ASN American Society of Nephrology

# Kidney News

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## Uzbekistan Children Died from Unregulated Cough Syrup and Resulting Nephrotoxicity

By Melanie Padgett Powers

For nearly 100 years, it has been known that diethylene glycol (DEG) is a highly toxic solvent that can cause kidney failure and death when ingested (1). Yet, hundreds—perhaps thousands—of children in resource-limited countries continue to die after consuming cough syrup or teething syrup made with DEG.

In November 2023, an Uzbekistan pediatric nephrologist, Nodira Murtalibova, MD, and coauthors reported in *Kidney360* on a poisoning outbreak in her country (2). Since September 2022, at least 120 children in Uzbekistan and neighboring Tajikistan experienced severe, unexplained oliguria and an altered mental state. Murtalibova et al. reported on 50 of these patients, aged 6 months to 10½ years, who were admitted to two hospitals in Tashkent, the capital of Uzbekistan.

Eighteen of the 50 children died—a mortality rate of 36%. All of the children required acute hemodialysis. Three of the surviving children are still receiving hemodialysis, whereas 29 children recovered their kidney function. However, the poisoning was likely just "the tip of the iceberg," Murtalibova said, because it is reasonable to assume that not all children who were poisoned were taken to the capital city's hospitals.

Murtalibova told *Kidney News* that it was an astute physician investigating the children's case histories in-depth who discovered that at least 36 of the children had been given the same brand of cough syrup at home for an upper respiratory illness and fever. The medication was manufactured at a company in India. In countries without strict pharmaceutical regulatory agencies and practices, previous reports have shown that some drug manufacturers have replaced propylene glycol or other ingredients with the less expensive DEG formula. Propylene glycol is a safe "solubilizer," which mixes and dissolves ingredients into a liquid formulation needed for children's medications (3).

DEG, on the other hand, is toxic when ingested because it forms the metabolite diglycolic acid, which can cause the type of end organ damage observed with DEG poisoning, said nephrologist Mark A. Perazella, MD, FASN, professor of medicine at Yale School of Medicine, New Haven, CT, and an expert on drug-related kidney toxicity.

*Continued on page 5*

## Growing Concern for Youths with Type 2 Diabetes

By Karen Blum

The prevalence of type 2 diabetes has been increasing dramatically among youths over the past decade, yet young people do not seem to be responding as favorably as adults to many existing diabetes medications, according to a Kidney Week 2023 presentation in cooperation with the American Diabetes Association.

Incidence data reported between 2003 and 2012 by investigators in the multicenter SEARCH for Diabetes in Youth study found "a constant and rather scary increase" in type 2 diabetes rates of approximately 7% per year and were higher among Native Americans and non-Hispanic Black youths in that time period (1), said Steven Kahn, MBChB, professor of medicine and director of the Diabetes Research Center at the University of Washington (UW) and staff physician at the U.S. Department of Veterans Affairs Puget Sound Health Care System in Seattle.

Updated data from 2 years ago (2) indicated that type 2 diabetes rates continued to increase but were observed more prominently in older adolescents (aged 15–19 years) and females than they were in younger children and males, Kahn said. Information from the International Diabetes Federation suggests that type 2 diabetes in youths is being recognized worldwide, including in countries such as Kuwait, Qatar, Japan, and Canada. "This is a disease that is becoming very prevalent," said Kahn. "If you haven't seen much of it up until now—especially as a nephrologist

*Continued on page 6*

## Inside

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.


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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.

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**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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# Uzbekistan Children Died from Unregulated Cough Syrup

*Continued from cover*

As a deputy editor of *Kidney360*, Perazella wrote an accompanying editorial: "Hiding in Plain Sight: Catastrophic Diethylene Glycol Poisonings in Children" (4).

## The poisoning cascade

DEG poisoning tends to start with gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea. The most prominent clinical manifestation is nephrotoxicity, causing acute kidney injury (AKI) and anion gap metabolic acidosis, Perazella said. As in Uzbekistan, patients then experience neurological problems, which can include encephalopathy, multiple peripheral and cranial neuropathies, and muscle weakness in all limbs. Oxygen levels drop, and patients become comatose and may die. In the Uzbekistan children, 46 of the 50 were placed on ventilators.

Overall, the National Children's Medical Center, in which Murtalibova practices, treated approximately 73 patients. Only two of them died at the hospital, she said. She credits the lower mortality rate to clinicians who quickly collaborated and brainstormed on how to adequately care for these children who were acutely ill. "In my hospital, we involved all specialists for treatment of these patients, including neurologists, pulmonologists, and ENT [ear, nose, and throat] doctors, and we had the opportunity to [provide] MRIs [magnetic resonance imaging] for these patients," she told *Kidney News*.

Many of the children became comatose, and the physicians did not know why. The MRIs revealed posterior reversible encephalopathy syndrome. A neurologist recommended that the children be treated with the osmotic diuretic mannitol, which can lower pressure and swelling in the brain, and with intravenous immune globulin (IVIG). "I think the main difference between the treatment from the two hospitals in Tashkent was the use of mannitol in every hemodialysis session and using IVIG," Murtalibova said.

During the outbreak, the National Children's Medical Center received resources, including hemodialysis filters, through Murtalibova's involvement in the International Pediatric Nephrology Association (IPNA). She is a mentee through the IPNA Junior Empowerment and Mentorship Program and sought support from her mentors. After the children's urinary function was restored, Murtalibova said urine analyses showed that most of the children had calcium oxalate dihydrate crystals. These can be caused by ethylene glycol, another contaminant that may have been in the medication.

## A call to action and awareness

Murtalibova wants her paper to raise awareness and spur a call to action regarding the lack of drug regulations, which can lead to severe illness and death, in resource-limited countries. "Last year was a very, very sad year for Uzbekistan," she said. "We lost so many children because we just did not know why this was happening." Once the cough syrup was identified as the cause of the severe illness, government officials warned people not to use it and directed pharmacists to remove it from shelves. (It is unknown whether the Indian manufacturer faced any consequences.)

Murtalibova said physicians in Uzbekistan know about safer, regulated drugs from regions, such as the United States and Western Europe, but their patients cannot afford these medications. "They're very expensive, so we cannot prescribe them. Indian drugs are cheaper…[but] my goal is to increase the awareness that these kinds of things can happen when we use these kinds of drugs."

Creating or improving the drug regulatory process in resource-limited countries is an uphill battle, Perazella said. "It's all about finances and income and poverty, and unfortunately, where this is happening is in countries that don't have a lot of money, so they can't have rigorous oversight like the US FDA [Food and Drug Administration] and the European Union," he said. Because of this disparity among countries, Murtalibova said it is critical that the global nephrology community—not only those in resource-limited countries—becomes aware of these toxic effects so clinicians can act fast to save lives.

