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Iptacopan Approval Marks the Start of a New Era for C3 Glomerulopathy

Additional C3G Drug Approvals Anticipated

By Bridget M. Kuehn

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News that the US Food and Drug Administration (FDA) approved iptacopan in late March to reduce proteinuria in patients with C3 glomerulopathy (C3G) marked a watershed moment for patients with the condition and their nephrologists (1). It is the first drug ever approved to treat the rare condition.

"C3G is a debilitating disease often affecting young people, impacting many aspects of their physical and emotional health, and our previous treatment options came with significant challenges," said Carla Nester, MD, MS, FASN, professor of pediatrics-nephrology at The University of Iowa in Iowa City, in a statement from the drug's manufacturer, Novartis (1). "This approval of [iptacopan] is historic for the entire C3G community, as now, for the first time, we have a therapy that is believed to treat the underlying cause of the disease, providing the potential for a new standard of care for patients," said Nester, who was the principal investigator on the phase 3 trial of the drug.

Iptacopan is an oral medication that helped reduce proteinuria by approximately one-third of patients with C3G in the phase 3 study reported by Novartis (2). It directly targets factor 3, which is part of a feedback loop in the alternative complement pathway and, in doing so, stops a buildup of C3 in the glomeruli that leads to damage and progressive kidney disease, often leading to kidney failure within 10 years. Previously, the standard treatment was steroids and mycophenolate, which often failed to provide relief and was associated with adverse effects, noted Matthew Sparks, MD, FASN, associate professor and director of the Nephrology Fellowship Program at Duke University School of Medicine in Durham, NC. When those options failed, he explained, clinicians would then move on to an infusion therapy like eculizumab, which required regular infusions and did not have much evidence supporting a benefit. The availability of a twice-daily oral medication that reduces

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Proposals Would Slash Federal Health Agency Spending, Cut Key Kidney Disease Programs

By Bridget M. Kuehn

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A federal "skinny budget" that slashes about one-third of the US Department of Health and Human Services' (HHS') discretionary spending and leaked details of proposed elimination of vital kidney health programs have raised alarm in the kidney community.

A president's budget proposal (1) is rarely accepted as is by Congress, and the current proposal was still being debated in the US House of Representatives at press time. Yet the dramatic nature of the cuts and a leaked proposal (2, 3) set off a flurry of advocacy efforts in the kidney community to protect vital funding and programs. For example, the leaked proposal called for elimination of the Kidney Innovation Accelerator (KidneyX) program, the National Institute on Minority Health and Health Disparities, the Centers for Disease Control and Prevention's (CDC's) National Center for Chronic Disease Prevention and Health Promotion, including the CDC's Chronic Kidney Disease Initiative, and other key kidney surveillance and health promotion programs.

"ASN continues to advocate for policies that improve health, generate knowledge, and strengthen the workforce," wrote ASN President Prabir Roy-Chaudhury, MD, PhD, FASN, in a "Dear Colleague" letter to ASN members (4), part of ASN's new Kidney Health Advocacy page (https://www.asn-online.org/policy/kidney-health.aspx). "This

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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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Iptacopan Approval Marks the Start of a New Era for C3 Glomerulopathy

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proteinuria could provide patients with a much-needed, evidence-backed alternative, he said.

"This is an amazing time because these are young people [who] have an incurable disease, [and] we've been basically giving them ineffective therapies that have a lot of toxicity for many, many years," Sparks said. "It ushers in a new era for nephrologists to start getting comfortable prescribing complement inhibitors."

Emerging C3G therapies

Iptacopan is also likely just the first in a series of complement inhibitor approvals for C3G, as FDA has also granted priority review of a supplemental new drug application for pegcetacoplan for the treatment of both C3G and immune complex membranoproliferative glomerulonephritis (MPGN) (3). Presented at Kidney Week 2024, results of a phase 3 trial for pegcetacoplan found that a twice-weekly infusion of the drug reduced proteinuria in patients with C3G or primary immune complex MPGN by 68% and stabilized patients' estimated glomerular filtration rates (eGFRs), with similar rates of adverse events in the pegcetacoplan and placebo arms (4).

Both of the trials' results are very promising. Yet Sparks noted that longer outcome data are needed. He explained that the trials show that the drugs reduce proteinuria, stabilize eGFR, and reduce C3 staining in kidney biopsies, which he and others hope will lead to improved long-term outcomes for the condition. Importantly, he said, the trials included patients with C3G who had a transplant. He noted that these patients can have a recurrence of their condition, but the medications may help enable them to keep their allografts longer.

The medications do come with some challenges. They are expensive; 60 iptacopan pills cost approximately $50,000, although payment assistance programs may be available through the drug's manufacturer (5). Because the therapies alter the complement system, patients will need to be vaccinated against infections with encapsulated bacteria like *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, Sparks explained. But because patients' underlying conditions may also make them vulnerable to such infections, those vaccines may be warranted anyway, he said.

Despite the potential downsides, Sparks noted that he has seen a dramatic positive change in the lives of a couple of his patients with C3G who are treated with these new complement inhibitors, of which iptacopan is already approved for immunoglobulin A nephropathy.

"As someone whose family has suffered from C3G across multiple generations, it is difficult to fully express the physical and emotional challenges of living with this unrelenting disease," said Lindsey Fuller, a patient with C3G and coleader of C3G Warriors, in the Novartis release (1). "To finally have an approved treatment—and one that can be taken orally—is something people with C3G have been waiting for. [The iptacopan] approval brings new hope for me, my family, and so many others."

Identification and education needed

C3G is considered an ultra-rare condition, affecting approximately one to three people per million, according to US registry data (6). Most nephrologists may only see one patient per decade, Sparks said. He also said that it is often undiagnosed until declining kidney function, proteinuria, and high blood pressure develop.

Sparks hopes that the US Preventive Services Task Force will eventually recommend routine screening for kidney diseases. But, until then, it is important for clinicians to assess symptomatic young patients for urinary protein using urine protein-to-creatinine ratio or urine albumin-to-creatinine ratio testing and to refer them to a nephrologist for care. Ultimately, a kidney biopsy is needed for diagnosis. It will also be important to help get nephrologists up to speed on the growing therapeutic options.

"Education is going to be really crucial [now] that these drugs exist," Sparks said. Further leading to confusion is that C3G used to be called MPGN, an umbrella term for several conditions, he noted. "This is a very fast, evolving era, which since you were in fellowship, may have changed a lot."

Sparks said it is also important to identify the exact cause of the patient's condition, which may be due to the development of antibodies to C3, C4, or C5 nephritic factors. He noted that testing the patient's serum for C3, C4, or C5 nephritic factor antibodies and genetic testing can help. Such testing may eventually help personalize care. He said that the next step should include studies to help match patients to the best drug for their condition. "We will likely need multiple different drugs because one drug may not be effective in all patients," he said.

Sparks shared that it is an exciting time to be a nephrologist with a growing number of kidney health-preserving drugs, including sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide agonists, and now a growing number of therapies targeting rare kidney diseases. He credited the Kidney Health Initiative with helping to make such new therapies possible, along with FDA's adoption of surrogate endpoints like the urine protein-to-creatinine ratio and eGFR for clinical trials. He noted that using longer-term endpoints such as kidney failure or a doubling of creatinine can be difficult in clinical trials for rare diseases. ■

References

1. Novartis. Novartis receives third FDA approval for oral Fabhalta® (iptacopan)—the first and only treatment approved in C3 glomerulopathy (C3G). March 21, 2025. Accessed May 7, 2025. https://www.novartis.com/news/media-releases/novartis-receives-third-fda-approval-oral-fabhalta-iptacopan-first-and-only-treatment-approved-c3-glomerulopathy-c3g
2. Novartis. Novartis presents latest phase III Fabhalta® (iptacopan) data in C3 glomerulopathy (C3G) showing clinically meaningful and statistically significant 35.1% proteinuria reduction vs. placebo. May 25, 2024. Accessed May 7, 2025. https://www.novartis.com/news/media-releases/novartis-presents-latest-phase-iii-fabhalta-iptacopan-data-c3-glomerulopathy-c3g-showing-clinically-meaningful-and-statistically-significant-351-proteinuria-reduction-vs-placebo
3. Robinson C. FDA grants priority review to pegcetacoplan for C3G and IC-MPGN. April 16, 2025. Accessed May 17, 2025. https://www.docwirenews.com/post/fda-grants-priority-review-to-pegcetacoplan-for-c3g-and-ic-mpgn
4. Nester CM, et al. VALIANT: A randomized, multicenter, double-blind, placebo (PBO)-controlled, phase 3 trial of pegcetacoplan for patients with native or post-transplant recurrent glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulonephritis (IC-MPGN) [Abstract]. *J Am Soc Nephrol* 2024; 35 (10S):SA-OR92. doi: 10.1681/ASN.2024qdwvz5bg
5. Drugs.com. Fabhalta prices, coupons, copay cards & patient assistance. Accessed May 7, 2025. https://www.drugs.com/price-guide/fabhalta
6. Smith RJH, et al. C3 glomerulopathy—understanding a rare complement-driven renal disease. *Nat Rev Nephrol* 2019; 15:129–143. doi: 10.1038/s41581-018-0107-2

Proposals Would Slash Federal Health Agency Spending

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[HHS budget] proposal is the first step in a very long process, and ASN will advocate at each step."

To do that, Roy-Chaudhury noted that ASN joined a coalition of more than 525 organizations to raise concerns about the cuts (5). A letter from the Coalition for Health Funding to the House and Senate Appropriations Committees highlights the vital role that the National Institutes of Health (NIH) and other health agencies play in supporting public health and promoting American leadership in scientific discovery.

"We call on you to reject the proposed budget cuts across HHS agencies and centers and instead work together to invest in our nation's health by ensuring that the essential programs that protect and further [Americans'] health remain adequately funded," the coalition letter states.

Controversial cuts

A leaked "passback" document shared between the White House's Office of Management and Budget and HHS was the first news to spark concern in the kidney community (1, 2). The proposal outlined a major reorganization at HHS that would include folding the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) into a new National Institute on Body Systems. It also called for dramatic budget cuts ranging from 30% to 100% of the budgets of various HHS departments and programs.

"If this goes through as written, it is devastating," said Daniel E. Weiner, MD, MS, FASN, ASN councilor and professor of medicine at Tufts University, Boston, MA. Yet he cautioned that such passback proposals are usually just a starting point in budget negotiations.

The president's skinny budget proposal, submitted to Congress shortly after the passback document leaked, is usually the second step in the process. That official document confirmed that the administration was seeking to cut about one-third of the HHS discretionary budget, although it contained few details about the cuts or reorganization plans. The next steps will be for the House and Senate to debate and approve a budget proposal, Weiner explained. Then legislators would have to create new government entities and appropriate funds for them, he said.

Weiner said that there has long been bipartisan support for funding NIH and programs focused on kidney diseases. Congress has regularly approved annual increases in the NIH budget appropriation over the past few decades that could be undone by the proposed cuts. That could make the across-the-board budget cuts unpopular with legislators, especially those representing districts with large academic medical centers that rely on NIH funding to support research, Weiner said. For example, recent news reports indicate that The University of Alabama at Birmingham and other research institutes in the state receive almost $400 million in NIH grant funding annually, which helps support about 4400 jobs in the state and contributes $916 million to the state's economy (6). "The scope of the cuts is going to be controversial," Weiner said. "People, regardless of party, like the NIH, and many congressional districts have a lot of NIH-funded research going on."

Academic centers across the United States are already reeling from the cancellations of research grants and proposed reductions in funding for indirect research costs like research

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support staff and equipment (7). The proposed budget cuts could further impact institutions nationwide and have ripple effects throughout kidney research. Weiner noted the potential loss of the institutional knowledge and skills of NIH-funded researchers. Additionally, the abrupt reductions in funding may disproportionately impact early-career researchers. "The risk is that we could lose a generation of researchers," he said. "That would be devastating to progress and to the role of the United States as the world leader in medical research."

Beyond their impact on kidney research and care, cuts to US research funding also have the potential to affect the administration's goals of reducing chronic diseases through its "Make America Healthy Again" initiative. Roy-Chaudhury emphasized these concerns in a recent letter to NIH Director Jayanta Bhattacharya, MD, PhD, stating, "Reducing investments in kidney research jeopardizes progress in tackling chronic diseases and runs counter to the administration's stated mission of improving kidney health for all Americans" (8).

Miriam Godwin, vice president of Health Policy and Clinical Outcomes at the National Kidney Foundation, noted that kidney disease is an under-recognized public health crisis and a leading cause of death in the United States, with many people only finding out that they have the condition when they have progressed to a late stage. Godwin said that the proposed 44% cut to the CDC budget and the proposals to eliminate its work to prevent chronic disease and instead focus only on infectious disease could also hamper kidney disease surveillance and prevention.

"It would eliminate CKD [chronic kidney disease] surveillance done by the CDC, and it would eliminate chronic disease prevention, preventative medicine, education, and support for healthy behaviors [provided to] states, territories, and cities," she said. "That is a fairly shocking magnitude of elimination, particularly given the administration's stance on [reducing] chronic disease." Weiner corroborated: "Kidney disease is an example of a high-impact chronic disease. It should be a target for intervention."

ASN also joined as a signatory on a letter from the Ad Hoc Group for Medical Research, which included 510 organizations (9). The group's letter advocates for at least $51 billion in NIH funding for 2026, a 9% increase over the 2025 funding level. "Robust support for medical research makes Americans healthier," the Ad Hoc Group wrote. "Patients across the country—from urban centers to rural communities—benefit from medical research supported by the NIH, which serves as the foundation for nearly every preventive intervention, diagnostic, treatment, and cure in practice today."

Rethinking reorganization

The consolidation of NIDDK into a new National Institute on Body Systems mimics a congressional proposal from 2024 to combine NIDDK with the National Heart, Lung, and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (10). Although ASN supported the idea of restructuring NIH to break down silos and reduce the fragmentation of kidney research across agencies, it opposed the proposed consolidation because of the potential to deprioritize kidney research (11). Weiner noted that kidney diseases may fit better in a new institute with cardiovascular and metabolic diseases. However, he also stressed that the key in any restructuring plan would be to ensure that kidney diseases would not be de-emphasized in such a move. "There are opportunities and risks," Weiner warned.

