.

Genetic testing plays a role in screening biologically related living donors, who, by virtue of positive family history, are at higher risk for kidney diseases. This excludes cases in which a clear, nongenetic cause is identified in the affected family member. The larger the number of affected family members, the greater the likelihood of a monogenic disease. Genetic workup is of particular importance in younger donors who may be in the presymptomatic stage of disease. In cases of collagen gene mutation, significant variability may exist in the age of onset as well as in disease progression, depending on mode of inheritance, and even within the same family. As such, a genetic diagnosis may be the only way to rule out the condition. Consensus guidelines recommend proceeding first with an evaluation of the affected family member, who is typically but not always the recipient candidate. If a genetic variant is identified as causative of the underlying kidney disease, then a focused genetic screening is performed on the biologically related donor (14). This sequential testing approach helps avoid any potential negative downstream effects related to false-positive results in an otherwise healthy donor if a full gene panel is performed directly on the donor.

Integration of genetic testing as part of a kidney transplant evaluation is fraught with challenges related to the cost and variable coverage, as well as potential delays in the evaluation that may arise from the need for sequential testing of recipient and donor. There are ethical considerations to take into account regarding a patient's autonomy and the implications on offspring. It is important to note that genetic testing should not be used to determine recipient candidacy for transplant, rather to help with managing their care. As such, a patient's refusal to proceed with genetic testing should not be ground for denial of candidacy. Although there has been more education, transplant nephrologists may not be comfortable with counseling, ordering, and following up on genetic tests. A genetic counselor's role is key in helping with these steps, as well as ensuring appropriate family counseling and arranging for further testing that is beyond the scope of transplantation. It is also important to ensure adequate follow-up on variants of uncertain significance that may later be reclassified as pathogenic. Ideally, an integrated system that allows the collaboration between a transplant nephrologist and the genetic team should be implemented (3, 5), but that is not possible in all transplant centers. Recent practice guidelines (for donor and recipient evaluation) were published that include resources for genetic counseling service, variant interpretation, and specific disease variant databases (12, 14).

In the future, the role of genetic testing will not be limited to identifying the monogenic basis of kidney diseases but may help identify susceptibility for malignancy, infection, and cardiovascular disease, which are main causes of morbidity and mortality post-transplant (15). As part of precision medicine, the use of pharmacogenomics may also help in individualizing immunosuppressive therapy.

In summary, the role of genetic testing is expanding in the context of kidney transplantation. Genetic testing can provide valuable information in a select group of patients that allows a more accurate estimation of risk of recurrence, help in management post-transplant, and screening of potential biologically related donors (Table). ■

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Table. Clinical scenarios for genetic testing in the context of kidney transplant evaluation

Evaluation task	Genetic test
Evaluation of recurrence risk	· FSGS: Genetic forms usually lower recurrence risk. · aHUS: Positive genetic finding is associated with higher recurrence risk and consideration for complement blockade pretransplant. · May be helpful in the consideration for combined liver–kidney transplant in certain forms of genetic amyloidosis and in primary hyperoxaluria
Screening of biologically related donors[a]	· Known or suspected collagenopathy (including kidney biopsy): Needed to screen potential presymptomatic affected donors · Unknown cause of kidney disease: Especially early onset, extrarenal manifestations, and positive family history · Interstitial nephritis with no clear causative agent · Cystic kidney disease including autosomal dominant polycystic kidney disease with biologically related donors younger than age 30
Management of extrarenal complications before and after transplant	· Fabry disease · Cystinosis · Tuberous sclerosis · Monitoring for malignancy: *WT1* mutation

[a]In addition to above conditions (FSGS and aHUS).

Living With Genetic Kidney Diseases

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Being diagnosed with a genetic kidney disease is a life-altering experience for those living with the condition and their families, often marked by uncertainty and a search for answers. *Kidney News* is grateful to the individuals living with kidney diseases and their families for sharing their personal journeys, from the challenges of receiving a diagnosis to the realities of living with a hereditary condition and what it may mean for the future.

Monica Starks

Journey of genetic discovery

In August 1999, I received the worst news of my life that would forever alter the course of my future. After being rushed to the emergency room by ambulance from work, I was diagnosed with stage 4 chronic kidney disease (CKD), with nephrotic syndrome identified as the underlying cause. When I shared this devastating diagnosis with my maternal grandmother, she revealed that her aunt had died from the very same illness. As more conversations unfolded, I learned that several other relatives had also battled this disease, including a cousin just 3 years older than me who lived only a few miles away. This experience taught me a painful but important lesson: Keeping family health issues secret—or simply failing to talk about them—can have serious consequences for loved ones who might be at risk.

Eighteen months after my diagnosis, I began in-center dialysis. Just 14 months later, I got married, and later that same month, I started training for nocturnal home dialysis. Everything moved very quickly since my condition had progressed to stage 5, which is classified as kidney failure. It's important to note that stages 1 through 3 are considered CKD, but stages 4 and 5 are advanced kidney disease, requiring immediate intervention.

After I received an initial kidney transplant, I got the complication of transplant rejection and focal segmental glomerulosclerosis, which brought concerns of recurrent disease. This led to me getting a DNA test, which stated that I have two mutations of *APOL1*. I was made to understand that I received one mutation from each parent, and one mutation does not automatically mean I would be diagnosed with CKD or kidney failure. Having two mutations made it more likely for my kidney disease to progress as fast as it did. This information helped with reevaluation for another kidney transplant. In January of 2025, I received another kidney transplant and am navigating a new journey, the gift of life.

I wish doctors understood that some patients have been caring for themselves for many years and know things about their bodies. Sometimes, no one listens to the patient and later finds out that the patient was correct. My hope for the future is that there will be more concern for preventative care instead of maintenance or postdiagnosis care. Many people are not formally diagnosed until they have kidney failure, and that is unacceptable with all of the modern technology that currently exists.

Walking through it together

My name is Beki, and I'm writing on behalf of my husband, Mike, to share our journey with primary hyperoxaluria type 1 (PH1). Mike was diagnosed in early 2024 at the age of 53, after his older brother received the same diagnosis in 2023. Both had endured a lifetime of kidney stones starting in their early teens. By the time Mike's brother was diagnosed, he was already in kidney failure. We lost his brother on Labor Day of 2024.

Because PH1 is a genetic condition, we expected Mike's results to come back positive. His sister also tested positive, although she isn't currently symptomatic. Still, knowing and living it are two very different things.

Mike was prescribed Oxlumo (lumasiran), a treatment that gave us real hope. Unfortunately, due to the medication's overwhelming cost and rising insurance premiums, he is no longer able to take it. Knowing there's help out there—but being unable to maintain it—has been heartbreaking, scary, and incredibly stressful.

Mike hasn't participated in clinical trials, but he has seen a geneticist and a nephrologist who understand PH1. Outside of those two, we haven't seen another practitioner who has even heard of the condition, let alone the complications that come with it. That lack of awareness is frustrating and isolating.

Mike Keister (second from right) with his wife Beki (middle), children, and grandson in 2021.

If we could share one thing with the medical community, it would be this: Rare diseases matter. Just because you don't see them every day doesn't mean they aren't life-changing for the people who live with them. Listen. Learn. Be open.

Our hope is simple: We dream of a cure—one Mike can be here to see. We want him to watch his kids, grandson, and future grandkids grow up. We want more holidays; more fishing trips;, and more quiet, ordinary days. And above all, we want people to know this disease exists and that families like ours are walking through it every single day.