Pediatric nephrologist Howard Trachtman, MD, FASN, adjunct professor of pediatrics at the University of Michigan, was horrified to hear of these deaths. He wonders if the international nephrology community can implement standards of care or help countries push for national legislation. But, he acknowledged, "It's going to be very difficult because the only reason why laws don't get implemented is because countries like Nigeria or India won't dedicate the resources that are necessary to police" these drug manufacturers.

Perazella's editorial outlines several other similar cases, including 78 children in Gambia with AKI after DEG poisoning from cough syrup made in India; 84 children with AKI in Nigeria from teething syrup made in Lagos; and 219 pediatric deaths in Panama from a European cough syrup that contained DEG, which was substituted and sold as pharmaceutical-grade glycerin from a company in China.

As Perazella pointed out, because there have been at least 60,000 bottles of cough syrup and lotions contaminated with DEG in recent years, the 219 reported deaths likely reflect only a fraction of the total mortality. Improved surveillance systems are needed to detect these poisoning events quickly to enable prompt notification of physicians and patients, Trachtman added.

Perazella said he titled his editorial *Hiding in Plain Sight* because "we've known about this for a long time. We've seen it happen time and time again, yet nothing seems to happen. Here it is in [2024], and these [unfortunate] children in Uzbekistan and the surrounding areas are dying and suffering serious complications of contamination of products. It just shouldn't happen."

In November 2023, after her paper was published online, Murtalibova attended the 15th Asian Congress of Pediatric Nephrology in Dubai, United Arab Emirates. A pediatric nephrologist from Bangladesh pulled her aside to discuss her paper. He told her that he had experienced a similar outbreak in his country, in which children were also poisoned by cough syrup with DEG. That outbreak occurred in 1992—over 30 years earlier. ■

### References


1. Hanif M, et al. Fatal renal failure caused by diethylene glycol in paracetamol elixir: The Bangladesh epidemic. *BMJ* 1995; 311:88–91. doi: 10.1136/bmj.311.6997.88
2. Murtalibova N, et al. Sudden spurt in pediatric patients with AKI in Uzbekistan: A call for international drug quality control and pharmaceutical legislation. *Kidney360* 2023; 4:1608–1609. doi: 10.34067/KID.0000000000000255
3. Drugs.com. Propylene glycol. November 9, 2023. https://www.drugs.com/inactive/propylene-glycol-270.html
4. Perazella MA. Hiding in plain sight: Catastrophic diethylene glycol poisoning in children. *Kidney360* 2023; 4:1534–1535. doi: 10.34067/KID.0000000000000269


## Correction and Clarification

The Policy Update "Achieving Kidney Health in a Warming World" by Zachary Kribs published in May 2023 *Kidney News* includes the statement, "Perhaps the greatest opportunity to improve the environmental impact of existing therapies for people with kidney failure is to reduce the water usage in dialysis. Globally, dialysis requires enough medically pure water to fill Lake Tahoe annually."

This estimate of the global water usage in dialysis is no longer believed to be accurate. A more accurate statement is that, globally, 265 billion liters of medically pure water is estimated to be used in dialysis every year, enough to fulfill the United Nations-recognized water needs of between 7 and 15 million people (1, 2). ■

### References


1. Ben Hmida M, et al. Water implications in dialysis therapy, threats and opportunities to reduce water consumption: A call for the planet. *Kidney Int* 2023; 104:46–52. doi: 10.1016/j.kint.2023.04.008
2. United Nations. Water. Accessed December 11, 2023. https://www.un.org/en/global-issues/water

# Growing Concern for Youths with Type 2 Diabetes

*Continued from cover*

because it tends to present later with kidney problems—let me assure you, you will be getting your practice soon."

The complications of the disease are significant, he said. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study (3) that followed youths with type 2 diabetes over time, starting at approximately aged 14 years, found that after 9 years of follow-up, 50% had some microvascular disease. Half of these adolescents also developed other health concerns such as hypertension, kidney diseases, and nerve disease within 9 to 15 years of follow-up. "Youth with diabetes are experiencing exactly what we see in adults but experience it at a really young age, and, therefore, it's going to have a major impact on their lives going forward," Kahn said.

Looking at interventions, the effects of glucose-lowering medications in youths compared with adults are not yet well known, he said, but comparing results from a trial by the TODAY Study Group (4) in youths with those from the A Diabetes Outcome Progression Trial (ADOPT) study (5) in adults may provide some clues, he said. In the TODAY trial, youths were randomized to receive either metformin alone or in combination with rosiglitazone or with lifestyle changes. By 36 months, approximately one-third of those taking metformin plus rosiglitazone failed to maintain glycemic control on those agents and had to try something else. The same was true for approximately 40% of those taking metformin along with lifestyle changes and half of those taking metformin alone. By contrast, among adults in the ADOPT trial randomized to rosiglitazone versus either metformin or glyburide, only approximately 10% had glycemic failure after 3 years.

A report that reviewed these and other studies indicated that the loss of beta cell function—the ability to adequately secrete insulin—is far greater and more rapid in youths than in adults (6), Kahn said, "suggesting that once [youths] get the disease to the time they will need insulin…is much too rapid in this cohort of our population."

Since 2000, a plethora of glucose-lowering medications have been available for adults with type 2 diabetes, Kahn said. Three of these classes—sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists—have made a big impact, but their performance among youths is still being uncovered. In one study of the GLP-1 receptor agonist liraglutide, youths taking the drug initially had a reduction in hemoglobin $A_{1c}$ ($HbA_{1c}$) levels within 3 months, but then that effect seemed to subside (7). Interestingly, Kahn noted, is that 12 months after starting therapy, a much smaller percentage of those taking an active drug versus placebo needed rescue medications. "Clearly, we're getting a benefit of the GLP-1 receptor agonist that slows progression of hyperglycemia, but it doesn't seem to slow progression of the disease."

In other classes, a recent study among youths comparing the DDP-4 agent linagliptin with placebo and the SGLT2 inhibitor empagliflozin with placebo, linagliptin had no impact on glycemia, whereas empagliflozin did produce a difference in $HbA_{1c}$. However, the disease did continue to progress despite intervention (8).

Medications approved for treating glycemia in type 2 diabetes in children continue to lag several years behind those for adults, Kahn said, but young people with diabetes are at increased risk for "devastating" complications. "We desperately need approaches that could stop or slow the development of these complications," such as through new medications, he said.

However, the future appears bright, he added, with a number of new agents being built around GLP-1s that are approved or being studied for type 2 diabetes in adults. These include orforglipron, tirzepatide (current clinical trial among youths), CagriSema, and retatrutide. Given how aggressive this disease can be in young people, Kahn said, "it's time that we should be using these agents wherever possible in youth."