Godwin echoed that concern, saying the kidney community is working to elevate recognition of kidney diseases and does not want to see them relegated to a "bullet point" in a larger institute. Godwin said that the National Kidney Foundation is advocating for kidney-focused programs to find a new home in the proposed Administration for a Healthy America to support the administration's goals of reducing chronic diseases. She noted that the current proposal is preliminary. Hence, it is not yet clear whether the administration will ultimately eliminate all of the programs or if it might reconstitute some in a different form. "We want to understand what is going to take place and do our best advocacy…to keep the programs, initiatives, funding important to our community," Godwin said.

ASN also joined a coalition of research, public health, and academic organizations calling for greater transparency and public debate before any large-scale layoffs or reorganization of US public health and science organizations (12). In a letter to the House and Senate Appropriations Committees' leaders on May 8, the coalition noted that the current ambiguity and lack of transparency were affecting staff morale and organizational efficiency at government science organizations. It also suggested that the current actions fall short of standards expected of government and private employers.

"We request the immediate public release of these plans and robust public and expert consultation *before* any irreversible actions are taken," the coalition wrote. "Without transparency, stakeholders vital to the scientific and health ecosystem, including researchers, scientists, public health professionals, [health care] providers, academic institutions, patient advocacy groups, and organizations dedicated to scientific integrity, are left unable to provide crucial feedback or prepare for potential disruptions. We risk undermining long-term research projects, interrupting essential public health detection, monitoring and reporting, damaging our national capacity to respond to health crises, and jeopardizing the scientific workforce pipeline."

Weiner recommended that nephrologists and other members of the kidney community pay attention to the ongoing budget and reorganization debates and respond strategically. For example, he suggested reaching out to congressional representatives to emphasize the importance of research to one's district and state and how the cuts could harm their constituents. ■

References

1. White House. The White House Office of Management and Budget releases the president's fiscal year 2026 skinny budget. May 2, 2025. Accessed May 9, 2025. https://www.whitehouse.gov/briefings-statements/2025/05/the-white-house-office-of-management-and-budget-releases-the-presidents-fiscal-year-2026-skinny-budget/
2. Faust J. New: A 64-page HHS restructuring proposal outlines sweeping cuts to US public health. *Inside Medicine*. April 16, 2025. Accessed May 1, 2025. https://insidemedicine.substack.com/p/new-a-64-page-hhs-restructuring-proposal
3. Sun LH, et al. Internal budget document reveals the extent of Trump's proposed health cuts. *The Washington Post*. April 16, 2025. Accessed May 1, 2025. https://www.washingtonpost.com/health/2025/04/16/hhs-budget-cut-trump/
4. Roy-Chaudhury P.; American Society of Nephrology. Dear Colleague letter to ASN members. April 2025. https://www.asn-online.org/policy/webdocs/ASN_President_Letter_April_2025.pdf
5. Coalition for Health Funding, et al. Letter to Chairs Capito and Aderholt and Ranking Members Baldwin and DeLauro, House and Senate Appropriations Committees, Labor, Health and Human Services, and Related Agencies Subcommittee. April 25, 2025. Accessed May 1, 2025. https://www.asn-online.org/policy/webdocs/HHS_FY26_Budget_Proposal_Letter.pdf
6. Angle A. NIH funding created $916 million in economic activity in Alabama; former UAB official warns of impacts from potential cuts. *Alabama Daily News*. March 25, 2025. https://aldailynews.com/nih-funding-created-916-million-in-economic-activity-in-alabama-former-uab-official-warns-of-impacts-from-potential-cuts/
7. Kuehn BM. HHS funding cuts and layoffs raise concern in the kidney community. *Kidney News*, May 2025; 17(5):1, 5, 6. https://doi.org/10.62716/kn.000782025
8. Roy-Chaudhury P.; American Society of Nephrology. Letter to Director Jayanta Bhattacharya. March 31, 2025. Accessed May 2, 2025. https://www.asn-online.org/policy/webdocs/NIH_Director_Bhattachara_Letter_3.31.25.pdf
9. Ad Hoc Group for Medical Research. The Ad Hoc Group fiscal year 2026 recommendation. April 7, 2025. Accessed May 1, 2025. https://www.asn-online.org/policy/webdocs/AdHoc_FY26Recommendation.pdf
10. House Energy & Commerce Committee Chairman Brett Guthrie. Chair Rodgers unveils framework for NIH reform, requests stakeholder input. June 14, 2024. Accessed May 2, 2025. https://energycommerce.house.gov/posts/chair-rodgers-unveils-framework-for-nih-reform-requests-stakeholder-input
11. Crews DC.; American Society of Nephrology. Letter to the Honorable Cathy McMorris Rodgers, chair, House Energy and Commerce Committee. August 16, 2024. https://www.asn-online.org/policy/webdocs/House_NIH_Reform_ASN_8.16.24_Final.pdf
12. American Psychological Association, et al. Letter to Chairman Crapo, Chair Cassidy, Ranking Member Wyden, and Ranking Member Sanders. May 8, 2025. Accessed May 9, 2025. https://www.asn-online.org/policy/webdocs/ASN_Govt_RIF_Letter_2025.pdf

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ASN Executive Vice President's Update

Debunking Myths About Nephrology and Nephrologists

By Tod Ibrahim

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As a discipline, nephrology is burdened by commonly held but incorrect perceptions. Unfortunately, these myths can make nephrology less appealing as a career option for medical students, residents, and future researchers and scientists; decrease how health systems value the specialty; and make it more difficult for ASN to advocate on behalf of the more than 850 million people worldwide living with kidney diseases.

Identifying the most insidious myths, presenting evidence to prove these misconceptions false, and providing a more realistic explanation will help change how nephrology and nephrologists are viewed. In *Meditations*, Roman emperor Marcus Aurelius expressed the Stoic perspective, "All things fade and quickly turn to myth: quickly too utter oblivion drowns them" (1). Rather than accept misperceptions that threaten the field, ASN and the rest of the kidney community must continue to strive to present facts and truth.

Myth: Nephrologists earn among the lowest compensation of all internal medicine specialties.

No one contends that nephrologists are compensated fairly. In most cases, nephrologists work harder—and longer hours, especially when considering the "windshield time" required to drive between dialysis units or transplant outreach clinics—to generate a reasonable wage. Additionally, payors fail to differentiate among the different types of nephrologists.

"Nephrology is cognitive and procedural, has a primary care component focused on identifying patients and slowing progression of kidney diseases, and includes the need to manage comorbidities," ASN Past President Anupam Agarwal, MD, FASN, and I observed in 2020 (2). "Nephrologists also provide 24-hour coverage—often for dialysis services for [patients who are critically ill]—an important service to health systems."

Among the 13 internal medicine specialties, nephrology ranks sixth for average compensation (3). Physician work relative value units (wRVUs), accounting for the time, effort and technical skill, judgment and mental energy, and stress to provide a service (2), are misvalued and unfairly favor procedure-based specialties (4). Unfortunately, wRVUs do not reflect changes in technology, which have vastly increased the efficiency of many procedures, thus allowing some physicians to generate more RVUs per hour than specialties requiring actual face time with complex patients, such as in nephrology (4).

ASN Past President Ronald J. Falk, MD, FASN, and former Kidney Week Education Committee Cochair Mitchell H. Rosner, MD, FASN, have argued, "Health care institutions must evolve their compensation systems to recognize and incentivize physician performance that keep people healthy and improve health for the patients in their care" (4). To help nephrology rise in the compensation rankings for internal medicine subspecialties, ASN must continue to advocate for this triad of value-based care, more accurate wRVUs, and subspecialization, in addition to a better understanding of all of the various sources of income that nephrologists generate beyond clinical revenue.

Myth: Less than 75% of nephrology fellowships are full when the academic year begins on July 1.

From appointment year (AY) 2009 to AY 2025, the percentage of nephrology fellowship positions filled in the Match decreased from 94.8% to 73.0% (5). The nadir was in AY 2016 when 59.2% of fellowship positions filled through the Match, and only 298 internal medicine residents applied for nephrology fellowships, down from 578 in AY 2009.

In AY 2013, the ratio of candidates to nephrology positions dropped below 1.00 (to 0.95) for the first time, reaching 0.59 in AY 2018, and rebounding to 0.80 in AY 2025 (5). Because this ratio is below 1.00, and more than 100 positions are not filled through the Match, graduating residents and others interested in nephrology fellowships (such as hospitalists leaving practice to pursue fellowship training) can readily find a fellowship position outside of the Match. Additionally, an increasing number of fellowship positions are filled outside of the Match by international medical graduates who do not complete residency training in the United States in a program accredited by the Accreditation Council for Graduate Medical Education (ACGME).

As a result, when nephrology fellowships start on July 1, they are nearly 100% filled. Since rejoining the Match in 2009, nephrology fellowship programs have kept pace with the growth in Americans who are at high and very high risk for kidney diseases (both are up 8%, with the number of fellowship programs expanding from 141 in 2009 to 152 in 2023) (5, 6). At the same time, the number of nephrology fellows has been virtually unchanged, increasing from 869 in July 2009 to 887 in July 2023 (the most recently available data). Approximately 490 first-year fellows are anticipated to start on July 1, 2025.

Nephrology is one of the few internal medicine specialties (along with endocrinology, geriatrics, and infectious diseases) that mandates an "all-in" policy for participating in the Match. Not surprisingly, specialties with more candidates than positions (such as cardiology, critical care medicine, and gastroenterology) do not mandate an all-in policy. This difference means that the more "popular" specialties are not bound by the Match's all-in rules and recruit candidates earlier (than nephrology). In addition to doing a better job celebrating the fact that nearly 100% of nephrology fellowship positions are filled, ASN must continue to advocate for a balanced playing field in which every internal medicine subspecialty adopts the all-in policy for the Match.

Myth: Nearly 20% of nephrologists fail to pass the American Board of Internal Medicine's (ABIM's) initial certification examination.

For the past 5 years, the pass rate for first-time takers of the nephrology initial certification examination has been 80% to 82% (7). During this 5-year period, only endocrinology, diabetes, and metabolism had a lower pass rate—falling to 74% in 2021 and 2022—while the lows for other specialties ranged from 95% for gastroenterology, 92% for infectious diseases, 90% for hematology and oncology, and 87% for rheumatology to 85% for cardiovascular disease and critical care medicine.

According to ABIM, the "ultimate pass rates" for initial certification examinations is 98% overall and 97% for nephrology. Importantly, nearly every nephrologist who does not pass the exam the first time passes the second time that they take it.

In addition to highlighting the fact that the ultimate pass rate for initial certification in nephrology is 97%—similar to all other internal medicine subspecialties—ASN must continue to advocate for ABIM to publicize the pass rates (for first-time takers) for all fellowship training programs, including nephrology. Currently, ABIM publicizes the pass rates for every internal medicine residency program but not fellowship programs because the smaller number of fellowship programs and fellows makes such dissemination difficult. This information is critical for applicants to nephrology fellowship training programs and others involved in educating the next generation of nephrologists.

Myth: Addressing disparities and inequities in kidney care is the same as promoting diversity, equity, and inclusion (DEI) in the workforce.

Between the Supreme Court's decision ending affirmative action (in Students for Fair Admissions, Inc. v President and Fellows of Harvard College) in June 2023 and President Donald J. Trump's Executive Order on "Ending Radical and Wasteful Government DEI Programs and Preferencing" in January 2025, the federal government is terminating programs that promote a diverse, equitable, and inclusive workforce, calling them "shameful," "immoral," and an "immense public waste" (8).

However, promoting workforce DEI efforts and addressing disparities and inequities are not the same. As National Institutes of Health (NIH) Director Jayanta (Jay) Bhattacharya, MD, PhD, asserted in April 2025, "the health and wellbeing of minority populations...as well as every American, are a central focus of the NIH and will continue to be..." (9). ASN agrees with Bhattacharya that it is time to address the fact that a disproportionate number of the more than 37 million people living with kidney diseases in the United States:

- have lower socioeconomic status (10, 11);
- live in rural and urban parts of the country (12, 13); and
- are African American or Black, Asian American, Hispanic or Latinx, Indigenous or Native American, and Native Hawaiian or Other Pacific Islander (14).

When compared with White Americans, these minoritized populations are up to four times more likely to develop kidney failure (15). Moreover, Black Americans are less likely to be identified as transplant candidates, referred for evaluation, placed on the kidney transplant waitlist, receive kidney transplants—especially pre-emptive transplants—or receive transplants from living kidney donors (16–22). They are also more likely to have organ offers declined for them (without their knowledge), receive lower-quality kidneys, and have poorer transplant graft survival.

Inequities in health care also affect the nation's economy with racial and ethnic health disparities costing the US economy $451 billion in 2018, a 41% increase from the previous estimate of $320 billion in 2014 (23). Additionally, the total burden of education-related

health disparities for persons with less than a college degree in 2018 reached $978 billion, about two times greater than the annual growth rate of the US economy in 2018.

To influence social determinants of health, particularly in populations at risk for and overburdened with kidney diseases, ASN launched a Health Care Justice Committee in January 2021 (24). Through this committee, ASN must continue to focus on addressing disparities and inequities in kidney care—including transplantation—across the United States while clarifying that workforce DEI is a separate issue.

Myth: The Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act has succeeded.

ASN and the rest of the kidney community—particularly the American Society of Transplantation, as well as the American Association of Kidney Patients, the American Society of Transplant Surgeons, and the National Kidney Foundation, among others—and numerous congressional champions deserve credit for successfully advocating that the Medicare program should continue to cover the cost of immunosuppressive drugs for transplant recipients. Before the law went into effect on January 1, 2023, Medicare would have stopped covering this cost after 36 months for Americans with successful kidney transplants.

According to the US Government Accountability Office (GAO), only "104 patients [were] enrolled in this benefit as of February 2024," despite more than 27,000 kidney transplants occurring in 2023, while an additional 146 patients "enrolled and then disenrolled in the benefit from January 2023 through February 2024 for various reasons, such as nonpayment of premiums" (25).