Paula Gonzalez

The long road to answers

For most of my life, I lived with unexplained pain. I first complained to my parents around age 8, but doctors brushed it off as "growing pains." I felt misunderstood and dismissed—too young, they said, to be dealing with something serious. When an optometrist noticed cornea verticillata, I was referred to an ophthalmologist, who told me Fabry disease was rare and unlikely in someone "young and healthy." It took another 2 years and a lot of persistence before I got answers.

At age 23, I was finally diagnosed with Fabry disease after my uncle, who had attended a medical conference, recognized my symptoms in the presentation of a typical patient with Fabry disease. A genetic test confirmed the diagnosis. There was no family history—my parents and sister tested negative for the gene. I was a spontaneous mutation, something that initially shocked doctors but explained years of pain and confusion.

The diagnosis was not a surprise to me—it was a relief. I always knew that something was wrong. Since then, I've been receiving enzyme replacement therapy every 2 weeks. I haven't participated in clinical trials yet, and during my pregnancies, the genetic counseling that I received didn't offer much new information—just confirmation that there was a 50% chance of passing on the gene.

Living with Fabry as a young adult presents unique challenges. It's not always visible, but the pain and fatigue make even basic tasks difficult. I often find myself having to justify my symptoms to health care professionals who underestimate the impact of the disease because of my age or outward appearance.

My hope is for better treatments—ideally a pill or gene therapy, so I won't need lifelong infusions. More importantly, I want health care professionals to recognize that this disease may not be as rare as it seems and to really *listen* to their patients. We know our bodies. Early recognition and belief in our symptoms can make all the difference in getting timely care.

Winning every day

I am Tyrone Wedgworth. I'm 58 years old, and I work as a deputy probation officer in Los Angeles. I suffer from Fabry disease, stage 4 chronic kidney disease, heart disease, and left ventricular hypertrophy.

For as long as I can remember, my cousin Wink and I suffered from body aches, chills, discomfort, dizzy spells, fevers, and headaches—episodes Wink called "the yah-yahs." (It's okay to laugh!) As a little boy, my mother took me to emergency rooms, urgent care clinics, and pediatric appointments. No doctor could solve the mysterious symptoms or the yah-yahs.

In 2005, an ophthalmologist discovered swirl patterns in my mother's cousin's eyes during a routine examination. A referral to Emory University led to a diagnosis of Fabry disease. In January 2006, Emory informed my family that Fabry disease was possibly present amongst us. Most of us took no action. Only a few relatives sought testing, including my mother and another cousin. My cousin was eventually the first of my family to receive treatment. In 2009, I tested positive for Fabry disease. I originally felt that this diagnosis was a death sentence because I knew very little about it.

Tyrone Wedgworth, Lethia (mother), and Tracy (sister) in May 2017, celebrating Mother's Day.

In 2011, Wink died of a massive heart attack at the young age of 46 years old. Still, I sought no treatment. Finally, in December 2022, a referral to Dr. Anjay Rastogi at UCLA's Connie Frank Kidney Transplant Center and General Nephrology was the catalyst to treatment. I began treatment in September 2023 and was the first to receive Fabrazyme (or gene replacement therapy) at Connie Frank. I now have in-home infusions twice a month. Nevertheless, I may still need a kidney replacement or dialysis. I hold on dearly to life every day.

From a very young age, I saw several family members get sick and die. We now know that complications from Fabry caused or contributed to their early deaths. I looked over my family tree, and I surmised that my great-great-grandmother suffered from Fabry disease. She died at an early age, and we know very little about her. The disease spread from one of her X chromosomes to my great-grandfather and then to each of his seven daughters (including my grandmother) through his X chromosome. My mother and I both suffer from Fabry disease, and unfortunately, my daughters received my X chromosome with the disease.

I encourage physicians to study and learn more about rare diseases, to follow up closely on their patients' concerns, and to consider reaching out to organizations for advice, education, and guidance. My hope for the future is to find a cure for Fabry disease.

I want everyone to know that I don't *have* Fabry disease. I *suffer* from Fabry, and despite this condition, I win every day. ■

Gene Therapy Without a Vector: Harnessing the Wild-Type *PKD1/2* Allele in ADPKD

By Arash Ataei and Matthew A. Sparks

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder, characterized by progressive cyst formation and kidney enlargement, ultimately leading to kidney failure in the majority of affected individuals (1). ADPKD is a genetically heterogeneous disorder primarily caused by mutations in the *PKD1* and *PKD2* genes, which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively, and together, account for the vast majority of cases. Prior to 2018, the mainstay of management was supportive care—hydration, blood pressure control, and management of comorbidities. Tolvaptan, a selective vasopressin V2 receptor antagonist, received US Food and Drug Administration approval in 2018 as the first disease-modifying therapy for ADPKD, following a narrowly favorable risk-benefit assessment due to its modest efficacy in slowing kidney volume growth and the associated risk of hepatotoxicity (2, 3). Notwithstanding initial concerns, its introduction marked a paradigm shift in the management of ADPKD, offering patients a therapeutic option that could delay the progression to kidney failure.

In today's world of targeted therapies and advanced therapeutics, ADPKD has lagged frustratingly.

Despite the name of this disease, we have not yet had a genetic therapeutic target. The microRNA (miRNA or miR) cluster miR-17~92 has been implicated to play an important role in cyst formation. miRNAs are small, noncoding RNA molecules, typically about 20–24 nucleotides long, that play a crucial role in regulating gene expression at the post-transcriptional level. First, miR-17~92 has been implicated to be upregulated in animal models of PKD. Mouse models with further upregulation of miR-17~92 have increased cyst formation in PKD models, and downregulated models have fewer cyst formations. Furthermore, inactivation of the miR-17~92 cluster in mice with PKD has slowed cyst growth (4). These findings, which were published in 2013, provide hope for targeted therapy.

A 2022 study challenged the traditional view that ADPKD arises solely from loss-of-function mutations in *PKD1* or *PKD2*, demonstrating instead that miR-17 binding to the wild-type *PKD1* or *PKD2* transcript significantly reduced its expression. This suppression of the unmutated allele, rather than the mutated one alone, contributed to a critical threshold of polycystin deficiency, triggering cystogenesis at a physiologic tipping point. This miR-17-binding site was eliminated using clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology, thereby stabilizing *PKD1* and slowing cyst growth. *PKD2* demonstrated similar findings. If these results were not enough, preventing miR-17 binding actually reversed cyst growth (5). Now, we enter an era of not only slowing the progression of PKD but the exciting possibility of reversing or preventing progression.

With these binding sites creating a target for therapeutics, RGLS4326 was discovered. This investigational drug is first in its class as a short oligonucleotide inhibitor of miR-17. This medication preferentially distributes in kidney tissue and collects in the cysts, ultimately displacing miR-17 and stabilizing *PKD1* and *PKD2* (Figure). Originally in mouse models, the same findings were recreated in human-derived tissues in vitro (6). RGLS4326 is administered subcutaneously with high levels of uptake seen in the kidney and the liver and then excreted by the kidneys. It has a long half-life of 8–11 days, and it does not interact with cytochrome P450 isozymes. In mouse and simian models, nearly 80% of the drug was recovered intact in urine (7). As this investigational drug recently completed a phase 1b clinical trial, it has caught the eye of many. In the study, nine patients were administered RGLS4326 subcutaneously every other week for four doses at a dose of 1 mg/kg. Several serum biomarkers were measured including PC1, PC2, kidney injury marker 1, neutrophil gelatinase-associated lipocalin, urea, and creatinine. Both PC1 and PC2 were shown to increase throughout the course of this study, suggesting decreased disease activity. None of the nine patients had any major adverse events, and any reported side effects were noted to be mild and transient (8). However, given the broad regulatory role of miR-17, careful monitoring for off-target effects remains essential.