The basis for the more aggressive loss of beta cell function in youths and its unresponsiveness to interventions remain an enigma, he added. But given the rapid increase in type 2 diabetes cases in young people, "it is incumbent on us that we urgently have to get a better understanding on the pathophysiology of diabetes in youth compared to adults, because that will ultimately allow us to develop interventions that in youth will have an ability to slow progression of disease that we desperately need," he said. ■



**References**

1. Mayer-Davis EJ, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *N Engl J Med* 2017; 376:1419–1429. doi: 10.1056/NEJMoa1610187
2. Lawrence JM, et al. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001–2017. *JAMA* 2021; 326:717–727. doi: 10.1001/jama.2021.11165
3. TODAY Study Group; Bjornstad P, et al. Long-term complications in youth-onset type 2 diabetes. *N Engl J Med* 2021; 385:416–426. doi: 10.1056/NEJMoa2100165
4. TODAY Study Group; Zeitler P, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012; 366:2247–2256. doi: 10.1056/NEJMoa1109333
5. Kahn SE, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; 355:2427–2443. doi: 10.1056/NEJMoa066224
6. Nadeau KJ, et al. Youth-onset type 2 diabetes consensus report: Current status, challenges, and priorities. *Diabetes Care* 2016; 39:1635–1642. doi: 10.2337/dc16-1066
7. Tamborlane WV, et al.; Ellipse Trial Investigators. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med* 2019; 381:637–646. doi: 10.1056/NEJMoa1903822
8. Laffel LM, et al.; DINAMO Study Group. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): A multicentre, randomized, double-blind, parallel group, phase 3 trial. *Lancet Diabetes Endocrinol* 2023; 11:169–181. doi: 10.1016/S2213-8587(22)00387-4

# Kidney Transplant Policy: What We Can Expect in 2024

By Rachel Nell Meyer

As 2024 dawns, it holds promise to be another transformative year in the kidney transplant policy space. In 2023, some of the most significant policy changes since the enactment of the original National Organ Transplant Act of 1984, which provided the framework for the US organ transplant system, were implemented. Many of these changes included top ASN advocacy goals, such as reforms intended to maximize patients' access to transplantation, an increase in transparency in the transplant process for patients and general nephrologists, and ensuring that all patients have access to transplantation regardless of geography, socioeconomic status, race and ethnicity, and sex or gender. The reforms initiated in 2023 are largely still ongoing as we enter 2024, and some will—by design—continue to evolve for years to come.

In response to continued challenges accessing transplant care experienced by too many people with kidney diseases, ASN's renewed focus on transplantation policy under the leadership of transplant nephrologists ASN Past President Michelle A. Josephson, MD, FASN; ASN Policy and Advocacy Committee Chair Roz B. Mannon, MD, FASN; and the late Barbara T. Murphy, MB BAO BCh, FRCPI (who would have served as ASN president in 2021), has increased advocacy for transformational changes to the US transplant system. The need for these improvements was championed by several bipartisan leaders in the US Congress, ultimately wrapped up in an initial reform bill, the Securing the US Organ Procurement and Transplantation Network (OPTN) Act.

Spearheading many of the changes to the transplant system is the Health Resources & Services Administration (HRSA), which oversees the OPTN. In March 2023, HRSA unveiled the OPTN Modernization Initiative, a sweeping set of goals aimed at increasing performance, accountability, and transparency in the US transplant system in the long term (1, 2).

Two key ways in which HRSA is working toward the OPTN Modernization Initiative goals are 1) increasing competition and allowing multiple contractors to help fill the functions of the OPTN (which had previously been held by a single contractor) and 2) establishing an independent OPTN board of directors (separate from any contractor's board of directors). Those aims received a significant boost when Congress passed the Securing the US OPTN Act last summer, a bill that revised existing law to allow for a more competitive bidding process and called for an independent board of directors, among other things (3). As ASN advocated to Congress in support of the legislation, by allowing multiple contractors, HRSA can ensure that each of the many important functions of the OPTN—including policymaking, organ matching, information technology, and data management—will be carried out by the best-in-class vendors, and a board of directors that is separate from those of any contractors will increase accountability in the system.

President Biden signed the bill into law in September 2023 (4), and in 2024, HRSA is anticipated to be fielding bids from multiple contractors for various functions of the OPTN for the first "transitional" phase of the OPTN Modernization Initiative, which will "support and enhance OPTN operations while the modernization process is underway" (2). In the future, overlapping the transitional phase (and potentially during 2024), HRSA anticipates issuing contracts for a "next generation" phase that will focus on designing, testing, and eventually implementing components like a modernized OPTN information technology system, which will allow it to serve patients better and more efficiently and transparently.

ASN is committed to continuing to advocate for the success of the OPTN Modernization Initiative, and championing needed increased funding to support it will be a hallmark of the society's appropriations advocacy in 2024. Last year, the Biden administration requested an additional $37 million for HRSA's organ and transplant-related budget, and although funding for the last fiscal year has not been finalized, it is evident that the large-scale modernization effort will require a substantial increase in funding to fully achieve its goals.

**The reforms initiated in 2023 are largely still ongoing as we enter 2024, and some will—by design—continue to evolve for years to come.**

Meanwhile, however, HRSA is already making moves to address another ASN policy priority: data collection regarding the progression between a patient's referral for transplant and duration to the waitlist (or sadly for many, not being waitlisted). Today, many patients and their nephrologists (as well as researchers) experience this post-referral period as a frustrating "black box."

But HRSA is not the only agency making big moves in the kidney transplant space. The Centers for Medicare & Medicaid Services (CMS) released a revised 2728 form in late 2023 that, among other items, will require the provision of information about when and where dialysis facilities refer patients to transplant centers for evaluation. Systematic data collection about referral, evaluation, and waitlisting decisions from both transplant centers (led by HRSA) and dialysis facilities (led by CMS) will help paint a complete picture of the patient journey, increase transparency, and hopefully uncover new opportunities for policymakers to help more patients overcome barriers along that journey and successfully gain access to the possibility of a kidney transplant. The timeliness of these changes was underscored by a recent study that found that fewer than one-half of patients with no other major comorbidities were waitlisted (5).

In 2024, we can expect to see more concerted policymaking efforts between CMS and HRSA. In late 2023, the agencies unveiled the Organ Transplantation Affinity Group, (OTAG) a collaboration between CMS and HRSA aimed at strengthening accountability, equity, and performance in the organ donation and transplantation system to improve access for patients (6). Given that CMS and HRSA are "working closely with our colleagues at other HHS [US Department of Health and Human Services] agencies" as part of OTAG, a task OTAG could potentially take on in 2024 is identifying solutions to address the large differences in reported patient outcomes across HHS datasets (6, 7).

An area sure to bring some controversy in 2024 is the evolution of CMS metrics for organ procurement organizations (OPOs). In 2021, CMS finalized new metrics to increase accountability for OPOs nationwide and is set to begin collecting data on those metrics in 2024. OPOs that perform the worst will be ineligible to compete for new contracts beginning in 2026, whereas the best performers will retain theirs. However, CMS has yet to release much detail about how those transitions will work—and a growing number of OPOs are being categorized as low performers. Meanwhile, the agency has indicated that it may also begin collecting data related to organ procurement from donor hospitals, and some researchers have pointed to ways in which CMS could revise the new metrics.