Currently, the benefit is "a safety net or last-resort coverage for patients because it only covers immunosuppressive drugs...as mandated" by the law. GAO found that this limited scope means that "some patients, such as those with chronic conditions, may not choose to enroll because the benefit does not cover services unrelated to immunosuppressive drugs, such as physician visits or laboratory tests." Some transplant recipients can initially pay for the benefit, but they are often overwhelmed by additional expenses like "premiums and coinsurance," concluded GAO (25).

While these limitations to the benefit were known at the time of passage, the low enrollment to date indicates that ASN, the American Society of Transplantation, and the rest of the community need to reassess the benefit provided by the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act as well as consider other policy strategies to better support kidney transplant candidates and recipients. At the same time, ASN must continue to make progress on transforming transplant.

For example, in addition to ensuring that ACGME begins to accredit transplant nephrology fellowship training programs, ASN must address out-of-sequence placement by improving the allocation system, maximize the success of the Increasing Organ Transplant Access Model from the Centers for Medicare & Medicaid Services, and facilitate kidney health data-sharing across agencies within the Department of Health and Human Services.

A quote often attributed to Aurelius but actually from an unknown Stoic provides a good conclusion: "Everything we hear is an opinion, not a fact. Everything we see is a perspective, not the truth" (26). In the intervening millennia, opinions and perspectives have continued to overwhelm facts and truth. Debunking these myths is intended to provide a more accurate assessment of nephrology and nephrologists at the one-quarter mark of the 21st century (Table). ■

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References

1. Aker E. Meditations by Marcus Aurelius. December 15, 2017. Accessed May 9, 2025. https://erselaker.com/blog/meditations-marcus-aurelius.html
2. Agarwal A, Ibrahim T. Stepping into the void: Remunerating, valuing, and understanding nephrologists. *Clin J Am Soc Nephrol* 2020; 15:1832–1834. doi: 10.2215/CJN.04660420
3. Gottlieb JD, et al. Who values human capitalists' human capital? The earnings and labor supply of U.S. physicians. University of Chicago, Becker Friedman Institute for Economics; July 14, 2023. Working paper no. 2023-95. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4510223
4. Rosner MH, Falk RJ. Understanding work: Moving beyond the RVU. *Clin J Am Soc Nephrol* 2020; 15:1053–1055. doi: 10.2215/CJN.12661019
5. Pivert KA.; American Society of Nephrology. ASN Data. First look: AY2025 Match. December 4, 2024. https://data.asn-online.org/posts/ay_2025_match/
6. *2024 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. US Renal Data System, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2024. https://usrds-adr.niddk.nih.gov/2024
7. American Board of Internal Medicine. Initial certification pass rates. 2020–2024. Accessed May 9, 2025. https://www.abim.org/Media/yeqiumdc/certification-pass-rates.pdf
8. The White House. Ending Radical and Wasteful Government DEI Programs and Preferencing. January 20, 2025. Accessed May 9, 2025. https://www.whitehouse.gov/presidential-actions/2025/01/ending-radical-and-wasteful-government-dei-programs-and-preferencing/
9. Wosen J. NIH director calls Trump's anti-DEI orders "misunderstood," downplays reorganization plans. But Bhattacharya says DEI-centric research is less impactful than broadly studying chronic disease. April 21, 2025. https://www.statnews.com/2025/04/21/nih-director-jay-bhattacharya-says-trump-dei-orders-misunderstood/
10. Nicholas SB, et al. Socioeconomic disparities in chronic kidney disease. *Adv Chronic Kidney Dis* 2015; 22:6–15. doi: 10.1053/j.ackd.2014.07.002
11. Han Y, et al. Mapping the overlap of poverty level and prevalence of diagnosed chronic kidney disease among Medicare beneficiaries in the United States. *Prev Chronic Dis* 2024; 21:E23. doi: 10.5888/pcd21.230286
12. Koppula S, et al. The delivery of kidney care in rural or sparsely populated settings. *Am J Kidney Dis* (published online April 29, 2025). doi: 10.1053/j.ajkd.2025.03.017
13. Centers for Medicare & Medicaid Services. Medicare monthly enrollment. Data.CMS.Gov. January 2025. Accessed May 9, 2025. https://data.cms.gov/summary-statistics-on-beneficiary-enrollment/medicare-and-medicaid-reports/medicare-monthly-enrollment
14. Gadegbeku CA, et al. Identifying, confronting, and addressing systemic racism in US nephrology. *Kidney News*, June 2021; 13(6):12–13. https://www.kidneynews.org/view/journals/kidney-news/13/6/article-p12_5.xml
15. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Kidney disease statistics for the United States. September 2024. Accessed May 9, 2025. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease

Continued on page 27

Table. How ASN is debunking myths about nephrology and nephrologists

Myth	ASN action
Nephrologists earn among the lowest compensation of all internal medicine specialties.	Advocate for value-based care, more accurate physician wRVUs, and subspecialization, as well as understand better all of the various sources of income that nephrologists generate beyond clinical revenue.
Less than 75% of nephrology fellowships are full when the academic year begins on July 1.	Celebrate the fact that nearly 100% of nephrology fellowship positions are filled, and continue to advocate for a balanced playing field in which every internal medicine subspecialty adopts the all-in policy for the Match.
Nearly 20% of nephrologists fail to pass ABIM's initial certification examination.	Highlight the fact that the ultimate pass rate for initial certification in nephrology is 97%—similar to all other internal medicine subspecialties—and continue to advocate for ABIM to publicize the pass rates (for first-time takers) for all fellowship training programs, including nephrology.
Addressing disparities and inequities in kidney care is the same as promoting DEI in the workforce.	Focus on addressing disparities and inequities in kidney care—including transplantation—across the United States while clarifying that workforce DEI is a separate issue.
The Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act has succeeded.	Revisit the scope and cost of the benefit provided by the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act, ensure that ACGME begins to accredit transplant nephrology fellowship training programs, address out-of-sequence placement by improving the allocation system, maximize the success of the Increasing Organ Transplant Access Model, and facilitate kidney health data-sharing across agencies within the Department of Health and Human Services.

Introducing the Role of the Kidney in Cardiovascular Disease Educational Tools Contest

Sponsored by the AHA Council on KCVD

By Matthew A. Sparks on behalf of the AHA Council on KCVD

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The American Heart Association (AHA) Council on the Kidney in Cardiovascular Disease (KCVD) presents The Role of the Kidney in Cardiovascular Disease Educational Tools Contest—an initiative to promote the development of innovative, high-impact educational resources that bridge the knowledge gap between heart and kidney health.

While the connection between kidney dysfunction and cardiovascular disease is well recognized by nephrologists, it remains underemphasized in medical education, including medical school, residency training, and primary care practice. As novel therapies such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists continue to reshape the clinical landscape, it is critical to develop accessible, far-reaching teaching tools that highlight the role of chronic kidney disease in cardiovascular outcomes.

The contest supports the creation of educational materials aimed at informing clinicians, trainees, and students about the significant impact of chronic kidney disease on cardiovascular disease, with the goal of improving awareness and ultimately, patient care.

- The teaching tool must enhance the learner's understanding of kidney and cardiovascular disease to impact clinical decision-making or awareness. For example, the tool can be a video series, interactive website, or podcast.
- The teaching tool must teach some aspect about the connection between the kidney and cardiovascular disease.
- One member of the submitting team must be an AHA member. Teams can consist of undergraduate, medical, or PhD students; trainees (resident, fellow, and postdoctoral); faculty; practicing physicians; researchers; or other health professionals. Each member of the team can only be involved in one submission. A corresponding member must be denoted.
- One member of the team must be a faculty member (i.e., they have completed all training and have a faculty position in either private practice or an institution).

The teaching tool will be submitted to and judged by the KCVD Scientific & Clinical Education Lifelong Learning (SCILL) Committee based on the following merits:

- Kidney and cardiovascular disease must be featured.
- The tool must be easily accessible.
- The tool must have feasibility for creation (i.e., it can be developed).
- A prototype of the tool should be submitted (does not have to be the final product).

Up to three teaching tools will be selected as winners:

- Each team will receive up to $2000 for further development of the tool.
- AHA's Council on the KCVD will publicize the tool.
- Winners will be announced at Scientific Sessions 2025 in November (https://professional.heart.org/en/meetings/scientific-sessions).
- The tool will be linked on the AHA website with a description.
- Each winner will make a video describing the tool.

All applications are due by August 8, 2025. For more information on the contest, scan the QR code. ■

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Guardian Ion: Intravenous Magnesium as a Nephroprotective Ally in Cisplatin Therapy

By Prakash Gudsoorkar

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Cisplatin remains the chemotherapeutic workhorse for various solid tumors, but its Achilles' heel is nephrotoxicity. Up to one in three patients experiences some degree of cisplatin-associated acute kidney injury (CP-AKI), jeopardizing future cancer therapy options and long-term kidney health (1). Against this backdrop, Gupta and colleagues deliver the largest known human study to date assessing whether a simple, inexpensive maneuver—prophylactic intravenous (iv) magnesium—can blunt CP-AKI risk (2). Their multicenter cohort analysis of 13,719 adults treated between 2006 and 2022 across five US cancer centers provides compelling real-world evidence that magnesium matters.

Study findings

Among the participants, 28.4% received iv magnesium (median, 2 g) on day 1 of cisplatin. Yet the primary composite of CP-AKI (twofold or more rise in serum creatinine or need for kidney replacement therapy) or death within 14 days occurred in 2.7% of magnesium recipients versus 5.3% of nonrecipients. After rigorous inverse-probability-of-treatment weighting that adjusted for more than 20 covariates—including cisplatin dose, comorbidities, baseline estimated glomerular filtration rate (eGFR), serum magnesium, and albumin—the adjusted odds ratio (aOR) was 0.80 (95% confidence interval [CI], 0.66–0.97). A complementary multivariable regression yielded an even stronger association (aOR, 0.71 [95% CI, 0.56–0.89]).

Benefit persisted across sensitivity analyses: widening the exposure window to include magnesium given up to 3 days before cisplatin (aOR, 0.79 [95% CI, 0.63–0.98]) or restricting analysis to doses ≥2 g (aOR, 0.71 [95% CI, 0.56–0.90]). Importantly, the protective signal extended to major adverse kidney events at 90 days (MAKE90), in which severe dysfunction or death was reduced by approximately 36% (aOR, 0.64 [95% CI, 0.43–0.95]).

Who benefits most?

The subgroup analysis showed clear effect modification: patients younger than 65 years had a 38% risk reduction (aOR, 0.62 [95% CI, 0.45–0.84]) versus no benefit in older adults (interaction p = 0.04); women derived protection (aOR, 0.64 [95% CI, 0.50–0.82]), but men did not (interaction p < 0.01); and those with a baseline eGFR of ≥90 mL/min/1.73 m^2 or serum magnesium of 2.0–2.2 mg/dL saw greater nephroprotection. An E-value of 1.48 indicates an unmeasured confounder would need to increase both iv magnesium use and CP-AKI odds by at least 48% to nullify these associations, underscoring their robustness.

Biological plausibility

Magnesium's renoprotection is biologically credible. Preclinical data show that magnesium upregulates proximal-tubular efflux transporters (multidrug resistance proteins 4 and 6), accelerates urinary platinum excretion, and dampens inflammatory cytokines (3). Clinical hypomagnesemia, common during cisplatin therapy, may therefore prime the kidney for injury (4). Gupta et al. (2) demonstrate that benefit accrues even when baseline magnesium values lie within the "normal" range (1.4–2.2 mg/dL), aligning with pilot randomized data from head-and-neck cancer, suggesting that prophylaxis works independently of frank deficiency.

Strengths and caveats

Key strengths include the robust sample size, geographic diversity, and comprehensive covariate adjustment, including competing nephrotoxins and exact cisplatin dosing. Heterogeneity in magnesium prescribing (5.5%–85.0% across centers) created a natural experiment, bolstering causal inference. However, data on fluid-hydration regimens, diuretic use, tumor stage, and the total number of cisplatin cycles were unavailable, representing potential unmeasured confounders. The signal of benefit disappeared in older and male patients, although subgroup analyses are exploratory and potentially underpowered. Finally, the observational design limits causal claims despite advanced weighting methods.

Clinical implications for nephrology and oncology

These data invite a low-cost protocol change for nephrologists embedded in chemotherapy-infusion units. A 2-g iv magnesium dose adds negligible infusion time and carries minimal risk. The roughly 50% relative reduction in MAKE90 could translate into thousands of avoided dialysis days, preserving chemotherapy eligibility nationwide. Still, the sex- and age-related heterogeneity urges personalized application and reinforces that magnesium is not a panacea; comprehensive hydration, dose optimization, and close biochemical monitoring remain pillars of CP-AKI prevention.

Research agenda

The logical next step is a pragmatic, adequately powered randomized clinical trial. Stratification by age, sex, and baseline kidney function should test whether the subgroup signals hold. Trialists must also capture cumulative cisplatin exposure, oral magnesium supplements, and postinfusion hydration volumes. Biomarker substudies assessing urinary kidney injury molecule-1 or neutrophil gelatinase-associated lipocalin could clarify mechanistic pathways and allow early efficacy readouts (5).

Moreover, magnesium's role beyond cisplatin warrants exploration. Could it mitigate nephrotoxicity from other platinum analogs or immune checkpoint inhibitors? Does chronic repletion improve long-term GFR trajectories in cancer survivors?