On April 30, 2025, Novartis announced that it entered a deal to acquire the medication—under the name farabursen—and the biopharmaceutical company that discovered it, Regulus Therapeutics. This acquisition was an $800 million deal, with another $900 million potential increase based on certain milestones (9).

In today's world of targeted therapies and advanced therapeutics, ADPKD has lagged frustratingly. Even the most notable update, Jynarque (tolvaptan), only promises a potential 5 years of dialysis-free survival based on post-market analysis (10). Although 5 years is certainly meaningful, that goal is often hard to achieve with side effects of severe polydipsia and polyuria. Although early in its development, farabursen offers to potentially impact cyst formation and even regression. As we await pivotal phase 3 trials, farabursen offers renewed hope for transforming the management of ADPKD and ushering it into the era of gene-targeted therapy. ■

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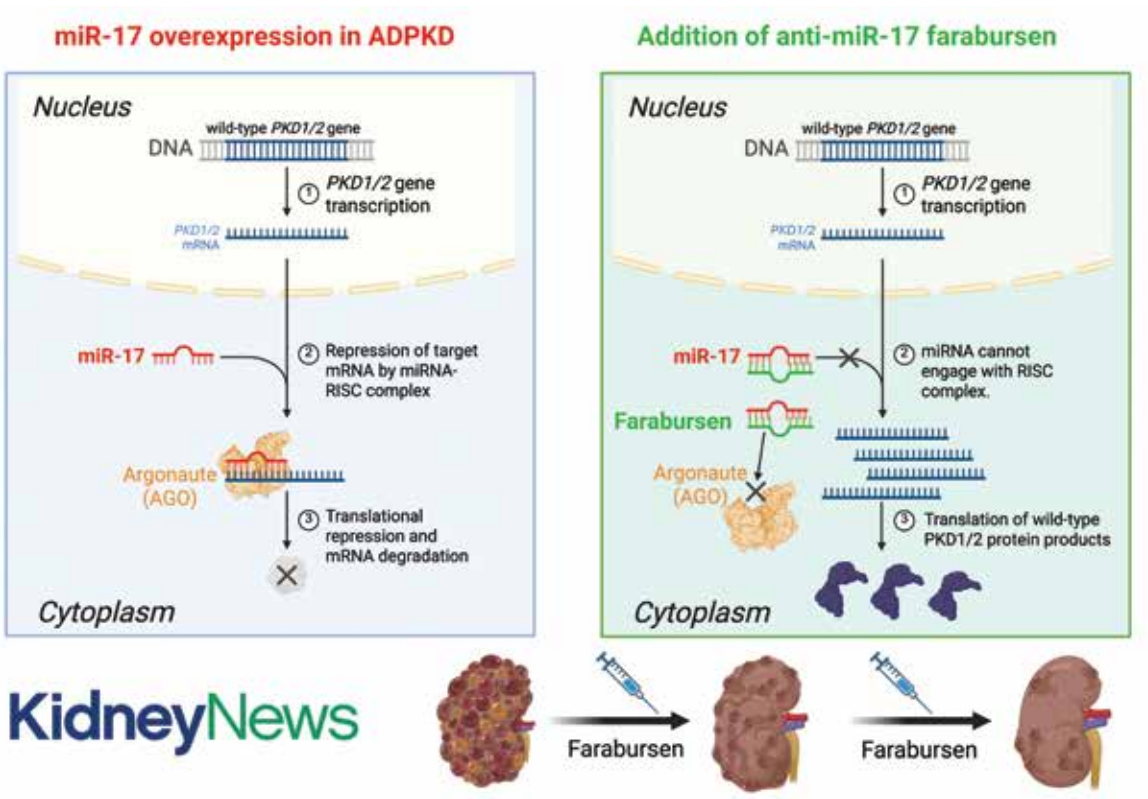
Figure. Schema of wild-type *PKD1/2* mRNA degradation in ADPKD



In ADPKD, miR-17 is overexpressed, which inhibits translation of wild-type *PKD1* and *PKD2* mRNA, promoting cyst growth. Farabursen preferentially accumulates in kidney tissue and inhibits miR-17, which prevents wild-type *PKD1* and *PKD2* mRNA degradation, resulting in production of wild-type PKD1/2 protein and decreasing cyst size in animal models. RISC, RNA-induced silencing complex. Figure created by Drs. Ataei and Sparks with BioRender.

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The 62nd ERA Congress: VISIONARY Trials, VALIANT Advances, and Beyond Nephrology

By Wisit Cheungpasitporn, Andrea Angioi, and Cristina Popa

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The 62nd European Renal Association Congress (ERA25), held in Vienna, Austria, showcased nephrology's evolving role as a precision-driven, multidisciplinary specialty. Under the #BeyondNephrology theme, ERA25 emphasized not only therapeutic breakthroughs but also the importance of rigorous negative and neutral trials that advance clinical science. The meeting also underscored nephrology's increasing integration of complex biological pathways, novel therapeutic platforms, and innovative clinical trial designs.

Several late-breaking and innovative trials highlighted this year's therapeutic expansion. The CONFIDENCE trial (NCT05254002) (1) demonstrated that finerenone combined with empagliflozin in chronic kidney disease (CKD) and type 2 diabetes reduced the urinary albumin-to-creatinine ratio by 52% at 180 days, supporting polypill strategies for kidney–cardiovascular protection. In immunoglobulin A nephropathy, the phase 3 VISIONARY trial (NCT05248646) showed a 51% proteinuria reduction at 9 months with sibeprenlimab (anti-a proliferation-inducing ligand [APRIL] monoclonal antibody). Complement-mediated glomerulopathies were further explored in the VALIANT trial (NCT05067127), which evaluated pegcetacoplan—a targeted C3/C3b inhibitor—in patients with C3 glomerulopathy and immune complex membranoproliferative glomerulonephritis. At 52 weeks, robust proteinuria reduction and stable kidney function were sustained, supporting long-term efficacy across complement-driven diseases.

The ACHIEVE trial (NCT03020303) evaluated spironolactone in patients on dialysis, finding no cardiovascular mortality benefit but increased risks of hyperkalemia and hypotension. These results align with findings from the ALCHEMIST trial (NCT01848639), providing clarity on mineralocorticoid receptor antagonism in this population. Importantly, neutral studies refine treatment algorithms, guide future trials, and avoid ineffective therapies.

ERA25 captured nephrology's current evolution: advancing mechanistic understanding while simultaneously addressing care equity and sustainability.

In transplantation, an international target trial emulation assessed expanded criteria deceased donor kidneys in high-risk recipients with diabetes and cardiovascular disease (2). Whereas expanded criteria deceased donor transplant offered limited survival benefits in select subgroups, early post-transplant mortality remained elevated, underscoring recipient selection challenges. Separately, a phase 1/2a trial (NCT03867617), presented during the Innovative Kidney Trials session, demonstrated that autologous regulatory T cell infusion combined with donor bone marrow induced low-grade chimerism in living donor kidney transplant, promoting donor-specific tolerance while maintaining safety. This early-phase work may help reduce immunosuppression in select patients.