Last but not least, the Center for Medicare and Medicaid Innovation is expected to make announcements related to transplant care in its suite of kidney care models. ASN has advocated both for changes to existing models to better incentivize and reward transplant access, as well as for a transplant-focused model that focuses on long-term outcomes (as opposed to 1- or 3-year time horizons, which are the focus in the current system).

Notably, this is the third consecutive administration that has made kidney transplantation an area of emphasis. Although it will be many months before we know what the 2024 US election will bring, it is a safe bet that kidney transplantation will remain on the agenda heading into 2025 and beyond, and ASN will continue to advocate to maximize patients' access to the optimal therapy: kidney transplant.

*Rachel Nell Meyer is the strategic policy advisor to the executive vice president at ASN.*

**References**

1. Health Resources & Services Administration. HRSA announces Organ Procurement and Transplantation Network Modernization Initiative. March 22, 2023. https://www.hrsa.gov/about/news/press-releases/organ-procurement-transplantation-network-modernization-initiative
2. Health Resources & Services Administration. The path forward. July 2023. https://www.hrsa.gov/optn-modernization/may-2023
3. US Senate Committee on Finance. Wyden, Grassley, Cardin, Young, Cassidy cheer organ transplant legislation becoming law. September 22, 2023. https://www.finance.senate.gov/chairmans-news/wyden-grassley-cardin-young-cassidy-cheer-organ-transplant-legislation-becoming-law
4. The White House. Bill signed: H.R. 2544. September 22, 2023. https://www.whitehouse.gov/briefing-room/legislation/2023/09/22/bill-signed-h-r-2544/
5. Husain SA, et al. Disparities in kidney transplant waitlisting among young patients without medical comorbidities. *JAMA Intern Med* 2023; 183:1238–1246. doi: 10.1001/jamainternmed.2023.5013
6. Moody-Williams JD, Nair S. Organ Transplantation Affinity Group (OTAG): Strengthening accountability, equity, and performance. CMS.gov, Centers for Medicare & Medicaid Services. September 15, 2023. https://www.cms.gov/blog/organ-transplantation-affinity-group-otag-strengthening-accountability-equity-and-performance
7. Yu M, et al. Discrepant outcomes between national kidney transplant data registries in the United States. *J Am Soc Nephrol* 2023; 34:1863–1874. doi: 10.1681/ASN.0000000000000194

ASN President's Update

# Tackling the Unacceptable Together

By Deidra C. Crews

This past year was tremendous for ASN, and I would like to thank Michelle A. Josephson, MD, FASN, for her outstanding tenure as the society's president. ASN was particularly fortunate to have Michelle, a transplant nephrologist, at the helm during a year when important and long-overdue changes to US transplant policy occurred—policy changes that Michelle valiantly championed throughout her career.

The year was capped off in many ways with a superb Kidney Week in Philadelphia, PA, which saw a return of much of the energy the meeting has historically been known for but that has been impacted during the COVID-19 pandemic. I am already excited to see (and feel) the kind of energy that Kidney Week 2024 will bring.

By way of introduction, for the many of you who I have not had the pleasure of meeting, I thought I would share a bit about my background. I was born and raised in southern Virginia (on the East Coast of the United States) in a relatively small manufacturing town. My father worked at the local Goodyear Tire and Rubber factory as a pipefitter, and my mother taught for many years and later served as principal of an elementary school. Both of my parents contributed in numerous capacities to our local community, instilling in me and my brother, who is now a structural engineer, a strong commitment to staying connected to our community and helping however, and whenever, we can.

My father has approximately 90 first and second cousins, so you can imagine how large my family is! Unfortunately, like far too many Black American families, mine has been significantly impacted by kidney diseases. It is not uncommon for chatter during our family reunions to include peer-to-peer encouragement to consider home dialysis modalities or celebrations of kidney transplant anniversaries.

I am the first physician in my family. My first exposure to career opportunities in medicine (aside from my family physician) came via the Medical Explorers' Club, established for school-aged students at our local hospital. It was led by a pathologist, Jack C. Turner, MD, who had a beautiful electron micrograph of a glomerulus hanging in his office—surely guiding me toward a career in nephrology.

After completing my undergraduate studies at the University of Virginia in nearby Charlottesville, I spent 3 years working at the United Network for Organ Sharing (UNOS), which manages the US organ transplant system. During my time at the UNOS Organ Center, I was immersed in the world of transplantation—particularly kidney transplantation. After matriculating into medical school at Saint Louis University School of Medicine (with the help of a recommendation letter from Dr. Turner), I was awestruck by our kidney physiology block during our second year and attending nephrologists like Wendy Weinstock Brown, MD, MPH, who taught me at the bedside. By the time I graduated medical school, I was certain I wanted to become a nephrologist.

It was during residency and nephrology fellowship training at The Johns Hopkins (JH) Hospital that my clinical and research interests in kidney health really began to take shape. My earliest experiences were in dialysis outcomes research, working with nephrologist Bernard G. Jaar, MD, MPH, FASN, and general internist Neil R. Powe, MD, FASN. After completing my training at the JH Bloomberg School of Public Health and the Welch Center for Prevention, Epidemiology and Clinical Research and joining the faculty at JH University, I began to move my focus "upstream" to explore social and behavioral risk factors for the development and progression of chronic kidney disease (CKD).

Through a series of studies, my colleagues and I chipped away at trying to find the root causes for racial and socioeconomic disparities in kidney health. We looked at factors such as access to healthy foods, insurance status, and experiences of discrimination. Around this time, as my passion for health equity research deepened, I continued to enjoy conducting observational/epidemiological research studies, but I developed a strong desire to lead clinical trials addressing disparities in CKD and its risk factors. In some way, I had grown weary of seeing report after report about disparate rates of CKD among people of color and people with low socioeconomic status with very few studies focused on addressing these disparities.

Working with general internists Edgar R. Miller, III, MD, PhD; L. Ebony Boulware, MD, MPH; Lisa A. Cooper, MD, MPH; and others, I pursued this line of investigation and currently co-lead a large research center award conducting four clinical trials to address cardiometabolic health inequities. Partnering with community members, including those with lived experiences with kidney diseases, has been essential to ensuring that our work is relevant and designed to be sustainable.

As my career has advanced, mentoring early career clinicians and scientists has been an important part of my day-to-day activity and a key source of my professional joy. I am the founding director of a research-intensive post-baccalaureate program for students with socioeconomically underresourced backgrounds. It has been amazing to watch them find their passions, including those who are budding kidney professionals and have attended Kidney Week as Kidney STARS (Students and Residents).