Conclusion

Gupta et al. (2) provide persuasive evidence that prophylactic iv magnesium halves the short-term burden of cisplatin nephrotoxicity without compromising oncologic care. While randomized confirmation is essential, the low risk, low cost, and strong biologic rationale argue for immediate consideration of magnesium supplementation in cisplatin hydration protocols, particularly for younger female patients with preserved renal reserve. In the ongoing fight to protect kidneys without blunting cancer efficacy, magnesium may be the small molecule that delivers outsized renal dividends. ■

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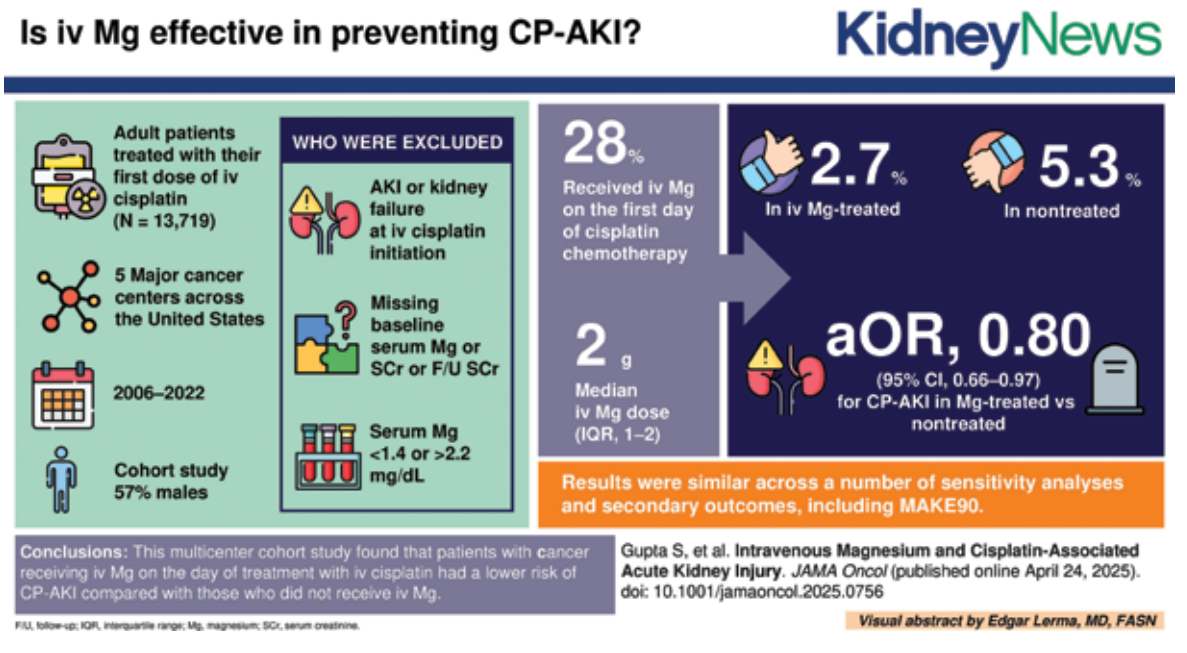
The author reports no conflicts of interest.

References

1. Manohar S, Leung N. Cisplatin nephrotoxicity: A review of the literature. *J Nephrol* 2018; 31:15–25. doi: 10.1007/s40620-017-0392-z
2. Gupta S, et al. Intravenous magnesium and cisplatin-associated acute kidney injury. *JAMA Oncol* (published online April 24, 2025). doi: 10.1001/jamaoncol.2025.0756
3. Saito Y, et al. Magnesium attenuates cisplatin-induced nephrotoxicity by regulating the expression of renal transporters. *Eur J Pharmacol* 2017; 811:191–198. doi: 10.1016/j.ejphar.2017.05.034
4. Lam M, Adelstein DJ. Hypomagnesemia and renal magnesium wasting in patients treated with cisplatin. *Am J Kidney Dis* 1986; 8:164–169. doi: 10.1016/s0272-6386(86)80020-8
5. Jana S, et al. Early diagnostic biomarkers for acute kidney injury using cisplatin-induced nephrotoxicity in rat model. *Curr Res Toxicol* 2023; 5:100135. doi: 10.1016/j.crtox.2023.100135



Metabolic Dysfunction-Associated Steatohepatitis: An Important Juncture in Liver-Kidney Crosstalk

By Sourabh Sharma, Chilaka Rajesh, and Manisha Dassi

https://doi.org/10.62716/kn.000632025

Metabolic-associated fatty liver disease (MAFLD) is an emerging epidemic, affecting one-fourth of the global population (1). Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive subtype of MAFLD, which is known to have various systemic implications. However, the implications of MAFLD on the kidney are largely underexplored because efforts typically focus on slowing the progression of chronic liver disease, and kidneys are seldom screened in people with kidney diseases by the treating hepatologists. As chronic kidney disease (CKD) becomes increasingly recognized as a major complication among individuals with metabolic disorders, it is crucial to comprehend the exact kidney histopathology in patients with MASH. The recent study by Pasternak et al. (2) comprehensively reports the kidney manifestations of MASH by detailing the kidney biopsy findings. The authors have reported immunoglobulin A nephropathy (IgAN) to be the second-most common glomerular disease in MASH, second to diabetic nephropathy. This study provides new perspectives on the liver-kidney crosstalk in MASH, prompting important questions regarding overlapping mechanisms as well as the necessity for integrated clinical care.

Out of 199 kidney biopsies from patients with MASH examined (2), nearly one-fourth (22.1%) had IgAN—a significantly higher prevalence compared with control groups. People with MASH and IgAN were older and had a significantly higher burden of comorbidities, which included diabetes, obesity, dyslipidemia, and cirrhosis. There was resemblance in histopathologic characteristics between MASH-related IgAN and primary IgAN. The higher occurrence of metabolic comorbidities in the MASH and IgAN cohort indicated that systemic metabolic dysfunction could intensify kidney damage, potentially accelerating the disease progression. This underscores the importance of increased clinical vigilance in people with MASH, especially those showing signs of proteinuria or worsening kidney function.

The precise pathophysiologic mechanisms connecting MASH to IgAN remain uncertain but are likely to be influenced by multiple factors. The key features of MASH—chronic inflammation, hepatic insulin resistance, oxidative stress, and immune dysregulation—could lead to kidney damage through endothelial dysfunction and increased immune activation. Also, in advanced stages, heightened hepatic insulin resistance and atherogenic dyslipidemia promote release of multiple proinflammatory cytokines and hepatokines, which exacerbate CKD progression in MASH. Furthermore, the significant prevalence of cirrhosis among people with MASH and IgAN indicates a potential involvement of altered liver metabolism and compromised clearance of IgA complexes, a phenomenon already noted in cases of IgAN associated with liver disease (2–7).

The results of the study by Pasternak et al. (2) have important clinical implications. Firstly, nephrologists should maintain a heightened awareness of the possibility of IgAN in people with MASH, especially those with metabolic conditions. Secondly, a collaborative strategy that includes treating clinicians, hepatologists, nephrologists, and pathologists is crucial for improving outcomes in this group. Implementing early kidney screening in MASH, along with proactive management of metabolic risk factors, could help reduce the advancement of kidney diseases. Lastly, additional research is necessary to clarify the specific molecular connections between MASH and IgAN, and to investigate potential treatments that target metabolic pathways to slow the progression of CKD, which may include sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists (8–10). The Figure depicts a diagnostic algorithm for IgAN in individuals with MASH.

It is time to consider MASH a multisystem disorder that has significant kidney implications. We need to screen patients with MASH early for kidney involvement to intervene and halt progression of CKD. ■

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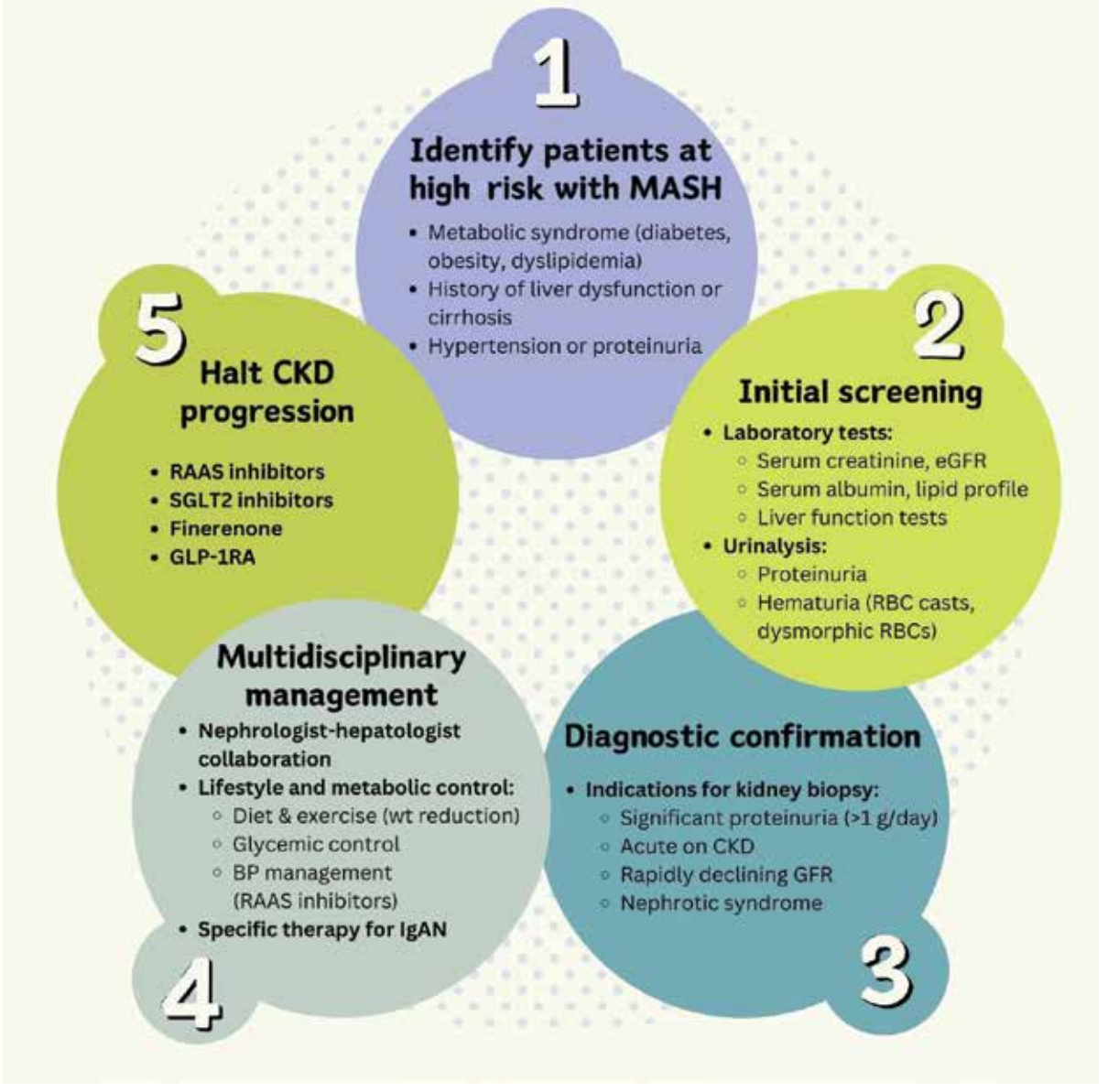
The authors report no conflicts of interest.

Figure. Diagnostic algorithm for IgAN in patients with MASH



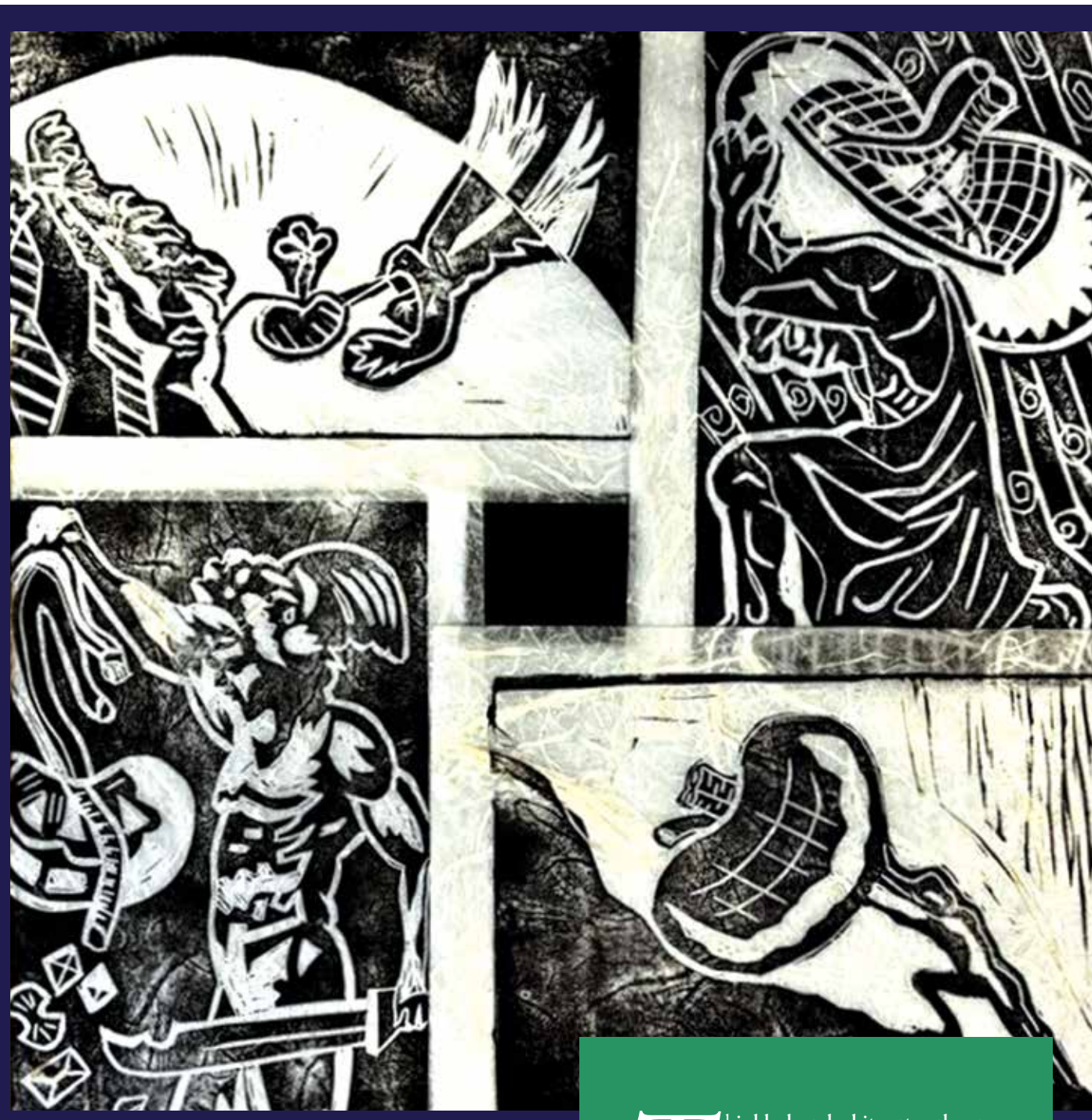
BP, blood pressure; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; RAAS, renin-angiotensin-aldosterone system; RBC, red blood cell; SGLT2, sodium-glucose cotransporter-2.