Diagnostic innovation continued to advance. Genomic testing expanded for CKD of unknown etiology, hereditary nephropathies, and syndromic conditions such as Alport syndrome, although challenges of cost and access persist. Artificial intelligence-powered transplant graft scoring models, integrating clinical and morphometric data, outperformed traditional indices, whereas retinal artificial intelligence platforms and poly-omic risk models offer promise for early CKD detection and individualized prognostication.

Care delivery optimization was explored in the NUDGE-CKD trial (NCT06300086) (3), a pragmatic study involving over 22,000 patients, which found that electronic nudges failed to improve physician adherence to guideline-directed therapies. The SWEETSTONE trial (NCT04911660) (4) demonstrated that sodium-glucose cotransporter-2 inhibitors reduced urinary supersaturation in those who form calcium and uric acid stones, suggesting potential utility beyond diabetic nephropathy. Predictive models for antineutrophil cytoplasmic antibody-associated vasculitis were also introduced.

ERA25 addressed structural challenges, with the Women of ERA Task Force survey documenting gender inequities. Environmental concerns placed dialysis and acute kidney injury at the center of sustainability discussions. Innovative live abstract sessions fostered author–audience collaboration, shifting from passive presentation to active participation. Community events like the Renal Run, Sounds and Science concert, and Young Nephrologists' Platform promoted engagement. These initiatives emphasized scientific excellence alongside nephrology's commitment to advocacy, mentorship, and planetary health.

ERA25 captured nephrology's current evolution: advancing mechanistic understanding while simultaneously addressing care equity and sustainability. The conference mirrored that our specialty's strength lies in bringing together molecular therapeutics and innovative trial design with practical solutions for systemic care challenges. ■

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Drs. Cheungpasitporn and Angioi report no conflicts of interest. Dr. Popa serves as coleader of the ERA social media team. The views expressed in this article are her own and do not necessarily reflect the views of ERA.

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The Influence of Glucarpidase on the Toxicity of High-Dose Methotrexate

By Tomaz Milanez, Vinay Srinivasan, and Edgar Jaimes

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Acute kidney injury (AKI) induced by high-dose methotrexate (HDMTX) is a serious condition that can occur in pediatric and adult patients with hematologic malignancies and osteosarcoma. AKI can lead to the delayed renal excretion of MTX and prolonged exposure to high concentrations of MTX, which can cause severe life-threatening adverse effects, including hepatotoxicity, myelosuppression, and mucositis. In addition to renal impairment, there are several clinical risk factors such as frailty and older age for delayed MTX elimination (1, 2).

The median incidence of renal HDMTX toxicity in 20 osteosarcoma clinical trials was 1.5% (range, 0%–12.4%). Among the patients, 0.6% developed grade 3 or 4 nephrotoxicity, and 0.08% of deaths were attributed to HDMTX-induced renal dysfunction (3). In two large series of patients treated with HDMTX for hematologic malignancies, renal toxicity of any grade was detected in 5% and 18% (4, 5).

Glucarpidase is a recombinant bacterial enzyme that quickly inactivates MTX. In 2012, it was approved by the US Food and Drug Administration for reducing toxic plasma MTX concentrations in patients with delayed MTX clearance from impaired renal function. The recommended dosage of glucarpidase is 50 U/kg as a single intravenous injection administered over 5 minutes (6). It should be given within 48 to 60 hours of the start of HDMTX infusion. The recommendations for glucarpidase in patients with HDMTX-associated AKI and delayed MTX elimination are based on an expert consensus and are supported by limited evidence-based data (1, 2).

In a recent study, Gupta et al. analyzed observational data from 708 patients with MTX-associated AKI (MTX-AKI) from 28 US cancer centers (7). Using a target trial emulation framework, the study aimed to estimate the causal effect of administering glucarpidase within 4 days of initiating HDMTX on the primary outcome of kidney recovery at hospital discharge. The secondary outcomes included time for kidney recovery, neutropenia, and transaminitis on day 7 and time to death.

When planning the study, the authors thoroughly considered all essential elements, including eligibility criteria, treatment strategies, assignment procedures, outcomes, follow-up, and statistical analysis, to accurately emulate the target trial using available observational data (8, 9). Multivariable logistic regression was used to adjust for confounding factors. Six sensitivity analyses and four subgroup analyses were conducted for the primary outcome.

The researchers compared outcomes between patients with MTX-AKI who received glucarpidase within 4 days of MTX initiation and those who did not. The primary outcome was defined as a composite of survival until hospital discharge without kidney replacement therapy dependence and with serum creatinine at less than 1.5-fold at baseline. From the 708 adult patients with MTX-AKI (median age of 64 years), 29.5% received glucarpidase. The majority (96.7%) had hematologic malignancies. Within this group, there were primary central nervous system lymphoma (29.2%), acute lymphoblastic leukemia (17.2%), and other lymphomas or leukemias (50.2%). More than half of the patients treated with glucarpidase had a 24-hour MTX level of less than 50 µM, which is below the threshold for glucarpidase treatment recommended by current guidelines. The median dose of glucarpidase was 50 U/kg (interquartile range, 43–50 U/kg).

Glucarpidase treatment was associated with higher adjusted odds of kidney recovery compared with no glucarpidase treatment (adjusted odds ratio [aOR], 2.70; 95% confidence interval [CI], 1.69–4.31). This association was consistent across all sensitivity analyses, including limiting glucarpidase receipt within 3 days of MTX initiation, adjusting for site and according to glucarpidase-prescribing patterns, limiting the analysis to patients treated with MTX during or after 2012, limiting the duration of MTX infusion to less than 12 hours, and limiting the dosage of glucarpidase to 50 U/kg or more.

The analysis of secondary outcomes showed that patients treated with glucarpidase had a faster time to kidney recovery (adjusted hazard ratio, 1.88; 95% CI, 1.18–3.33) and a lower risk of grade 2 or more neutropenia (aOR, 0.50; 95% CI, 0.28–0.91) and grade 2 or more transaminitis (aOR, 0.31; 95% CI, 0.13–0.77) on day 7 compared with patients not treated with glucarpidase. There was no difference in the time to death within the first 90 days (adjusted hazard ratio, 0.76; 95% CI, 0.49–1.18).