I have had the honor to not only serve ASN but also to represent the society in partnerships with the National Kidney Foundation, the American College of Physicians, and the Council of Medical Specialty Societies. These partnerships—which span kidney, internal medicine, and medical specialty communities—and others will be key to the work that lies ahead for ASN and our vision of "a world without kidney diseases."

This year, I plan to focus on four broad goals that will continue the momentum of both ASN and the broader ASN Alliance for Kidney Health. These goals leverage our success in 2023 in reforming transplant policy to speed progress on the We're United 4 Kidney Health campaign's other priorities to intervene earlier, accelerate innovation, and achieve equity (1).

Aligned with my research focus and my family background, I am eager to emphasize, as a first goal, the We're United 4 Kidney Health's fourth priority of achieving equity and eliminating disparities in kidney health. It is not acceptable that in 2024, *where* you live so strongly influences *whether* you live and whether your kidneys function optimally (2). Nor is it acceptable that historically marginalized communities experience lags in accessing effective therapies for slowing CKD progression, such as sodium-glucose cotransporter-2 inhibitors (3).

We have a real opportunity to make progress on this priority during 2024 that builds upon the accomplishments of the National Kidney Foundation–ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases (4) and leverages increasing focus on kidney health equity among research funders (5) and payers (6). This work is urgent, as profound inequities in kidney health will likely worsen as a consequence of climate change (7).

Several objectives will guide our efforts to achieve equity, including:

- Identify health and public policy levers that could support kidney health equity and health care justice.
- Ensure all ASN clinical initiatives operate within a context of health equity.
- Encourage investment in kidney health equity research.
- Seize opportunities to expand awareness and education about kidney diseases to populations experiencing disparities.

The second goal builds on the progress we have already made in implementing the 10 recommendations from the ASN Task Force on the Future of Nephrology's final report (8). To continue this progress, we must focus on helping nephrology fellowship training program directors navigate the new Accreditation Council for Graduate Medical Education (ACGME) requirements, which will go into effect on July 1, 2024. We will also need to ensure the success of the ASN–American Society of Transplantation Task Force on ACGME Accreditation for Transplant Nephrology.

Given the workforce challenges that many of our colleagues are facing, I am excited that ASN is joining forces with the American Nephrology Nurses Association to identify ways to strengthen the kidney care team. In addition, we have developed a partnership with the American Nephrologists of Indian Origin to address issues faced by graduates of international medical schools, particularly surrounding visas and immigration. And we willl continue to develop ASN's version of cardiology's Core Cardiovascular Training Statement ("COCATS"), which is intended to standardize nephrology training.

As a third goal for 2024, ASN will start to produce "Kidney Health Guidance" to support the ability of clinicians caring for patients with kidney diseases to access up-to-date, timely evidence that can guide their treatment plans. ASN, which is one of the few medical societies that has historically not produced such information to help guide clinical practice, will issue its first guidance in 2024. Please stay tuned for more information about this effort in the coming months.

Of course, producing Kidney Health Guidance builds on other ASN clinically focused efforts—from Nephrologists Transforming Dialysis Safety (NTDS) to the relationship with Home Dialysis University (HDU) to "wins" in the legislative and regulatory arenas—toward improving care for people with kidney diseases. From a budget perspective, ASN's three largest operations are Kidney Week, publications (including the three peer-reviewed journals: *CJASN*, *JASN*, and *Kidney360*, as well as *Kidney News*), and ASN Excellence in Patient Care (which includes NTDS and the relationship with HDU).

My fourth and final goal for this upcoming year is to galvanize the kidney community to advocate for increased and coordinated public and private funding for kidney research across the entire spectrum, starting with basic/fundamental research and extending to implementation research. Although it was thrilling to learn about new discoveries and treatment insights at Kidney Week 2023, support for kidney research still lags far behind many other disciplines. This unacceptable reality must change, and I am optimistic that it *will* change as excitement for new therapeutics mounts.

Investment in research will only result in improved therapies for the millions of people with or at risk for kidney diseases if payers, particularly insurers and the Centers for Medicare & Medicaid Services (CMS), accept these treatments and pay a fair price for them. Outreach to insurers and CMS will be an important part of our advocacy, as will expanded partnerships with primary care physicians, cardiologists, endocrinologists, rheumatologists, and any other specialty that treats people with diseases that affect the kidney (9).

Although I am especially excited about these four priorities for 2024, they are just the beginning of all that I know we will accomplish together during the coming year. ASN has always been my professional home, and I am deeply honored and privileged to serve as ASN president. Working together with ASN members like you, my fellow councilors, and the hundreds of members who volunteer to serve the society; other colleagues in the kidney community; and the society's staff, I know that nephrology's ascension will continue in 2024.

*Deidra C. Crews, MD, ScM, FASN, is professor of medicine at Johns Hopkins University School of Medicine, deputy director of the Johns Hopkins Center for Health Equity, and ASN president.*

To comment on Dr. Crews' editorial, please contact email@asn-online.org

**References**

1. American Society of Nephrology. We're United 4 Kidney Health. https://4kidneyhealth.org/
2. Nguyen KH, et al. Structural racism, historical redlining, and incidence of kidney failure in US cities, 2012–2019. *J Am Soc Nephrol* 2023; 34:1493–1503. doi: 10.1681/ASN.0000000000000165
3. Gregg LP, et al. Predictors, disparities, and facility-level variation: SGLT2 inhibitor prescription among US veterans with CKD. *Am J Kidney Dis* 2023; 82:53–62.e1. doi: 10.1053/j.ajkd.2022.11.017
4. Delgado C, et al. A unifying approach for GFR estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *Am J Kidney Dis* 2022; 79:268–288.e1. doi: 10.1053/j.ajkd.2021.08.003
5. Crews DC, et al. Designing interventions addressing structural racism to reduce kidney health disparities: A report from a National Institute of Diabetes and Digestive and Kidney Diseases Workshop. *J Am Soc Nephrol* 2022; 33:2141–2152. doi: 10.1681/ASN.2022080890
6. Centers for Medicare & Medicaid Services. Health equity programs and healthcare resources. September 29, 2023. Accessed December 14, 2023. https://www.cms.gov/priorities/health-equity/minority-health/equity-programs
7. Baker A. Chronic kidney disease is poised to become the black lung of climate change. *Time*, August 9, 2023. Accessed December 14, 2023. https://time.com/6303020/chronic-kidney-disease-climate-change/
8. Rosenberg ME, et al. Reimagining nephrology fellowship education to meet the future needs of nephrology: A report of the American Society of Nephrology Task Force on the Future of Nephrology. *Clin J Am Soc Nephrol* 2023; 18:816–825. doi: 10.2215/CJN.0000000000000133
9. Ndumele CE, et al.; American Heart Association. Cardiovascular-kidney-metabolic health: A presidential advisory from the American Heart Association. *Circulation* 2023; 148:1606–1635. doi: 10.1161/CIR.0000000000001184

# Nephrology Match 2023: Fellows' Perspectives

Embarking on a nephrology fellowship in the United States involves a unique mix of hopes, challenges, and fears in light of recent match outcomes. In this brief article, three aspiring nephrologists—Alessandra Tomasi, MD, chief medical resident; Farhana Begum, MD, chief medical resident; and Ian Lewis, DO, first-year nephrology fellow—share their insights into the nuances of the match process and what they mean to the current workforce.