References

1. Umbro I, et al. Nonalcoholic fatty liver disease and the kidney: A review. *Biomedicines* 2021; 9:1370. doi: 10.3390/biomedicines9101370
2. Pasternak E, et al. Kidney biopsy findings in people with MASH. *Kidney Int Rep* 2025; 10:1575–1578. doi: 10.1016/j.ekir.2025.02.008
3. Mantovani A, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: An updated meta-analysis. *Gut* 2022; 71:156–162. doi: 10.1136/gutjnl-2020-323082
4. Targher G, Byrne CD. Non-alcoholic fatty liver disease: An emerging driving force in chronic kidney disease. *Nat Rev Nephrol* 2017; 13:297–310. doi: 10.1038/nrneph.2017.16
5. Samuel VT, Shulman GI. Nonalcoholic fatty liver disease as a nexus of metabolic and hepatic diseases. *Cell Metab* 2018; 27:22–41. doi: 10.1016/j.cmet.2017.08.002
6. Meex RCR, Watt MJ. Hepatokines: Linking nonalcoholic fatty liver disease and insulin resistance. *Nat Rev Endocrinol* 2017; 13:509–520. doi: 10.1038/nrendo.2017.56
7. Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. *J Hepatol* 2020; 72:785–801. doi: 10.1016/j.jhep.2020.01.013
8. Filardi T, et al. Managing cardio-renal-metabolic risk in patients with type 2 diabetes: The role of finerenone. *J Diabetes Complications* 2024; 38:108741. doi: 10.1016/j.jdiacomp.2024.108741
9. Herat LY, et al. Targeting features of the metabolic syndrome through sympatholytic effects of SGLT2 inhibition. *Curr Hypertens Rep* 2022; 24:67–74. doi: 10.1007/s11906-022-01170-z
10. Wilbon SS, Kolonin MG. GLP1 receptor agonists-effects beyond obesity and diabetes. *Cells* 2023; 13:65. doi: 10.3390/cells13010065

Nephrocentric Greek Tragedies

https://doi.org/10.62716/kn.000842025



Artwork by Brian Rifkin, MD. Rifkin is a general and interventional nephrologist in Hattiesburg, MS. In addition to printing, he also creates watercolor, acrylic, and oil paintings. His art pieces often combine his love of medicine, nature, and humor. Rifkin sells his artwork at local craft fairs and art galleries, and he enjoys gifting pieces at medical conferences.

This black and white artwork contains four lino prints of nephrocentric Greek tragedies: Perseus holding Medusa's kidney with stones spilling out (top left); Atlas holding the weight of the kidney world (top right); Prometheus having his kidney torn out for bringing fire (knowledge) to humankind (bottom left); and Sisyphus pushing a kidney uphill as punishment for cheating death (bottom right). ■

Artificial Intelligence in AKI Prediction: Validating the Epic Hospital-Acquired AKI Model

By Wisit Cheungpasitporn, Charat Thongprayoon, and Kianoush Kashani

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Acute kidney injury (AKI) remains a significant challenge in patients who are hospitalized, contributing to increased morbidity, mortality, and health care costs (1). Machine learning-based models offer the potential for early AKI detection and timely intervention. However, rigorous external validation is necessary before clinical integration (2).

A recent study published in *The New England Journal of Medicine Artificial Intelligence* (3), "External Validation of a Commercial Acute Kidney Injury Predictive Model," evaluated the Epic Risk of HA [Hospital-Acquired]-AKI model in a large health care system. This gradient-boosted ensemble model incorporates demographic, comorbidity, and clinical data to predict HA-AKI.

The study analyzed 39,891 patient encounters over 5 months, demonstrating moderate discrimination with an area under the receiver operating characteristic curve (AUROC) of 0.77 (95% confidence interval [CI], 0.76–0.78) at the encounter level and 0.76 (95% CI, 0.76–0.76) for a 48-hour prediction (Figure, A). The median lead time before HA-AKI onset was 21.6 hours, suggesting a window for early intervention. However, the model exhibited overprediction in high-risk subgroups and poor calibration, particularly for the higher AKI stages, that could impact clinical reliability.

Performance and limitations

The model achieved an area under the precision recall curve (AUPRC) of 0.49 at the encounter level and 0.19 at 48 hours, indicating moderate discrimination but suboptimal precision. Performance varied across subgroups, particularly in patients with higher baseline serum creatinine (Figure, B) or comorbidities such as congestive heart failure, diabetes, and hypertension. The model performed best at lower creatinine levels (AUROC, 0.79 for <0.50 mg/dL) but showed poor discrimination in the 3.50- to 3.99-mg/dL range (AUROC, 0.50), highlighting limitations in patients with high risk.

The model demonstrated better negative predictive value than positive predictive value, suggesting utility in ruling out HA-AKI. However, a high false-positive rate at lower thresholds may lead to unnecessary interventions, raising concerns about alert fatigue. Compared with other HA-AKI predictive models, the Epic Risk model outperformed logistic regression models but underperformed relative to advanced machine-learning models such as neural networks. External validation performance (AUROC, 0.77) was lower than internal validation performance (AUROC, 0.85), highlighting concerns regarding generalizability.

Clinical implications and future directions

Despite moderate predictive ability, previous studies on HA-AKI clinical decision support alerts have shown mixed results (4–7). Some reports indicate that HA-AKI alerts do not reduce dialysis initiation, mortality, or AKI progression. However, nephrotoxin-avoidance alerts and pharmacist involvement have shown potential benefits (8–10). The median lead time of 21.6 hours suggests that structured intervention pathways, rather than standalone alerts, may improve the clinical impact.

Further multicenter validation is needed to determine the model's performance across diverse health care settings, to assess the model's performance on prospective datasets, and to evaluate its performance in clinical settings to investigate its impact on the processes of care and clinical outcomes (2). Future studies should evaluate whether clinician response to model predictions improves outcomes, such as optimizing fluid management and avoiding nephrotoxins (2). More interpretable AI models are required to enhance transparency and trust in predictive tools.

The Epic Risk of HA-AKI model offers moderate predictive ability but is not yet ready for widespread clinical use without further validation. It may be most effective when integrated with structured interventions rather than used as an isolated risk score. This study underscores both the promise and the limitations of commercial AI-based HA-AKI prediction tools. ■

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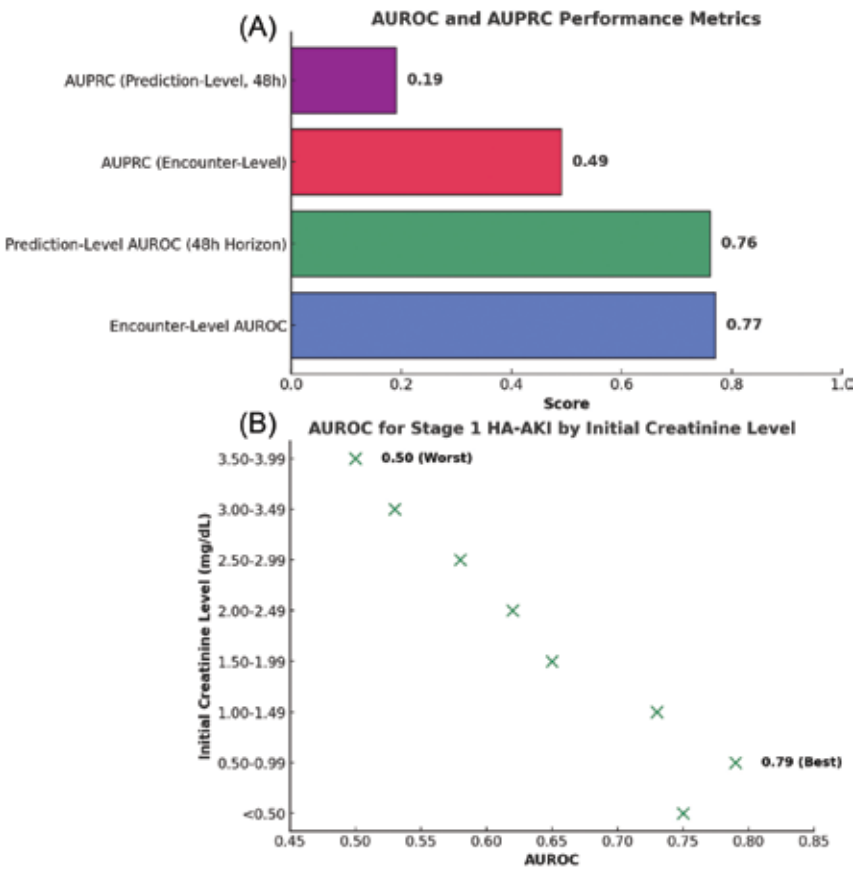
The authors report no conflicts of interest.

Figure. Performance metrics of the Epic Risk of HA-AKI predictive model



(A) The model demonstrated moderate discrimination (AUROC: 0.77 encounter level; 0.76 for 48-hour prediction), but lower AUPRC values (0.49 and 0.19, respectively) indicate challenges in handling imbalanced data. (B) The model performed best at lower creatinine levels (AUROC = 0.79 for <0.50 mg/dL) but showed poor discrimination at higher levels, particularly in the 3.50- to 3.99-mg/dL range (AUROC = 0.50), highlighting limitations in patients who are high risk.

References

1. Alfieri F, et al. Continuous and early prediction of future moderate and severe acute kidney injury in critically ill patients: Development and multi-centric, multi-national external validation of a machine-learning model. *PLoS One* 2023; 18:e0287398. doi: 10.1371/journal.pone.0287398
2. Cheungpasitporn W, et al. Advances in critical care nephrology through artificial intelligence. *Curr Opin Crit Care* 2024; 30:533–541. doi: 10.1097/MCC.0000000000001202
3. Dutta S, et al. External validation of a commercial acute kidney injury predictive model. *NEJM AI* 2024; 1:AIoa2300099. https://ai.nejm.org/doi/full/10.1056/AIoa2300099
4. Hodgson LE, et al. The ICE-AKI study: Impact analysis of a clinical prediction rule and electronic AKI alert in general medical patients. *PLoS One* 2018; 13:e0200584. doi: 10.1371/journal.pone.0200584
5. Wilson FP, et al. Electronic health record alerts for acute kidney injury: Multicenter, randomized clinical trial. *BMJ* 2021; 372:m4786. doi: 10.1136/bmj.m4786
6. Park S, et al. Impact of electronic acute kidney injury (AKI) alerts with automated nephrologist consultation on detection and severity of AKI: A quality improvement study. *Am J Kidney Dis* 2018; 71:9–19. doi: 10.1053/j.ajkd.2017.06.008
7. Zhao Y, et al. Effect of clinical decision support systems on clinical outcome for acute kidney injury: A systematic review and meta-analysis. *BMC Nephrol* 2021; 22:271. doi: 10.1186/s12882-021-02459-y
8. Scott J, et al. Acute kidney injury electronic alerts: Mixed methods normalisation process theory evaluation of their implementation into secondary care in England. *BMJ Open* 2019; 9:e032925. doi: 10.1136/bmjopen-2019-032925
9. Bailey S, et al. Implementation of clinical decision support to manage acute kidney injury in secondary care: An ethnographic study. *BMJ Qual Saf* 2020; 29:382–389. doi: 10.1136/bmjqs-2019-009932
10. Kim K, et al. Real-time clinical decision support based on recurrent neural networks for in-hospital acute kidney injury: External validation and model interpretation. *J Med Internet Res* 2021; 23:e24120. doi: 10.2196/24120

Revolutionizing Patient Education: Using ChatGPT to Improve Knowledge of Treatments for Glomerular Diseases

By Suman Behera and Srikanth Bathini

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Medical professionals strive to offer excellent patient care, but patient comprehension of diseases is often overlooked. Glomerular diseases are complex conditions with a wide range of etiologies, mechanisms, and treatment alternatives. They necessitate complex treatment plans that frequently include immunosuppressive drugs and lifestyle changes. Given the complexities involved, patients with glomerular diseases might find it difficult to comprehend the reasoning behind these therapies, which could result in nonadherence, reduced efficacy, and increased morbidity. Artificial intelligence tools such as ChatGPT can bridge the knowledge gap and enable patients to actively participate in their care (1).

ChatGPT is an advanced language model that offers an opportunity to enhance patient education. Its capabilities can be used by medical practitioners to create personalized, interactive, and simple explanations of treatment choices. Patients who are overwhelmed by the complexity of their ailment or who have low health literacy may find this especially helpful.

The average American reads at a seventh- to eighth-grade level, according to the Literacy Project (1, 2). This may make it difficult to effectively communicate medical information to a wide range of reading levels.

Using a standard questionnaire, Abdelgadir et al. asked GPT-3.5 and GPT-4 about 67 glomerular conditions. The authors then provided updated responses appropriate for those with only an eighth-grade education or less. The answers were independently assessed by nephrologists who scored the answers from 1 to 5 (in which 1 was the lowest, and 5 was the highest). The responses to each question, as graded by the researchers, were averaged to a score (1).

Explanations generated by GPT-4 had good accuracy while being comprehensive (Table). However, when tailored to an eighth-grade education or lower, the explanations showed a reduced accuracy score. The authors stated, "While simplified text improves readability and comprehension, there is often a loss in specificity and accuracy" (1). Additionally, responses from GPT-4 showed higher accuracy than GPT-3.5.

ChatGPT offers several advantages for patient education, like personalization, accessibility, and patient engagement.