The results of this study using a target trial emulation framework suggest that glucarpidase may improve both renal and extrarenal outcomes in adult patients with MTX-AKI, which may have significant implications for clinical practice. Randomized control trials are needed to confirm these findings and explore the efficacy of glucarpidase in terms of the impact on overall survival. Additionally, high-quality data from randomized control trials are required for larger populations of patients with osteosarcoma, various stages of MTX-AKI, and plasma MTX levels that do not meet currently suggested guideline thresholds. ■

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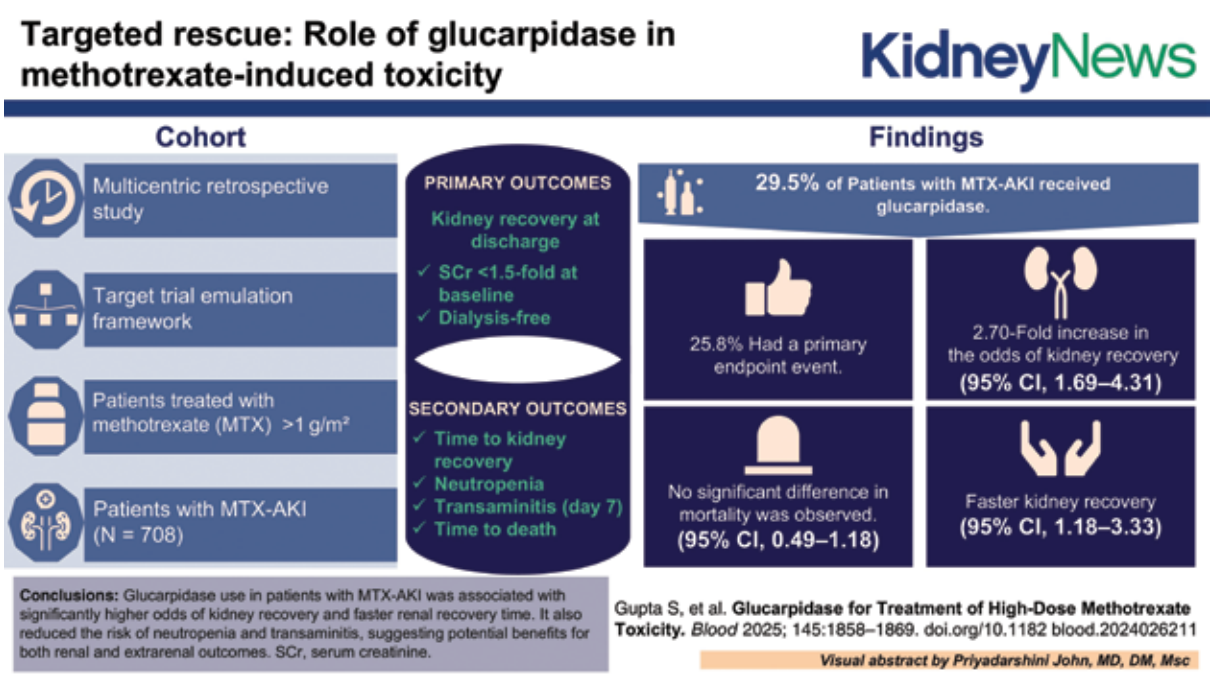

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Fluid Resuscitation in Diabetic Ketoacidosis: A Nuanced Clinical Decision

By Muneeb Iqbal

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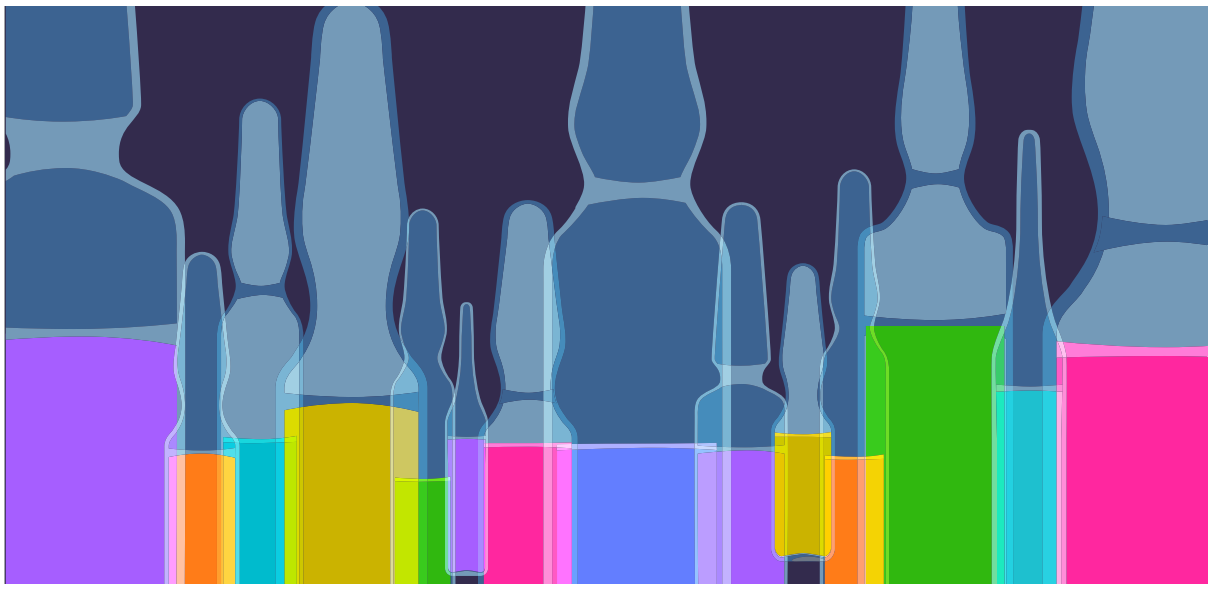

Navigating the complexities of fluid resuscitation in diabetic ketoacidosis (DKA) presents an intriguing challenge for fellows striving to combine physiology, evidence, and clinical guidelines. A recent article published in *The New England Journal of Medicine* (1) provides an insightful case vignette of a young woman presenting to the emergency department with DKA and poses a compelling question: Should balanced crystalloids like Lactated Ringer's/Hartmann's (LR) solution or isotonic normal saline (NS) be the preferred intravenous fluid for volume resuscitation?

As fellows, we often find ourselves balancing the theoretical ideals presented in studies with the practicality of bedside medicine. The physiologic argument for balanced crystalloids resonates deeply. LR solution—containing 130 mmol/L of sodium, 109 mmol/L of chloride, and approximately 4 mmol/L of potassium—reduces the risk of hyperchloremic metabolic acidosis, a complication observed with excessive volumes of NS (Table). Additionally, emerging evidence from studies such as the Intravenous Fluids in Adults With Diabetic Ketoacidosis in the Emergency Department (BRISK-ED) trial protocol (2) and a meta-analysis published in *Frontiers in Endocrinology* (3) suggests that balanced fluids may accelerate DKA resolution, offering an inviting glimpse into what may become a paradigm shift in fluid management (4).

Yet, the practicality of NS cannot be dismissed. Widely available and embedded in most clinical guidelines (5), its higher sodium and chloride contents (both 154 mmol/L) quickly correct electrolyte deficits, a keystone of DKA management. Perhaps most appealing is the ease of potassium supplementation—a critical consideration given the total-body potassium depletion observed in patients with DKA. The ability to tailor potassium concentrations with saline-based solutions dependent on serum levels offers a pragmatic advantage for fellows managing the complex electrolyte abnormalities and potential life-threatening consequences often faced in managing hyperglycemic emergencies. This approach aligns with practices advocating premade bags of potassium-containing saline solutions, which mitigate the risks associated with concentrated electrolytes—a class of high-risk drugs that can pose significant safety concerns, especially on general wards (6). Concentrated potassium ampoules, although effective, are often limited to controlled environments like intensive care units or specialized wards, further underlining the logistical challenges.

While LR does contribute a modest amount of potassium, studies have shown that this load is clinically nonsignificant even in patients with advanced chronic kidney disease for whom potassium excretion is impaired (7). In such patients, the dilutional effects and overall volume distribution ensure that LR does not independently precipitate dangerous hyperkalemia (8). Another point lies in the lactate component of LR. In patients with decompensated cirrhosis, the liver's reduced capacity to metabolize lactate may raise concerns about lactate accumulation (9).