Alessandra Tomasi, MD

Farhana Begum, MD

Ian Lewis, DO

**Alessandra Tomasi, MD, is chief medical resident and instructor in medicine with the Mayo Clinic College of Medicine and Science, Rochester, MN.**

I interviewed for fellowship from an office at our downtown campus. It was a shared space with my co-chiefs, who were often on the other side of a very thin wall. Early on in the season, one of them commented that my interviews sounded "the most fun." Reflecting on my experience over the 3 months leading up to the Match, I agree.

I have known I wanted to be a nephrologist since my fourth year of medical school. I came into the fellowship interview season with the goal of finding a program that would empower and challenge me to grow as a physician, educator, researcher, and leader. Throughout several weeks of interviews, it became clear that each program shared this same goal. Through virtual social events, open houses, and the interview days themselves, I quickly felt that everyone I interviewed with was invested in bettering the future of our field and that they knew this started with recruiting their trainees.

During my interviews, we discussed career goals, tracks, advanced degrees, and other opportunities. Faculty all over the country offered advice and insight into the 5-year plans that I shared. I felt many of my interviews mirrored meeting a new mentor with a shared investment in my future—regardless of where I would ultimately match. Through these interactions, I learned about myself through the lens of others and their own experiences, and I began to shift some of my own career and fellowship goals. This was unexpected to me and something I am incredibly grateful for.

Ultimately, through the nephrology match process, I connected with a community that, despite a very wide geographic range, felt close. Meeting many of these individuals at Kidney Week 2023 further solidified this impression. I look forward to investing in next year's applicants and elevating them as they experience their own personal and professional growth.

**Farhana Begum, MD, is chief resident with the Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.**

My experience applying for nephrology fellowship last year was incredible. I had the pleasure of interviewing at wonderful academic programs throughout the country. I was thoroughly impressed by the progressive changes that several programs are implementing to provide an excellent training experience—such as point-of-care ultrasound training and home dialysis education. Throughout my application process, I had the pleasure of meeting and connecting with incredible nephrologists—relationships I hope to continue to foster over the course of my career. I personally was looking for an academically rigorous training program that would expose me to the various facets of nephrology, give me a well-rounded education, and allot me time and resources to pursue my own career interests. Because I am interested in glomerular diseases, I was seeking a program that would provide me with that exposure. I also desired a supportive environment with excellent mentors.

The interviews that stood out to me most were with those who took the time to review my application and were extremely knowledgeable about their program. A part of my interview days, which I enjoyed and sought out, was watching fellow didactics and observing fellows engaging with one another in work rooms/lecture rooms. I would recommend this for future cycles, as it not only shows applicants the quality of education that fellows are receiving but also allows applicants to observe fellows and faculty in their work environment. Additionally, it would be wonderful to see programs showcasing the scholarly work/publications of their fellows along with the work of faculty. Ultimately, when speaking to my co-applicants, I think that nephrology programs that provided exposure to adequate outpatient nephrology, subspecialties, and home dialysis modalities; offered resources for research; and were front-loaded to provide second years with time to pursue their career interests were favored. However, location and the culture of a program remained highly prioritized among all applicants.

**Ian Lewis, DO, is a first-year renal fellow with the Medical College of Wisconsin, Milwaukee.**

I developed an appreciation for nephrology during my internal medicine residency. After experiencing several rotations, I knew that I would not be happy in any other specialty. It is a privilege to care for patients with kidney diseases, who often feel overwhelmed with the weight of their illness. It is no secret that interest in nephrology has been declining. I was constantly reminded that I should consider other choices in internal medicine. I was fortunate to join a fellowship program that offered the best resources to treat my future patients in all facets of general nephrology, including transplantation, onconephrology, POCUS (point-of-care ultrasonography), and in-house renal pathology.

In our program, fellows are the first contact for other medical teams on their respective services and take ownership of the patients they are caring for. With fewer available renal fellows and less filled services, opportunities for patient education and advancing medical knowledge with residents and students are going to be limited. Additionally, the thought of less education and more frequent call shifts may exacerbate the problem and drive others away from our field. Lack of fellows may discourage applicants who are interested but undecided about fully committing to nephrology. This hesitation often stems from the perceived cost with increased workload, stress, and fewer benefits compared with practicing general internal medicine as hospitalists or primary care physicians immediately after residency. While each unfilled program may handle this situation differently, one potential mitigation involves a continued, heavy focus on inpatient medicine into the second year, which could detract from much-needed outpatient training, involving home hemodialysis and peritoneal dialysis. Additionally, academic centers with in-house fellowships may face challenges in hiring future faculty members if additional clinical responsibilities and coverage arise due to a scarcity of trainees, potentially shifting the focus away from research and medical education. I am passionate about nephrology and all that we offer, but real changes must be made to safeguard our specialty and ensure a thriving future.

# APRIL: A Key Factor in the Pathogenesis of IgA Nephropathy

By Bobby Chacko, Mohit Mathur, and Dana V. Rizk

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide, affecting approximately 2.5 per 100,000 individuals (1). Until recently, guidelines primarily focused on supportive care (2). IgAN has multifactorial pathogenesis and occurs due to a complex interplay of environmental factors like exposure to mucosal antigens and genetic susceptibility. These factors lead to a dysfunctional mucosal immune response, producing galactose-deficient IgA1 (Gd-IgA1) and the downstream cascade referred to as the 4-hit hypothesis (Figure 1). However, the 4-hit hypothesis does not explain all aspects of IgAN pathogenesis; for example, 16% of healthy individuals showed deposited glomerular IgA without any signs of kidney diseases (3). Gd-IgA1 is also found in healthy subjects, indicating that additional abnormalities must take place before the disease develops (4). Regardless of these underlying mechanisms, B cells are thought to play an important role in the pathogenesis. Two B cell growth factors, a proliferation-inducing ligand (APRIL) and B cell activating factor (BAFF), have overlapping but distinct roles in the initiation of IgAN through promotion of B cell activation and generation of Gd-IgA1 (5).