- **Personalization:** ChatGPT can adjust explanations to individual patients' learning styles, medical history, and treatment goals.
- **Accessibility:** By allowing patients to access educational materials enabled by ChatGPT at their convenience, health care professionals may alleviate some of their stress related to time constraints.
- **Patient engagement:** Interactive explanations have the potential to empower and engage patients by promoting a better understanding of the various treatment options.

To maximize the potential of ChatGPT in patient education, health care professionals should collaborate with technology experts to ensure that the content is accurate and patient-centered. They should also continually assess the impact of ChatGPT on patient comprehension, compliance, and outcomes.

Adopting innovative technologies like ChatGPT can transform patient education. These tools may ultimately improve the standard of medical care and outcomes for those with glomerular diseases, due to an improved understanding of the disease and management. However, further enhancements are required for improving the material generated by artificial intelligence tools for their accuracy and understandability. The process of creating educational materials that effectively meet the needs of every patient can be guided by the use of readability formulas like the Simple Measure of Gobbledygook index, the Flesch-Kincaid Grade, and the Flesch Reading Ease score (1).

To enable patients to actively participate in their care and promote a more collaborative and patient-focused approach to health care, it is our responsibility as health care practitioners to fully understand and use these modern technologies. ■

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The authors report no conflicts of interest.

References

1. Abdelgadir YH, et al. Enhancing patient comprehension of glomerular disease treatments using ChatGPT. *Healthcare (Basel)* 2024; 13:57. doi: 10.3390/healthcare13010057
2. Mamedova S, Pawlowski E. Adult literacy in the United States. *Data Point*. National Center for Education Statistics, U.S. Department of Education; July 2019:NCES 2019-179. https://nces.ed.gov/pubs2019/2019179.pdf

Table. Accuracy and readability assessment of GPT-4's responses to glomerular disease terms

	General Explanation (95% CI of Mean)	Tailored Explanation (95% CI of Mean) [a]	*p* Value [b]	Difference (95% CI) [c]
Accuracy [d]	4.56 ± 0.66 (4.41–4.73)	3.99 ± 0.39 (3.90–4.09)	<0.0001	0.57 (0.46–0.69)
Readability				
Grade level [e]	12.85 ± 0.93 (12.62–13.07)	8.44 ± 0.72 (8.26–8.62)	<0.0001	4.41 (4.18–4.64)
FRE score [f]	25.73 ± 6.98 (24.03–27.43)	60.75 ± 4.56 (59.63–61.86)	<0.0001	35.01 (33.29–36.74)

[a] Tailored for patients at or below 8th grade level. [b] A paired two-sided *t* test. [c] Mean of differences and 95% confidence intervals (CIs). [d] Accuracy is scaled from 1 to 5: 1 = completely incorrect, 2 = mostly incorrect, 3 = partly correct and partly incorrect, 4 = correct but not comprehensive, and 5 = correct and comprehensive. [e] Grade level is the average of the Flesch–Kincaid Grade (FKG) Level and Simple Measure of Gobbledygook (SMOG) Index. [f] Flesch Reading Ease (FRE) scores range from 0 to 100, with higher scores indicating easier-to-read text.

Image of a table from Abdelgadir YH et al. (1) reprinted with permission.

KRYSTEXXA **can change the course** of uncontrolled gout[1]

In the MIRROR trial, KRYSTEXXA with methotrexate:

DEMONSTRATED EFFICACY

71% (n=71/100) vs 39% (n=20/52) patient response* compared to KRYSTEXXA alone during Month 6 (*P*<0.0001)[1]

ESTABLISHED SAFETY PROFILE

4% (n=4/96) of patients experienced infusion reactions vs 31% (n=15/49) of patients treated with KRYSTEXXA alone

6-12 months of KRYSTEXXA may reverse years of urate deposition[1]

Best results were seen at 6-12 months.[1] Optimal treatment duration has not been established.[1] Individual results may vary.

KRYSTEXXA has not been studied to reverse damage to the kidneys, heart, or any of the body's organs.

*The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

The MIRROR RCT was a 52-week, randomized, double-blind, placebo-controlled trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA (8 mg Q2W) coadministered with 15 mg/week oral methotrexate and 1 mg/day oral folic acid (n=100) vs KRYSTEXXA with placebo (n=52).[1,2]

Q2W, once every 2 weeks; sUA, serum uric acid.

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

KRYSTEXXA can dissolve years of systemic urate deposition[3,4]

ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

Congestive Heart Failure: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Botson JK, et al. *Arthritis Rheumatol.* 2023;75:293-304. **3.** Sundy JS, et al. *JAMA.* 2011;306:711-720. **4.** Dalbeth N, et al. *Joint Bone Spine.* 2024;91:105715.

AMGEN Rare Disease

KRYSTEXXA® pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment.

Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency *[see Contraindications]*. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials.

In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis *[see Warnings and Precautions]*
- Infusion Reactions *[see Warnings and Precautions]*
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia *[see Warnings and Precautions]*
- Gout Flares *[see Warnings and Precautions]*
- Congestive Heart Failure *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 24-week clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	KRYSTEXXA 8 mg every 2 weeks (N=85) n[a] (%)	Placebo (N=43) n (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively *[see Data]*.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, a total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria, nausea or vomiting.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA *[see Warnings and Precautions, Adverse Reactions]*
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known *[see Warnings and Precautions, Contraindications]*.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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The Path to Precision in Acute Kidney Injury

By Michael Strader

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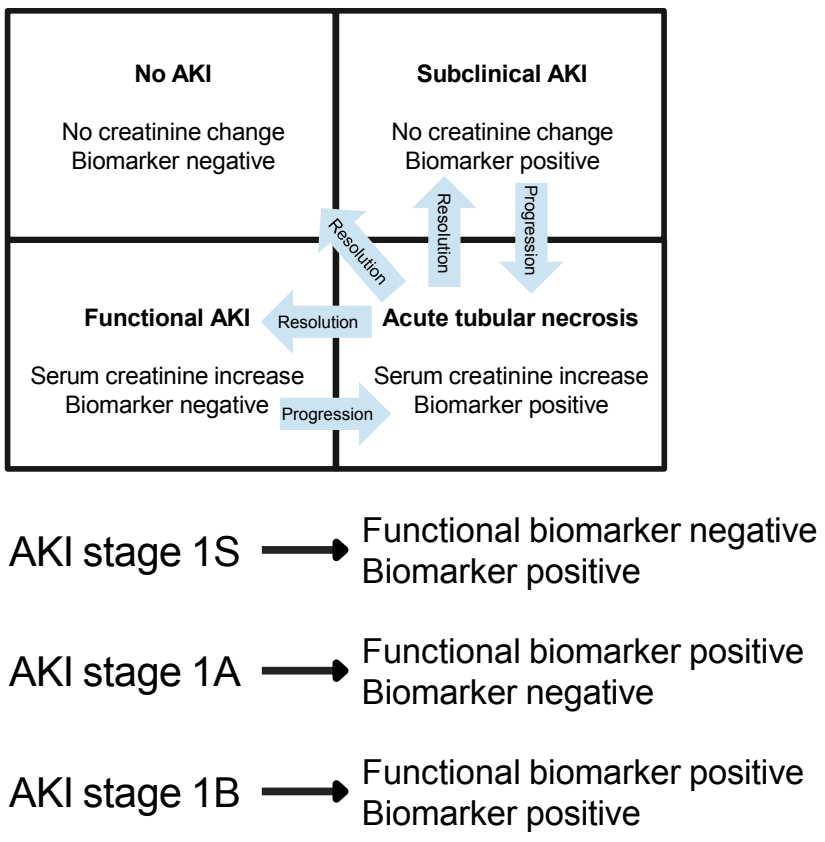
The clinical syndrome of acute kidney injury (AKI) is a common complication within the hospital and intensive care unit (ICU) settings. It is associated with negative economic and health outcomes, such as new or worsening chronic kidney disease, dialysis, or death. Despite the insight into AKI outcomes, current diagnostic tools such as serum creatinine and urine output, which are categorized as functional biomarkers, are limited in the syndrome of AKI (1). In clinical practice, the limitations of functional biomarkers become evident when clinicians must differentiate "prerenal" or functional AKI—characterized by reduced kidney perfusion without tubular injury—from intrinsic injury, such as acute tubular necrosis (ATN), as this distinction impacts management.

To overcome the limitations of functional biomarkers, the 10th Acute Disease Qualitative Initiative (ADQI) meeting proposed the use of novel biomarkers in AKI, and the 23rd ADQI meeting proposed augmenting the Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria with novel damage biomarkers for the diagnosis and staging of AKI (Figure 1) (2, 3). This has set the groundwork for redefining AKI and identifying subphenotypes (e.g., hepatorenal syndrome, sepsis-associated AKI, acute interstitial nephritis, and ATN).

Figure 1. Modified AKI guideline based on functional markers



The modified KDIGO AKI guideline is based on functional biomarkers, which are serum creatinine and urine output, and novel biomarker status (positive/negative). Adapted from Murray et al. (2) with BioRender.com.

As clinical medicine evolves, the goal of precision medicine through phenotyping becomes achievable. In AKI, some novel urinary biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (TIMP-2 × IGFBP-7), and C-C motif chemokine ligand-14 (CCL14), have been developed for clinical use. In some cases, these biomarkers have been implemented into clinical practice due to their superiority in identifying subphenotypes (Figure 2).

uNGAL

A common clinical scenario is trying to differentiate "prerenal" (functional) from "intrarenal," such as ATN AKI. Urinary NGAL (uNGAL) is upregulated in the presence of tubular injury, making it a valuable tool for distinguishing functional AKI—such as hypovolemia, cardiorenal syndrome, and hepatorenal syndrome—from ATN (4–6). It has demonstrated clinical utility in the heterogeneous adult population with AKI, particularly in patients with liver cirrhosis, in whom a negative NGAL test suggests the diagnosis of hepatorenal syndrome—especially if they have not responded to fluid resuscitation—and may guide the use of vasoactive agents (e.g., terlipressin) (5, 7, 8).

Another common clinical scenario is identifying patients at high risk for persistent severe AKI (PS-AKI), with the goal of modifying treatment to prevent progression. This is where uNGAL has shown utility, particularly in the pediatric ICU population. The uNGAL (ProNephro AKI) test was recently approved by the US Food and Drug Administration (FDA) for clinical use. It helps identify pediatric patients at risk of developing PS-AKI (stage 2/3 AKI) within 48–72 hours of ICU admission and thus allows clinicians to adjust management—such as avoiding nephrotoxic agents—to reduce AKI incidence or severity (9, 10).

As uNGAL becomes more integrated into clinical practice, its limitations must be acknowledged. In the presence of a urinary tract infection, uNGAL levels may be elevated, complicating interpretation—particularly when distinguishing between functional and intrinsic AKI in adults or predicting AKI severity in pediatric populations. Therefore, clinical context remains essential, and uNGAL should be interpreted alongside standard tools such as clinical history, examination findings, imaging, and fractional excretion of sodium (6, 9, 10).

TIMP-2 × IGFBP-7

AKI is common in the ICU, and early identification of patients at risk is clinically important. TIMP-2 × IGFBP-7 (NephroCheck), a cellular stress biomarker, has demonstrated utility in the adult ICU population and received FDA approval for early detection of patients at risk of developing moderate-to-severe AKI (stage 2/3) within 12 hours of ICU admission. Its role in guiding clinical management was clearly demonstrated in the Biomarker-Guided Implementation of the AKI Bundle (PrevAKI-mc) study, in which the implementation of the KDIGO care bundle was used in patients above the threshold for high risk and led to reduction in AKI severity (11).

CCL14

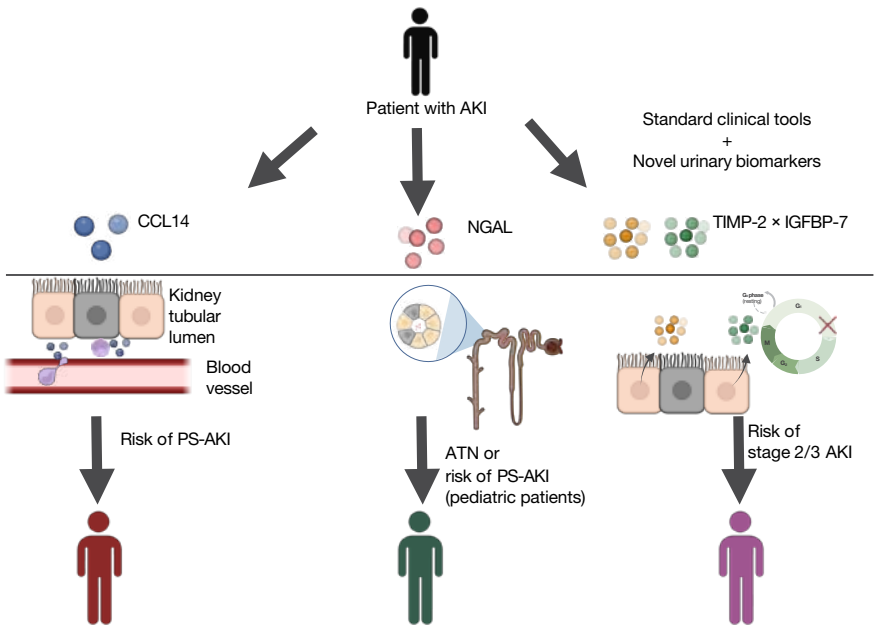
More recently, CCL14, a renal inflammation cytokine involved in the chemotaxis of monocytes and macrophages, shows promise in identifying the cohort of patients at greatest risk of PS-AKI. Knowing which people living with severe AKI are likely to stay at stage 2/3 AKI can aid clinical decision-making regarding the need for frequent monitoring and potentially guide dialysis initation (1, 12).

Conclusion

As novel biomarkers begin their translation into clinical practice, it can be seen how each tool may be implemented to identify subphenotypes and guide clinical practice. Interestingly, all of these tools show their power when used with standard clinical tools, such as clinical examination and functional biomarkers. Therefore, despite these biomarkers showing promise in their respective clinical situations, the basics of clinical history, examination, and standard tools play an integral role in identifying and managing these subphenotypes.