What stands out in this debate is the absence of robust randomized trials definitively favoring one approach over the other (10). As a result, one is left to navigate the nuances based on physiology, emerging evidence, and the operational constraints of their institutions. As nephrology fellows, we are uniquely positioned to appreciate the interplay between electrolyte management and fluid choices. Lessons from DKA resuscitation extend beyond this condition, informing our decisions in varied contexts like acute kidney injury or hypernatremia.

Fluid choice in DKA management illustrates the delicate balance between pathophysiology and practicality. While the debate continues, it remains an opportunity for fellows to refine their skills and make thoughtful, evidence-based decisions in the best interest of their patients. ■

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Table. Physiologic comparison of intravenous fluids for volume resuscitation

Property	Isotonic NS (0.9%)	Balanced crystalloids (LR)
Chloride concentration	154 mmol/L	109 mmol/L
Sodium concentration	154 mmol/L	130 mmol/L
Potassium concentration	0 mmol/L	~4 mmol/L
Risk of hyperchloremic acidosis	Higher due to chloride overload	Lower, as values are closer to plasma levels
Ease of potassium supplementation	Easily supplemented with potassium chloride	More challenging to directly adjust potassium supplementation

Certification Pathways for Point-of-Care Ultrasound in Nephrology

By Adina S. Voiculescu, Daniel W. Ross, Andrew A. Moses, and Vandana Dua Niyyar

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Point-of-care ultrasound (POCUS) has emerged as a transformative tool in nephrology, offering real-time, noninvasive insights that can significantly improve patient outcomes (1, 2). As an adjunct to physical examination, POCUS is increasingly used across the spectrum of clinical conditions for people living with kidney diseases. Ultrasound evaluation of the kidneys and bladder is well-recognized in the management of acute and chronic kidney diseases and kidney failure (3). POCUS has an increasing role in the management of cardio-renal syndrome, guiding diuretic therapy through volume assessment (4). POCUS findings suggestive of fluid overload in patients on dialysis have been shown to reduce hospital admissions related to fluid imbalance (5). Additionally, POCUS improves the success rates of dialysis access utilization, reducing procedural complications and enhancing patient safety (6, 7).

However, the successful integration of POCUS into nephrology practice goes beyond equipment availability—it necessitates structured, comprehensive training to ensure competency. Both didactic and hands-on training are crucial for nephrologists to properly apply and interpret ultrasound techniques in appropriate clinical applications. This type of training is sparse in nephrology fellowships across the country and is mostly due to the lack of trained teachers despite a strong interest from learners (8). A select few centers have been able to implement training during fellowship following recently published blueprints and core curricula (9, 10).

Furthermore, most institutions require certification to obtain privileges for practice and billing for POCUS, making a unified certification pathway in nephrology critical for widespread implementation. The American Society of Diagnostic and Interventional Nephrology (ASDIN) recognized this need and instituted formal pathways to certifications in three key areas of ultrasound in nephrology (11). An ASDIN renal ultrasound certification had been offered since 2005, and it has now been updated. Additional certifications for POCUS in volume assessment and basic dialysis access ultrasound have been developed and have been offered since 2023.

To obtain certification, nephrologists are required to send proof of participation in didactic training or courses and maintain a portfolio of required studies to be submitted for review. The most current ASDIN certifications require at least 16 hours of didactic training, with a minimum of 8 hours dedicated to hands-on ultrasound courses (Figure). ASDIN offers online lectures for continuing medical education (CME) that include 4 hours of basic ultrasound lectures as well as 4 hours of organ-specific lectures (Table 1). In addition, an 8-hour hands-on course is offered as a precourse at the national ASDIN meeting each year. Alternative hands-on courses offered at ASN, the National Kidney Foundation, the International Society of Nephrology, or other societies are also accepted toward certification.

Additionally, the certification process mandates evidence of supervised training, during which practitioners must complete a specific number of studies (Table 2), accompanied by a letter from the trainer confirming competency. The longitudinal requirement for both supervised and independent studies following an initial training course ensures a high-quality certification process.

By fostering education and certification in POCUS, ASDIN helps nephrologists stay at the cutting edge of patient care, reinforcing the role of ultrasound as a critical tool in modern nephrology practice. ■

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Table 1. Online lectures with CME offered by ASDIN in preparation for certification for point-of-care ultrasound

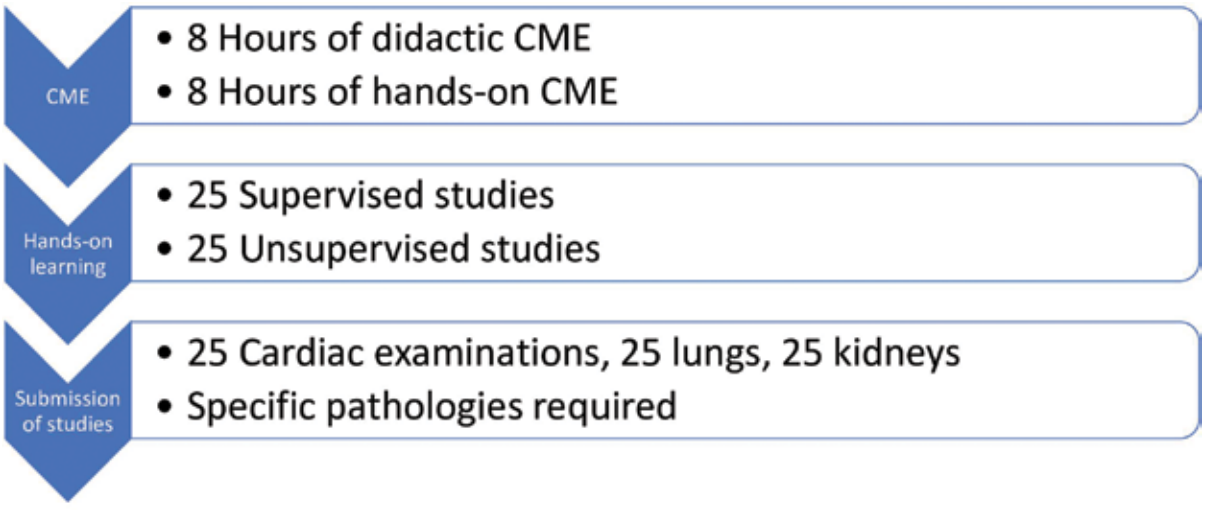
ASDIN online lectures for CME: Basics and renal ultrasound
Ultrasound physics
Ultrasound instrumentation
Ultrasound interpretation basics
Ultrasound Doppler and color
Basic renal ultrasound
Renal ultrasound pathologies
Renal transplant basics
Renal transplant pathologies
ASDIN online lectures for CME: Heart, lung, and dialysis access
Focused cardiac examination/inferior vena cava
Focused lung exam
Volume assessment and interpretation
Dialysis access physical examination
Dialysis access ultrasound
Dialysis access ultrasound pathologies
Dialysis access ultrasound-guided cannulation

Compiled from the ASDIN course catalog (12).