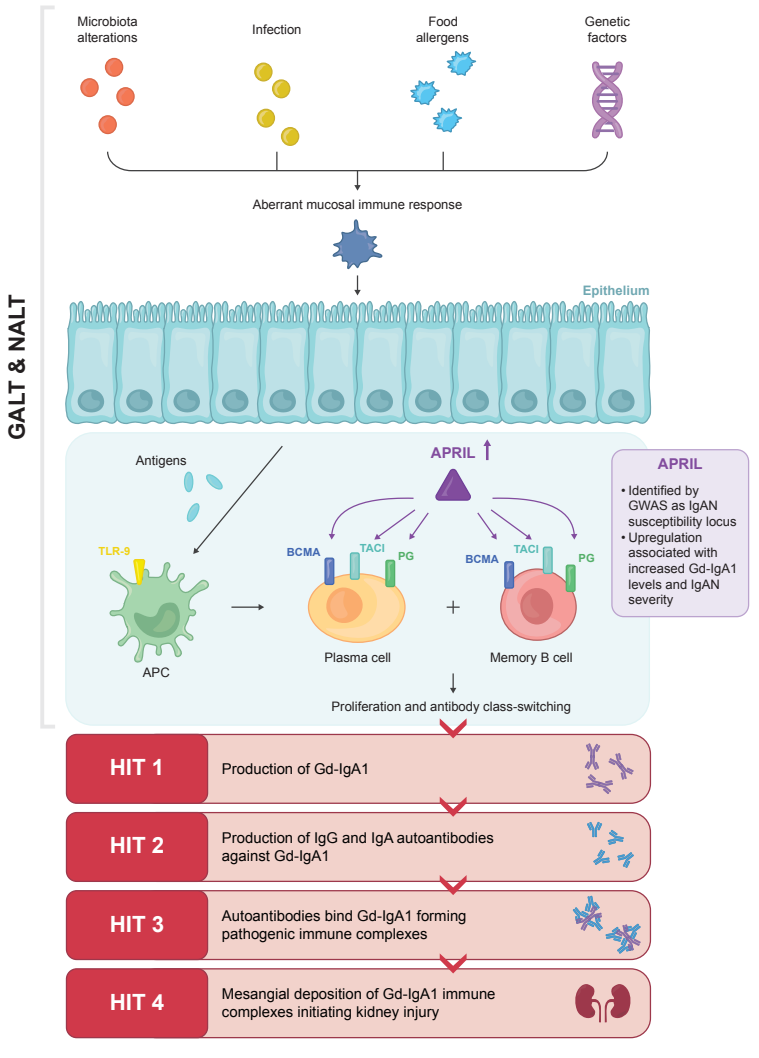
Under physiological conditions, APRIL, BAFF, and their receptors have specific roles in B cell maturation and survival (Figure 2). BAFF binds to three receptors: 1) the BAFF receptor; 2) the B cell maturation antigen (BCMA); and 3) the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) to regulate earlier stages of B cell homeostasis, development, and maturation of primary B cells. APRIL binds strongly to BCMA and with lower affinity to TACI to modulate the function of later stages of B cell and plasma cell maturation and survival in bone marrow and mucosa. APRIL also binds cell surface proteoglycans, which may increase localized APRIL concentration and signaling. APRIL and BAFF also have independent roles in B cell Ig isotype class-switching (5).

Disruption of B cell tolerance is one potential mechanism underlying the role of APRIL in immune-related conditions. Through its function in IgA class-switching and survival of IgA-producing plasma cells, APRIL has a key role in the pathophysiology of IgAN. Elevated APRIL levels result in increased production of Gd-IgA1, providing a critical link to hit 1 of the 4-hit hypothesis (Figure 1) (5–7). Increased APRIL and Gd-IgA1 levels have been linked to IgAN disease severity and progression to kidney failure, whereas the relevance of elevated BAFF levels in IgAN are less well established (5). IgAN recurrence post-transplant is preceded by an increase in serum APRIL levels. In alignment with these clinical observations, genome-wide association studies have identified APRIL as a key susceptibility locus for IgAN (5).

Two anti-APRIL agents (sibeprenlimab [NCT05248646] and zigakibart [NCT05852938]) are in phase 3 clinical development, and three TACI fusion protein antagonists (povetacicept [NCT05732402], atacicept [NCT04716231], and telitacicept [NCT05799287]), which bind and inhibit both APRIL and BAFF, are in phases 1/2 (povetacicept) and 3 (atacicept and telitacicept) (6, 8). Sibeprenlimab, a humanized IgG2 monoclonal antibody that blocks APRIL, demonstrated significant reduction in proteinuria and stabilization of the estimated glomerular filtration rate compared with placebo at 12 months in a phase 2 study of 155 patients with IgAN, with an acceptable safety and tolerability profile. Complete suppression of APRIL and an approximate 65% reduction in pathogenic Gd-IgA1 levels were observed with sibeprenlimab (9). Patients receiving sibeprenlimab had a preserved serologic response to the mRNA COVID-19 vaccination (10), and the COVID-19 infection rate was higher in the placebo cohort at the end of the trial (9). In addition, a phase 1/2, open-label study of zigakibart showed a clinically meaningful and sustained reduction in proteinuria through 12 months (11). The safety of dual APRIL and BAFF inhibitors needs to be established in larger studies, given the important role played by these cytokines in B cell survival (12).