The goal to precision is looking bright, and the potential of a panel of biomarkers for different clinical scenarios may pave the way forward in AKI diagnosis and management.

Figure 2. Subphenotyping people with AKI using standard clinical tools and novel biomarkers



The use of standard clinical tools (clinical history, examination, imaging, the fractional excretion of sodium, the urine protein:creatinine ratio, and the albumin:creatinine ratio) and novel biomarkers can lead to subphenotyping people with AKI. CCL14 leads to the chemotaxis of macrophages (purple cells) from the bloodstream toward necrotic tubular cells (blue kidney tubular lumen cells) in the setting of AKI. NGAL in the setting of AKI is upregulated at the distal convoluted tubule in the setting of ATN. uNGAL is approved by FDA for the identification of PS-AKI in the pediatric population. TIMP-2 × IGFBP-7 is upregulated in settings of cellular stress and leads to cell-cycle arrest. G, gap; M, mitosis; S, synthesis. Created with BioRender.com.

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References

1. Ostermann M, et al. Acute kidney injury. *Lancet* 2025; 405:241–256. doi: 10.1016/S0140-6736(24)02385-7
2. Murray PT, et al.; ADQI 10 workgroup. Potential use of biomarkers in acute kidney injury: Report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int* 2014; 85:513–521. doi: 10.1038/ki.2013.374
3. Ostermann M, et al. Recommendations on acute kidney injury biomarkers from the Acute Disease Quality Initiative consensus conference: A consensus statement. *JAMA Netw Open* 2020; 3:e2019209. doi: 10.1001/jamanetworkopen.2020.19209
4. Duff S, et al. Absence of kidney tubular injury in patients with acute heart failure with acute kidney injury. *Circ Heart Fail* 2024; 17:e011751. doi: 10.1161/CIRCHEARTFAILURE.123.011751
5. Gambino C, et al. Diagnostic and prognostic performance of urinary neutrophil gelatinase-associated lipocalin in patients with cirrhosis and acute kidney injury. *Hepatology* 2023; 77:1630–1638. doi: 10.1002/hep.32799
6. Côté JM, et al. Clinical implementation and initial experience of neutrophil gelatinase-associated lipocalin testing for the diagnostic and prognostic assessment of acute kidney injury events in hospitalized patients. *Nephron* 2022; 146:306–314. doi: 10.1159/000518611
7. Côté JM, et al. Clinical implementation of NGAL testing to improve diagnostic assessment of AKI episodes in a Canadian center. *Can J Kidney Health Dis* 2022; 9:20543581221118991. doi: 10.1177/20543581221118991
8. Puthumana J, et al. Systematic review and meta-analysis of urine neutrophil gelatinase-associated lipocalin for acute kidney injury in cirrhosis. *Kidney Int Rep* 2024; 9:2278–2281. doi: 10.1016/j.ekir.2024.04.050
9. Goldstein SL, et al. Derivation and validation of an optimal neutrophil gelatinase-associated lipocalin cutoff to predict stage 2/3 acute kidney injury (AKI) in critically ill children. *Kidney Int Rep* 2024; 9:2443–2452. doi: 10.1016/j.ekir.2024.05.010
10. Goldstein SL, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. *Kidney Int* 2020; 97:580–588. doi: 10.1016/j.kint.2019.10.015
11. Zarbock A, et al. Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: The PrevAKI-multicenter randomized controlled trial. *Anesth Analg* 2021; 133:292–302. doi: 10.1213/ANE.0000000000005458
12. Hoste E, et al.; RUBY Investigators. Identification and validation of biomarkers of persistent acute kidney injury: The RUBY study. *Intensive Care Med* 2020; 46:943–953. doi: 10.1007/s00134-019-05919-0

ASN Advocates for ESRD PPS and Medicare Advantage Reform

By Lauren Ahearn, Mallika L. Mendu, Suzanne Watnick, and David White

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In the midst of daily, or even hourly, changes proposed by Donald J. Trump's presidential administration that impact health care, ASN advocates for policies that support people living with kidney diseases, their families, and their nephrologists and kidney health professionals. Because the administration has focused initially on the nation's public health infrastructure, much of ASN's efforts—usually in collaboration with other nephrology, scientific, and health care organizations—have supported the National Institutes of Health, the US Food and Drug Administration, and the Centers for Disease Control and Prevention.

At the same time, two of ASN's four committees charged with advocating for policies to support nephrology—the ASN Policy and Advocacy Committee and the ASN Quality Committee—are working on additional reforms that are important in the kidney community. "We are at a pivotal juncture to be able to guide policy and quality programs that profoundly impact our patients with kidney disease," said author Mallika L. Mendu, MD, MBA, FASN, chair of the ASN Quality Committee. "The work our committees are leading related to the Medicare ESRD [End-Stage Renal Disease] Program's Prospective Payment System [PPS] and Medicare Advantage [MA] aims to advance care for our patients, support our nephrology practitioners, and improve care delivery across the nation."

ASN is currently pursuing two main reforms in this arena:

1. reimagining the current Centers for Medicare & Medicaid Services (CMS) ESRD PPS, commonly referred to as the "bundle" and
2. establishing more transparency, consistency, and focus on quality in MA plans for Americans living with kidney diseases, including those receiving dialysis care under the Medicare ESRD Program.

"The ASN policy goal is to advocate and improve care on behalf of people living with kidney diseases throughout the nation," announced author Suzanne Watnick, MD, FASN, chair of the ASN Policy and Advocacy Committee and the inaugural ASN Kidney Health Policy Scholar-in-Residence. "Led by the two committees, these projects are critical to improve value, innovation, and, above all, patient outcomes, as well as to help nephrology practitioners to better care for people living with kidney diseases."

Transforming CMS ESRD PPS for enhanced value and patient-centered care

Through the two committees, ASN has formed an ESRD PPS Reform Workgroup. ASN believes that CMS ESRD PPS, with a foundational framework stemming from legislation in 2008 and initiated in 2011, is ripe for transformation, presenting significant opportunities to better align payment with improved patient outcomes, promote value-based care, incentivize innovation, and enhance patient choice. Besides being woefully underfunded, much of ESRD PPS is arguably frozen in a time dating back to George W. Bush's second term and Barack Obama's first term as presidents of the United States.

The workgroup is currently in early discussions on the need for substantial reform to meet the aforementioned goals while also addressing less-than-optimal outcomes for Americans with kidney failure who require dialysis or transplant to survive. The workgroup is committed to:

- improving patient outcomes and quality of life;
- increasing adoption of value-based care models;
- ensuring greater patient choice and access to preferred treatment modalities, particularly home dialysis;
- speeding integration of innovative and cost-effective technologies;
- reducing health care costs in the long term; and
- providing greater ability to customize care to individuals with kidney failure.

Exploring achievable policy changes, the workgroup is also joining in similar conversations with the broader kidney care community. For this effort to succeed, all stakeholders must come together in this discussion and, ideally, reach agreement on the optimal policy changes. Through the workgroup, the ASN Policy and Advocacy Committee and ASN Quality Committee will ensure that ASN contributes its goals and perspectives to the ongoing conversation throughout the kidney community.

"We are at a pivotal juncture to be able to guide policy and quality programs that profoundly impact our patients with kidney disease."

MA in the kidney health space

Since the implementation of the 21st Century Cures Act in 2021, Medicare beneficiaries with kidney failure have been allowed to enroll in MA plans. As a result, enrollment in MA plans by Americans with kidney failure has skyrocketed, with an estimated 53% of Medicare-eligible beneficiaries (to the Medicare ESRD Program) now enrolled in MA plans (1). This rapid shift of people living with kidney diseases from traditional Medicare fee-for-service to MA plans has brought with it a host of questions about care quality, access, and patient outcomes.

Recognizing these challenges, ASN has launched an in-depth investigation into how well MA plans are serving patients. This effort will also help ASN determine what policy changes might be needed to ensure high-quality, equitable care.

Led by the ASN Quality Committee's MA Workgroup, this project will culminate in a comprehensive manuscript expected to be submitted for publication by the end of the year. In this publication, the workgroup will systematically evaluate the current state of the quality of care delivery across MA plans to people living with kidney diseases, including those undergoing dialysis. The workgroup will also develop a set of targeted policy recommendations to incentivize improved outcomes. The workgroup's manuscript will include three components:

1. analyze the existing literature on the quality of care for Medicare beneficiaries with kidney failure enrolled in MA to assess whether current research provides a clear picture of care outcomes and highlights where further studies are needed;
2. examine and evaluate the MA Star Ratings program as it relates to kidney disease outcomes, which includes determining whether the current MA Stars quality measures (such as Kidney Health Evaluation for Patients with Diabetes) are applicable and effective for people living with kidney diseases, and identify any unintended consequences; and
3. identify kidney disease outcomes that MA plans should incentivize, and propose strategies to achieve these improvements; examine whether current nephrologist reimbursement models in MA support high-quality, value-based care; and identify how payment reforms could help drive better outcomes.

As the number of beneficiaries from the Medicare ESRD Program enrolled in MA plans continues to climb, ensuring that these plans deliver high-quality, patient-centered care has become a pressing priority. Through the ASN MA Workgroup's project, ASN is taking a critical step toward understanding the current landscape and identifying concrete ways to increase accountability, improve outcomes, and close gaps in kidney care.

To keep track of ASN's policy efforts on these two reforms and more, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's Kidney Health Advocacy webpage (https://www.asn-online.org/policy/kidney-health.aspx). For real-time updates from ASN Policy, follow @ASNAdvocacy on X. ■

Lauren Ahearn is the senior quality and regulatory affairs associate, and David White is the senior regulatory and quality officer at ASN. Mallika L. Mendu, MD, MBA, FASN, is the ASN Quality Committee chair. Suzanne Watnick, MD, FASN, is the ASN Policy and Advocacy Committee chair and the ASN Kidney Health Policy Scholar-in-Residence.

Reference

1. The Medicare Payment Advisory Commission (MedPAC). *March 2025 Report to the Congress: Medicare Payment Policy*. March 13, 2025. https://www.medpac.gov/document/march-2025-report-to-the-congress-medicare-payment-policy/

Post-Transplant Thrombotic Microangiopathy: More Insights Into a Challenging Entity

By Bassam G. Abu Jawdeh

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Thrombotic microangiopathy (TMA) is a clinical phenotype that may be precipitated by multiple pathogenic processes. Complement-mediated TMA (C-TMA), also known as atypical hemolytic uremic syndrome, is caused by mutations in or antibodies to complement-regulating proteins. These mutations and acquired antibodies lead to overactivation of the alternative complement pathway—a crucial component of the innate immune system—causing endothelial cell injury and vascular microthrombi formation. Except for renal-limited TMA, which is often difficult to identify, recognizing the TMA phenotype is relatively easy and is based on the triad of organ or kidney injury, thrombocytopenia, and evidence of microangiopathic hemolysis. It is, however, challenging to discern the underlying pathogenic culprit with absolute certainty. This is owed to the fact that the TMA differential is broad, and in C-TMA, an underlying genetic variant is not always identified. Furthermore, a "second hit" is often required to unmask an underlying genetic predisposition and manifest it clinically. Eculizumab and ravulizumab are humanized monoclonal antibodies against complement C5—the most downstream of the complement proteins—that have been approved for the treatment of C-TMA/atypical hemolytic uremic syndrome. Therefore, it is prudent to identify kidney transplant recipients (KTRs) at risk for post-transplant C-TMA since they would benefit from anti-C5 therapy to prevent or treat early recurrence (1).

KTRs are unique when it comes to TMA risk factors. This is because transplantation is associated with several triggers that could act as a second hit for C-TMA or possibly precipitate de novo TMA without an underlying genetic variant. Triggers include ischemia-reperfusion injury (IRI), calcineurin inhibitor (CnI) use, infections associated with immunosuppression, autoimmune disease (often being the cause of native kidney function loss), in addition to donor-specific antibodies with or without antibody-mediated rejection. While genetically based, approximately one-third of patients with C-TMA do not have an identified genetic variant. Moreover, when a variant is identified, the magnitude of its effect in influencing TMA is not always known. The lack of a specific genetic or biochemical diagnostic test for C-TMA muddles the picture further, particularly when trying to determine the need to initiate and, perhaps more importantly, to continue longer-term anti-C5 therapy.

Merzkani et al. recently published a study investigating post-transplant TMA and providing interesting insights into its etiology and clinical outcomes (2). In a retrospective study of 3535 KTRs, the authors identified 68 patients who were diagnosed with TMA. Importantly, 63 of the 68 patients (93%) had comprehensive genetic complement testing, and in cases of variants of unknown significance (VUS), functional testing was pursued to determine their significance. The authors divided their cohort into three groups: group 1, C-TMA (42 patients); group 2, IRI/CnI-TMA (14 patients); and group 3, other TMA (12 patients).

Patients with C-TMA had underlying genetic variants, and this group was enriched with patients who were younger and whose native kidney disease was in the setting of hypertension and/or pre-eclampsia. In keeping with previous literature, the study showed that hypertension is often the second hit unmasking C-TMA, as opposed to being the sole culprit responsible for kidney injury (3). Interestingly, one-third of KTRs in this group developed TMA that was initially labeled as de novo. It was not until post-transplant genetic testing was performed that they were relabeled as recurrent. Furthermore, 78% of those with recurrence experienced early allograft loss. This underscores the importance of suspecting C-TMA in young people with kidney failure associated with hypertension and pre-eclampsia and considering peri-transplant anti-C5 therapy.

The patients with IRI/CnI-TMA were older compared with the first group (aged 55 years versus aged 38 years) and had an increased delayed graft function rate and longer cold ischemia time. This is expected since kidneys with higher delayed graft function risk and longer cold ischemia time are less likely to be allocated to younger patients and more likely to precipitate IRI. The CnI trough was not higher in this group compared with the other groups. Although patients responded to CnI cessation, the reintroduction of CnI later, after the resolution of TMA, was not associated with recurrence. These findings suggest that CnI exacerbates IRI-induced TMA as opposed to causing it by itself.