Table 2. Required didactic training, number of studies needed to be performed during the hands-on training, and number of studies that need to be submitted for review

Certification requirements	POCUS certification	Renal certification	Basic dialysis access ultrasound certification
Total didactic training, hours	16	16	16
Online CME, hours	8	8	8
Hands-on course CME, hours	8	8	8
Minimum hands-on training studies, No.	50	60	60
Supervised studies, No.	25	30	40
Unsupervised studies, No.	25	30	20
Submitted studies for review by ASDIN (must include specific pathologies), No.	25	20	20

Figure. Pathway to POCUS certification through ASDIN



The authors report no conflicts of interest.

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Toward a Targeted Therapy in Calciphylaxis: Is Interleukin-6 the Key?

By Aarushi Varshney and Matthew A. Sparks

https://doi.org/10.62716/kn.001052025

Calciphylaxis is a rare but life-threatening complication primarily affecting people with kidney failure, with mortality rates ranging from 45% to 80% (1). Clinically, it presents with severe pain and nonhealing skin ulcers, leading to significant morbidity and a diminished quality of life. Histologically, it is marked by microvascular calcification, thrombosis of subcutaneous vessels, and subsequent tissue necrosis. Despite its severity, the molecular mechanisms underlying calciphylaxis remain poorly understood, and no US Food and Drug Administration-approved therapies currently exist. Current treatments, such as hyperbaric oxygen and sodium thiosulfate, are based on limited evidence and lack well-powered randomized clinical trials (2).

A recent study by Napoleon et al., published in *Science Translational Medicine*, provides new insights into the disease's pathogenesis (3). To investigate endothelial dysfunction in calciphylaxis, the authors exposed dermal microvascular endothelial cells to serum from 40 people with kidney failure and calciphylaxis and 40 matched controls. Proteomic analysis revealed that interleukin-6 (IL-6) was the most significantly upregulated protein in endothelial cells exposed to calciphylaxis serum. This was accompanied by increased phosphorylation of Janus kinase-2 (JAK2) and signal transducer and activator of transcription-3 (STAT3), key components of the IL-6 signaling pathway, which was attenuated by tocilizumab, an anti-IL-6 receptor (IL-6R) antibody, confirming IL-6-dependent activation.

Further analysis showed elevated kynurenine levels in calciphylaxis serum, a known IL-6 inducer, and increased a disintegrin and metalloprotease 17 (ADAM17) expression, which facilitates IL-6R shedding, in endothelial cells. Cycloheximide treatment, which blocks protein synthesis, reduced IL-6 levels, confirming de novo IL-6 production by endothelial cells in response to calciphylaxis serum.

Spatial transcriptomic analysis of skin biopsies revealed that calciphylaxis lesions, particularly in blood vessels and surrounding adipose tissue, exhibited upregulation of genes involved in IL-6 signaling and thrombosis. Evidence of intercellular communication with IL-6 and vascular endothelial growth factor pathways suggested a coordinated inflammatory and prothrombotic response.

The study also identified thymidine phosphorylase in endothelial cells as a regulator of tissue factor activity through IL-6 signaling. Both tocilizumab and olamkicept, a selective trans-IL-6 inhibitor, significantly reduced tissue factor activity in calciphylaxis samples. Cell–cell interaction analyses confirmed that IL-6 directly upregulates tissue factor expression in cutaneous cells, establishing the possibility of the thymidine phosphorylase–IL-6–tissue factor axis as a central driver of disease pathogenesis.

These findings position IL-6 as a promising therapeutic target. Agents such as siltuximab (anti-IL-6) and tocilizumab (anti-IL-6R) may disrupt this pathogenic cascade and prevent thrombosis, offering a potential shift from current treatment paradigms. However, limitations include the use of post-onset calciphylaxis samples and sera used in these studies, the absence of an animal model, and the confounding proinflammatory state of chronic kidney disease, which itself elevates IL-6 levels.

Despite these limitations, the study raises important questions about the utility of IL-6 and tissue factor as biomarkers for disease activity and treatment response. This work represents a significant step forward in understanding calciphylaxis and opens the door to targeted therapies that could transform patient outcomes. Looking ahead, future research should focus on validating these findings in prospective clinical studies and developing reliable biomarkers to monitor disease progression and therapeutic efficacy. The establishment of animal models will be critical for preclinical testing of IL-6-targeted therapies. Additionally, exploring combination therapies that modulate both systemic inflammation and local vascular pathology may offer synergistic benefits. Ultimately, these advances have the potential to lead to disease-modifying treatments for calciphylaxis, offering new hope to patients affected by this devastating condition. ■

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The authors report no conflicts of interest.

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Tirzepatide Demonstrates Benefits in Obesity-Related HFpEF

https://doi.org/10.62716/kn.000882025

For patients who have obesity-related heart failure with preserved ejection fraction (HFpEF)—commonly associated with chronic kidney disease (CKD)—long-term tirzepatide therapy improves cardiovascular and kidney function, according to a clinical trial report in the *Journal of the American College of Cardiology*.

The phase 3 SUMMIT trial enrolled 731 patients with obesity (body mass index, ≥30 kg/m^2) and HFpEF (left ventricular ejection fraction, ≥50%). The sample was enriched to enroll more people with CKD, with a prevalence of approximately 60%.

Patients were randomly assigned to treatment with placebo or tirzepatide for a median of 104 weeks. Outcomes of interest included cardiovascular death, worsening cardiovascular function, and change in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) after 52 weeks of treatment. To account for potential confounding effects of obesity and changes in muscle mass, the estimated glomerular filtration rate (eGFR) was assessed by both creatinine and cystatin C measurements at 12, 24, and 52 weeks.

People with CKD had worse heart failure, based on functional class, KCCQ-CSS score, a 6-minute walk test, and N-terminal pro–B-type natriuretic peptide and cardiac troponin T levels. The presence of CKD was also associated with an increased risk of worsening heart failure.

The tirzepatide group had lower rates of major adverse heart failure events, accompanied by improvement in quality of life and functional capacity. Tirzepatide was associated with absolute reductions in primary events compared with placebo: 11.3% versus 17.0% in people with CKD and 3.4% versus 9.8% in those without CKD.

Kidney function was consistently approximately 9 mL/min/1.73 m^2 lower with eGFR-cystatin C versus eGFR-creatinine. By both measures, eGFR was increased at 52 weeks with tirzepatide, with substantial variation among patients. At 12 weeks, tirzepatide was associated with a reduction in eGFR-creatinine but not eGFR-cystatin C. By 52 weeks, all patients receiving tirzepatide showed improvement in eGFR-cystatin C, while eGFR-creatinine improved only in patients with CKD.

The SUMMIT trial highlights the functional impairment and unfavorable prognosis associated with obesity-related HFpEF and CKD. The new findings show that long-term tirzepatide therapy leads to improvement in kidney function, as measured by both creatinine and cystatin C, among other clinical benefits.

"Baseline eGFR did not influence the magnitude of the relative risk reduction produced by tirzepatide on major adverse heart failure outcomes or its effect to enhance health status," the researchers conclude. They also note the difficulties posed by the eGFR measurement in patients with obesity receiving incretin-based therapies [Packer M, et al.; SUMMIT Trial Study Group. Interplay of chronic kidney disease and the effects of tirzepatide in patients with health failure, preserved ejection fraction, and objesity: The SUMMIT Trial. *J Am Coll Cardiol* 2025; 85:1721–1735. doi: 10.1016/j.jacc.2025.03.009]. ■

COVID-19 Linked to Adverse Kidney Outcomes in Youths

https://doi.org/10.62716/kn.000862025

COVID-19 is associated with an increased risk of adverse kidney outcomes in children and adolescents—particularly those with a previous history of chronic kidney disease (CKD) or acute kidney injury (AKI), reports a study in *JAMA Network Open*.

The analysis included 487,378 pediatric patients with confirmed COVID-19, drawn from 19 centers participating in the National Institutes of Health's Researching COVID to Enhance Recovery (RECOVER) initiative. A control group consisted of 1.4 million children and adolescents without COVID-19. Participants were enrolled between March 1, 2020, and May 1, 2023, with follow-up to December 1, 2024.

Outcomes of interest included new-onset CKD stage 2 or higher or stage 3 disease in people with pre-existing CKD. The analysis also included a composite outcome of 50% or greater decline in estimated glomerular filtration rate (eGFR), an eGFR of 15 mL/min/1.73 m^2 or less, or kidney failure and among people with pre-existing CKD or acute-phase AKI, eGFR declines of 30%, 40%, or 50%.

The patients were 51% male with a mean age of 8.2 years representing a range of comorbid conditions. Those with COVID-19 were at significantly increased risk of new-onset stage 2 or higher CKD: hazard ratio (HR), 1.17 and stage 3 or higher CKD: HR, 1.35.

Youths with pre-existing CKD were at increased risk of experiencing a composite outcome event between 28 and 179 days: HR, 1.15. This risk was even higher for people with acute-phase AKI: HR, 1.29.

There are limited data on the risk and outcomes of post-acute sequelae of SARS-CoV-2 infection, or "long COVID," in pediatric patients. Although the overall incidence of post-acute sequelae of SARS-CoV-2 in youths appears similar to that in adults, there are differences in the symptoms and course of COVID-19.

This large US cohort study is, according to the authors, among the "most comprehensive" studies of long-term kidney outcomes of COVID-19 among children and adolescents. Findings suggest that young patients with COVID-19 are at increased risk of adverse kidney outcomes, including new-onset CKD and decreased kidney function.

The researchers call for further studies of the "intricate pathways" by which the observed associations may develop [Li L, et al.; RECOVER Consortium. Kidney function following COVID-19 in children and adolescents. *JAMA Netw Open* 2025; 8:e254129. doi: 10.1001/jamanetworkopen.2025.4129]. ■

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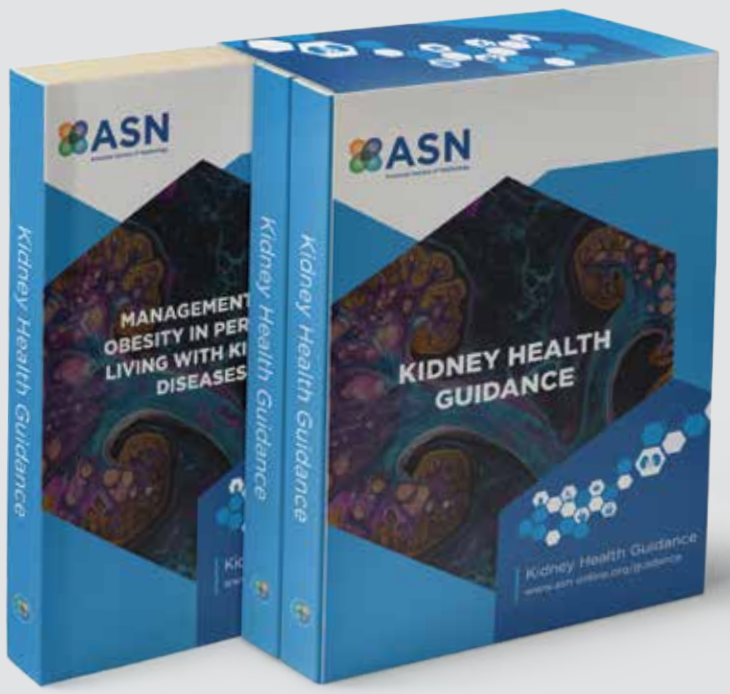

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Correction and Clarification

Correction and Clarification to "Iptacopan Approval Marks the Start of a New Era for C3 Glomerulopathy" (June 2025)

https://doi.org/10.62716/kn.001242025

The article "Iptacopan Approval Marks the Start of a New Era for C3 Glomerulopathy" by Bridget M. Kuehn, published in the June 2025 issue of *Kidney News* (1), included inaccuracies related to an interview with Matthew Sparks, MD, FASN. The original article was published online on June 6, 2025, and updated on June 20, 2025, to address the following:

1) **Clarification:** Pegcetacoplan was granted priority review of a supplemental new drug application for the treatment of both C3 glomerulopathy (C3G) and immune complex membranoproliferative glomerulonephritis (MPGN). The original article omitted the word "immune."
2) **Correction:** The article mis-stated the list of encapsulated bacteria relevant to recommended vaccination against infections. This correct list includes *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.
3) **Clarification:** Dr. Sparks noted that some of his patients with C3G have experienced positive change while treated with the new complement inhibitors, of which iptacopan is already approved for immunoglobulin A nephropathy. The original article incorrectly stated that these patients were treated with iptacopan.
4) **Correction:** The article inaccurately stated that "nephrotic factors" are tested using a biopsy. The corrected statement is that testing a patient's serum for C3, C4, or C5 nephritic factor antibodies, along with genetic testing, can help identify the cause of the condition. ■

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1. Kuehn BM. Iptacopan approval marks the start of a new era for C3 glomerulopathy. *Kidney News*, June 2025; 17(6):1, 5. doi: 10.62716/kn.000942025

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In IgA Nephropathy (IgAN)

IF YOU DON'T **TARGET UNDERLYING CAUSES EARLY,** **THE EFFECTS** CAN HAVE LASTING CONSEQUENCES[1]

Turn down Gd-IgA1: elevated levels can lead to downstream kidney damage[2]

Most IgAN patients will progress to kidney failure and dialysis or transplant within their lifetime.[1]

An immune-directed treatment approach is essential to change the course for patients with IgAN.[1,3]

FOCUS ON THE GUT-KIDNEY AXIS, A KEY SOURCE OF THE DISEASE: the majority of Gd-IgA1 is thought to be produced in the gut—specifically in the Peyer's patches of the ileum[4]

ADDRESS UNDERLYING CAUSES EARLY: the draft 2024 KDIGO guideline* recommends simultaneously managing IgAN causes and CKD consequences[3]

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EXPLORE THE CLINICAL RATIONALE FOR EARLY INTERVENTION WITH A DISEASE-MODIFYING THERAPY

*Draft submitted for public comment and subject to change.

CKD=chronic kidney disease; Gd-IgA1=galactose-deficient immunoglobulin A1; KDIGO=Kidney Disease: Improving Global Outcomes.

References: 1. Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727–738. **2.** Chang, Li X-K. The role of immune modulation in pathogenesis of IgA nephropathy. *Front Med (Lausanne)*. 2020;7:92. doi:10.3389/fmed.2020.00092 **3.** Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2024 clinical practice guideline for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV). Public Review Draft; August 2024. Accessed June 4, 2025. https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf. **4.** Lim RS, Yeo SC, Barratt J, et al. An update on current therapeutic options in IgA nephropathy. *J Clin Med*. 2024;13(4):947. doi:10.3390/jcm13040947

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