In group 3, TMA was attributed to various etiologies and occurred much later after transplant (median, 455 days) compared with groups 1 (median, 7 days) and 2 (median, 5 days). The incidence of cytomegalovirus infection was higher in this group compared with the other groups, and 4 of the 12 patients experienced cellular and antibody-mediated rejection, suggesting infection and alloimmunity as potential causes of TMA. None of the KTRs in this group had underlying genetic variants, and 83% had renal-limited TMA, which could be nonspecific. Patients in this group were arguably the most heterogenous and did not respond to CnI cessation or to anti-C5 therapy when attempted.

The strength of the study is the comprehensive genetic testing that was carried out. Consistent with previously published literature, 67% of patients had identified genetic variants or complement protein autoantibodies. Interestingly however, among the 17 patients whose genetic testing was initially interpreted as VUS, 12 were subsequently recharacterized as deleterious variants based on structure-function analysis. This serves as evidence that our knowledge of the genetics of C-TMA continues to rapidly evolve, rendering VUS a dynamic classification category. Perhaps one of the main takeaway points of this study is not to dismiss VUS but rather interpret them within the context of other TMA risk factors. ■

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The author reports no conflicts of interest.

References

1. Zuber J, et al. Use of highly individualized complement blockade has revolutionized clinical outcomes after kidney transplantation and renal epidemiology of atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 2019; 30:2449–2463. doi: 10.1681/ASN.2019040331
2. Merzkani M, et al. Thrombotic microangiopathy after kidney transplantation: Insights into genetic etiology and clinical outcomes. *Kidney Int Rep* 2025; 10:1152–1162. doi: 10.1016/j.ekir.2025.01.026
3. Timmermans S, et al.; Limburg Renal Registry. C5b9 formation on endothelial cells reflects complement defects among patients with renal thrombotic microangiopathy and severe hypertension. *J Am Soc Nephrol* 2018; 29:2234–2243. doi: 10.1681/ASN.2018020184

The Latest Xenotransplant: A Step Forward Despite Challenges

By Lisa Schwartz

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Xenotransplantation continues to advance through patient pioneers like Towana Looney, who was 53 at the time of surgery, of Alabama, the longest-living recipient of a genetically engineered pig kidney to date. Her kidney, which was transplanted in November 2024 at New York University (NYU) Langone Health, lasted 130 days—the longest any pig kidney has functioned in a human body—before her body began to reject the organ (1). Looney had 4 months and 9 days of living free from the constraints and side effects of dialysis before the kidney was removed on April 4, 2025. Although she has since returned to dialysis, she is thankful for the second chance she was given and remains hopeful for the future of xenotransplantation.

"I'm so grateful to have been given the opportunity to be part of this incredible research. For the first time since 2016, I enjoyed time with friends and family without planning around dialysis treatments. Though the outcome is not what anyone wanted, I know a lot was learned from my 130 days with a pig kidney—and that this can help and inspire many others in their journey to overcome kidney disease," Looney said in a statement (1).

Researchers and transplant surgeons do not view the rejection of Looney's pig kidney as a failure, but as another step forward in refining the groundbreaking field of xenotransplantation.

"Towana Looney's genetically engineered pig kidney functioned well for over four months, and she was able to enjoy life without dialysis for the first time in nine years. In early April, she had a reduction in renal function due to acute rejection. What triggered the rejection episode after a long period of stability is being actively investigated, but it followed a lowering of her immunosuppression regimen to treat an infection unrelated to the pig kidney," said Robert Montgomery, MD, PhD, H. Leon Pachter, MD, Professor; chair of the Department of Surgery; and director of the NYU Langone Transplant Institute, in an NYU Langone statement. "The decision was made by Ms. Looney and her doctors that the safest intervention would be to remove the kidney and return to dialysis rather than giving additional immunosuppression. This preserves future possibilities for transplantation for her as knowledge and innovations progress."

Clinical trials push forward with progress and hope

Preventing rejection of an animal organ despite the use of immunosuppressant drugs remains a challenge in xenotransplantation. Several clinical trials, however, are investigating new approaches and innovations to overcome this and other barriers.

At Massachusetts General Hospital, Tim Andrews received a genetically engineered pig kidney in January at the age of 66 as part of eGenesis' multipatient study under the US Food & Drug Administration-authorized Expanded Access pathway (2). According to the company, eGenesis is currently the only biotechnology firm developing pig kidneys that carry three classes of genetic modifications designed to improve compatibility and prevent rejection. The pig kidneys have seven human genes to reduce the human immune response, reduce inflammation, and reduce clotting caused by incompatibility. Multiple endogenous pig retroviruses have also been removed from the pig's genome to reduce the risk of infection with a pig virus.

United Therapeutics also recently announced US Food & Drug Administration clearance of its clinical study of the UKidney (3). According to the company, the UKidney is an investigational xenokidney from a pig with 10 gene edits. Six human genes are added to the pig genome to facilitate immunological acceptance and compatibility of the organ in the human recipient, while four porcine genes are inactivated: three that contribute to porcine organ rejection in humans and one that can cause organ growth. The first xenotransplant in the trial is expected in mid-2025. Looney's pig kidney was developed by Revivicor, a division of United Therapeutics.

Furthermore, in May 2024, researchers at NYU Grossman School of Medicine and the Broad Institute of Massachusetts Institute of Technology and Harvard University published two analyses of xenotransplants that revealed changes at the single-cell level in the organs and recipients' bodies before, during, and immediately after the xenotransplantation surgeries, according to an NYU Langone Health press release (4). The study found that while genetically modified pig kidneys transplanted into humans did not face immediate rejection (likely due to immunosuppressants), they did provoke significant immune responses at the cellular level. The study provided researchers with vital insights to benefit future engineering of pig kidneys for human transplant.

Celebrating a 130-day milestone

Despite its failure, Looney's record-breaking transplantation is being touted as a milestone, paving the way for future studies and xenotransplants.

"Towana's willingness to endeavor into the unknown to help solve the nation's organ shortage crisis will impact many more lives after her," stated Montgomery. "We celebrate her tremendous courage and sacrifice. She lived with a pig kidney longer than any other human in history, and the field has learned a great deal from her. Her contribution has furthered the hope and promise of genetically engineered pig organs as an alternative source to human organs" (1). ■

References

1. New York University (NYU) Langone Health. Pig kidney recipient returns home after transplant breakthrough at NYU Langone Health. February 25, 2025. Update April 11, 2025. Accessed April 29, 2025. https://nyulangone.org/news/pig-kidney-recipient-returns-home-after-transplant-breakthrough-nyu-langone-health
2. eGenesis. eGenesis announces second patient successfully transplanted with genetically engineered porcine kidney. February 7, 2025. Accessed May 5, 2025. https://egenesisbio.com/press-releases/egenesis-announces-second-patient-successfully-transplanted-with-genetically-engineered-porcine-kidney/
3. United Therapeutics. United Therapeutics Corporation announces FDA clearance of its investigational new drug application for the UKidney xenotransplantation clinical trial. February 3, 2025. Accessed May 5, 2025. https://ir.unither.com/press-releases/2025/02-03-2025-120011819
4. New York University (NYU) Langone Health. Studies reveal cell-by-cell changes caused when pig hearts & kidneys are transplanted into humans. May 21, 2024. Accessed May 6, 2025. https://nyulangone.org/news/studies-reveal-cell-cell-changes-caused-when-pig-hearts-kidneys-are-transplanted-humans

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Lorundrostat Shows Efficacy in Uncontrolled Hypertension

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The highly specific aldosterone synthase inhibitor lorundrostat lowers blood pressure (BP) in patients with uncontrolled, treatment-resistant hypertension, reports a clinical trial in *The New England Journal of Medicine*.

The multicenter phase 2b trial targeted patients with uncontrolled hypertension, defined as an office BP measurement of 140/90 mm Hg or higher despite treatment with two to five antihypertensive medications. Eligible patients received a standardized 3-week antihypertensive regimen. Those with an average 24-hour ambulatory BP of 130/80 mm Hg or higher were randomly assigned to receive placebo; stable-dose lorundrostat, 50 mg/day; or adjustable-dose lorundrostat, with dosage increased to 100 mg/day if systolic BP remained at 130 mm Hg or higher after 4 weeks.

Change in 24-hour average systolic BP was assessed in a double-blind fashion after 12 weeks of treatment, with adjustment for placebo. Secondary outcomes included a placebo-adjusted change in 24-hour systolic BP at 4 weeks in the combined lorundrostat groups.

In the study, there were 285 patients who were randomized. Among the patients, the mean age was 60 years, 60% were male, and 53% were Black. Lorundrostat produced greater least-squares mean reductions in 24-hour systolic BP: –15.4 mm Hg in the stable-dose group and –13.9 mm Hg in the adjustable-dose group compared with –7.4 mm Hg with placebo. With adjustment for placebo, BP reductions were –7.9 mm Hg with stable-dose and –6.5 mm Hg with adjustable-dose lorundrostat.

For the combined lorundrostat groups, placebo-adjusted change in 24-hour average systolic BP was –5.3 mm Hg at 4 weeks. At that time, systolic BP was under 125 mm Hg in 41% of patients treated with lorundrostat compared with 18% with placebo (odds ratio, 3.3). On safety analysis, 5% of patients in the stable-dose lorundrostat group and 7% in the adjustable-dose group had potassium levels greater than 6.0 mmol/L compared with none in the placebo group.

The new trial shows greater reductions in BP with lorundrostat versus placebo in patients with uncontrolled hypertension. The ongoing, phase 3 Launch-HTN trial (NCT06153693) will evaluate lorundrostat's effects on kidney function [Laffin LJ, et al.; Advance-HTN Investigators. Lorundrostat efficacy and safety in patients with uncontrolled hypertension. *N Engl J Med* 2025; 392:1813–1823. doi: 10.1056/NEJMoa2501440]. ■

How Would Waiting List Expansion Affect Transplant Wait Times?

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To shorten kidney transplant wait times, strategies for waiting list expansion must prioritize increased donation of deceased- and living-donor organs, suggests a simulation study in *JAMA Network Open*.

The researchers conducted a decision-analytic study using a Markov model to evaluate the effects of different approaches to waiting list expansion on kidney transplant wait times. The model included a simulated cohort of more than 660,000 patients (mean age, 58.7 years), who received dialysis between 2022 to 2032. The cohort represented diverse racial and ethnic backgrounds, including Black (41%) and Hispanic (25%) patients.

The model addressed the impact of two degrees of waiting list expansion: 10% and 50%, alone or in addition to expanded supplies of deceased-donor kidneys (by 10%, 25%, 50%, and 100%) and living-donor organs (by 25%, 50%, 100%, and 200%). Effects of these scenarios on median time to transplant were estimated using the Kaplan-Meier survival analysis.

On its own, waiting list expansion was associated with increases in median kidney transplant wait time. Wait time increased from 32.8 months under the "status quo" strategy to 36.8 months with a 10% waiting list expansion and up to 52.6 months with 50% expansion. The expansion scenarios were associated with increased waiting list additions, removals, and deaths.

Strategies to increase deceased- and living-donor donation yielded significant increases in organ supply: from 1911 to 20,035 additional kidneys. Under these scenarios, median wait times ranged from 23.7 to 34.5 months with 10% waiting list expansion and from 34.2 to 49.4 months with 50% waiting list expansion.

On its own, waiting list expansion is likely to increase wait times for kidney transplantation, the decision analysis suggests. The prolonged wait times "can only be alleviated by drastically increasing organ supply," the researchers write. They add that reducing the discard rate of deceased-donor organs appears inadequate to offset the effects of waiting list expansion [Caldwell JS, et al. Kidney transplant wait times under waiting list expansion scenarios. *JAMA Netw Open* 2025; 8:e251665. doi: 10.1001/jamanetworkopen.2025.1665]. ■

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16. Mullen J.; Association of American Medical Colleges. How our organ transplant system fails people of color. November 29, 2022. Accessed May 9, 2025. https://www.aamc.org/news/how-our-organ-transplant-system-fails-people-color
17. Kizer K, et al., eds. *Realizing the Promise of Equity in the Organ Transplantation System*. The National Academies Press; 2022. https://nap.nationalacademies.org/read/26364/chapter/1
18. Simpson DC, et al. The African American Transplant Access Program: Mitigating disparities in solid organ transplantation. *NEJM Catal Innov Care Deliv* 2024; 5. doi: 10.1056/CAT.24.0140
19. Nonterah CW, et al. A nominal group technique study of patients who identify as Black or African American and access to renal transplantation. *Prog Transplant* 2023; 33:141–149. 10.1177/15269248231164164
20. Patzer RE, et al. The role of race and poverty on steps to kidney transplantation in the southeastern United States. *Am J Transplant* 2012; 12:358–368. doi: 10.1111/j.1600-6143.2011.03927.x
21. Ng Y-H, et al. Does racial disparity in kidney transplant waitlisting persist after accounting for social determinants of health? *Transplantation* 2020; 104:1445–1455. doi: 10.1097/TP.0000000000003002
22. Purnell TS, et al. Dismantling structural racism as a root cause of racial disparities in COVID-19 and transplantation. *Am J Transplant* 2021; 21:2327–2332. doi: 10.1111/ajt.16543
23. National Institute on Minority Health and Health Disparities, National Institutes of Health. NIH-funded study highlights the financial toll of health disparities in the United States. May 16, 2023. Accessed May 9, 2025. https://www.nih.gov/news-events/news-releases/nih-funded-study-highlights-financial-toll-health-disparities-united-states
24. American Society of Nephrology. Health Care Justice Committee. Accessed May 9, 2025. https://www.asn-online.org/about/committees/committee.aspx?panel=HCJC
25. U.S. Government Accountability Office. Kidney transplants: Medicare coverage of immunosuppressive drugs. August 8, 2024. GAO-24-107230. https://www.gao.gov/assets/gao-24-107230.pdf
26. Sadler G. Practical rationality: 10 Definitely fake quotes not from the Stoic emperor Marcus Aurelius. Medium. August 14, 2022. https://medium.com/practical-rationality/10-definitely-fake-quotes-not-from-marcus-aurelius-4c0294e4ea65

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