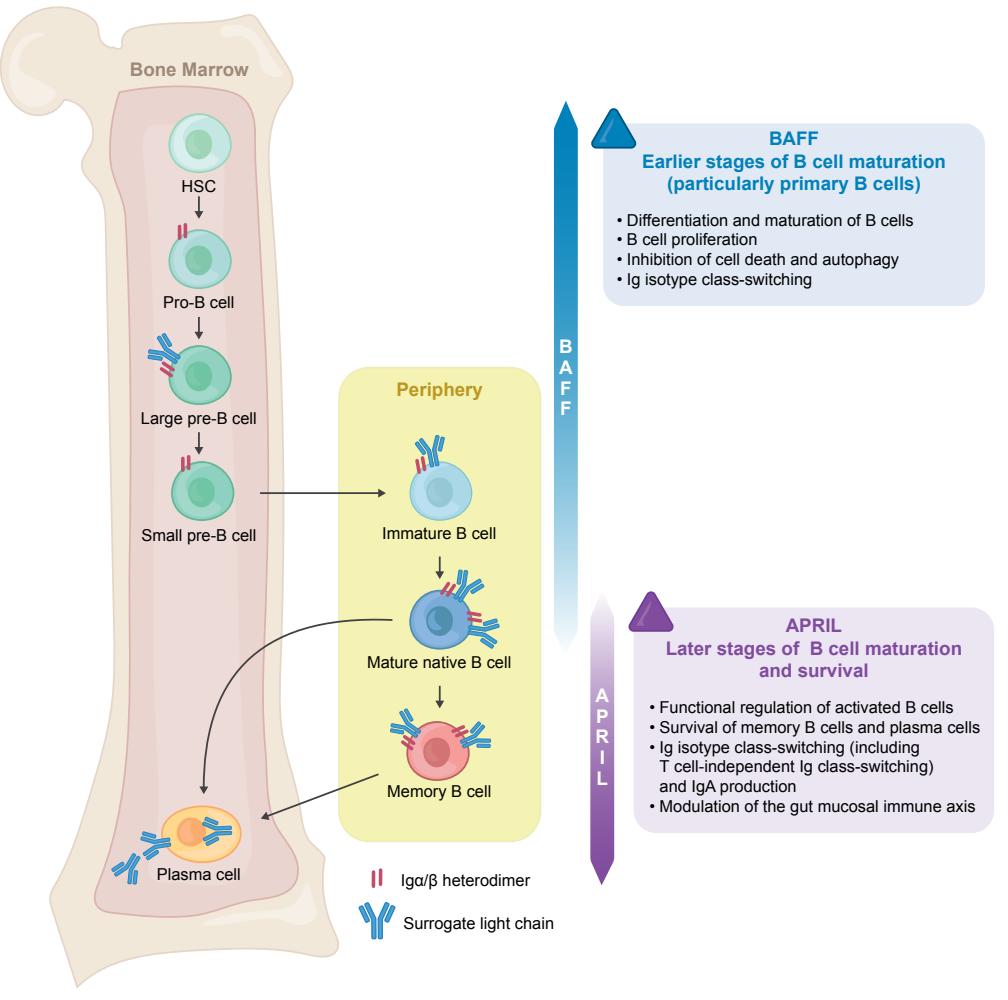
Continued on page 12

**Figure 1. Role of APRIL in the pathogenesis of IgAN—the tonsil- and gut-kidney axis**




APC, antigen-presenting cell; GALT, gut-associated lymphoid tissue; GWAS, genome-wide association study; NALT, nasal-associated lymphoid tissue; PG, proteoglycan; TLR-9, Toll-like receptor 9. See Mathur et al. (5) and Gesualdo et al. (13).

**Figure 2. Roles of APRIL and BAFF in the normal physiology of B cell maturation and survival**




HSC, hematopoietic stem cell. See Mathur et al. (5).

# APRIL: A Key Factor in the Pathogenesis of IgA Nephropathy

*Continued from page 11*

In conclusion, APRIL and BAFF are key factors in B cell biology and IgAN pathogenesis (5, 7). Preliminary clinical data show promise for APRIL as an important therapeutic target. As for all immunomodulatory therapies, studies will need to be vigilant in monitoring and assessing the risk:benefit profile of these exciting, new treatments. ■

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**References**

1. Pattrapornpisut P, et al. IgA nephropathy: Core curriculum 2021. *Am J Kidney Dis* 2021; 78:429–441. doi: 10.1053/j.ajkd.2021.01.024
2. Rovin BH, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021; 100:753–779. doi: 10.1016/j.kint.2021.05.015
3. Suzuki K, et al. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. *Kidney Int* 2003; 63:2286–2294. doi: 10.1046/j.1523-1755.63.6s.2.x
4. Gentile M, et al. Immune abnormalities in IgA nephropathy. *Clin Kidney J* 2023; 16:1059–1070. doi: 10.1093/ckj/sfad025
5. Mathur M, et al. A proliferation-inducing ligand (APRIL) in the pathogenesis of immunoglobulin A nephropathy: A review of the evidence. *J Clin Med* 2023; 12:6927. doi: 10.3390/jcm12216927
6. Gleeson PJ, et al. IgA nephropathy in adults—treatment standard. *Nephrol Dial Transplant* 2023; 38:2464–2473. doi: 10.1093/ndt/gfad146
7. Cheung CK, et al. Targeting APRIL in the treatment of IgA nephropathy. *Clin J Am Soc Nephrol* (published online October 6, 2023). doi: 10.2215/CJN.0000000000000338
8. Selvaskandan H, et al. IgA nephropathy: An overview of drug treatments in clinical trials. Expert *Opin Investig Drugs* 2022; 31:1321–1338. doi: 10.1080/13543784.2022.2160315
9. Mathur M, et al.; ENVISION Trial Investigators Group. A phase 2 trial of sibeprenlimab in patients with IgA nephropathy. *N Engl J Med* (published online November 2, 2023). doi: 10.1056/NEJMoa2305635
10. McCafferty K, et al. COVID vaccine responses during sibeprenlimab treatment of IgA nephropathy (IgAN): An interim analysis. *Nephrol Dial Transplant* 2023; 38(Suppl 1):3347. https://academic.oup.com/ndt/article/38/Supplement_1/gfad063a_3347/7195384
11. Barratt J, et al. Updated interim results of a phase 1/2 study of BION-1301 in patients with IgA nephropathy. *Nephrol Dial Transplant* 2023; 38(Suppl 1):4337. https://academic.oup.com/ndt/article/38/Supplement_1/gfad063c_4337/7196269
12. Kaegi C, et al. Systematic review of safety and efficacy of atacicept in treating immune-mediated disorders. *Front Immunol* 2020; 11:433. doi: 10.3389/fimmu.2020.00433
13. Gesualdo L, et al. The mucosal immune system and IgA nephropathy. *Semin Immunopathol* 2021; 43:657–668. doi: 10.1007/s00281-021-00871-y

# A Bump in the Road for MIPS

By David L. White

After years of difficulty ensuring continuous, predictable payments for physicians, Congress finally enacted its version of a solution in 2015. However, in the last couple of years, uncertainty again threatens the goal of a more stable payment system. ASN is working to ensure that stability continues as some changes to that system loom on the horizon.

The Medicare Access and CHIP (Children's Health Insurance Program) Reauthorization Act of 2015 (MACRA) ended the troubled Sustainable Growth Rate (SGR) formula, which often left Congress addressing a "doc fix" annually to prevent significant cuts in payment rates for participating Medicare clinicians over the SGR's 17-year lifespan. MACRA required the Centers for Medicare & Medicaid Services (CMS) to implement an incentive program, the Quality Payment Program (QPP). There are two pathways through which clinicians can choose to participate in the QPP:

- Merit-based Incentive Payment System (MIPS): If you are a MIPS-eligible clinician, you will be subject to a performance-based payment adjustment through MIPS.
- Advanced Alternative Payment Models (APMs): If you decide to take part in an Advanced APM, you may earn a Medicare incentive payment for sufficiently participating in an innovative payment model.

The program began in earnest in 2017, and the MIPS pathway ran smoothly in its first 3 years. Until, of course, 2020 when the COVID-19 pandemic arrived. The avalanche that was COVID-19 included more than just the tragedy of lost lives and compromised health, it also overtook the delivery, quality measurement, and payment structures of care built into Medicare's system and those of other payers as well. As a result, the MIPS program offered hardship waivers and other delays in the program during 2020 and 2021.

As in most cases involving payment models in Medicare, there is a 2-year delay between a performance year and a payment year. Therefore, the exceptions applied to MIPS in 2020 and 2021 softened the blow of cost issues from those in payment years 2022 and 2023. For 2024, MIPS participants need to re-evaluate their standing in the program in anticipation of a very different payment landscape for this year based on 2022 data.

With a majority of nephrologists in the United States participating in the MIPS pathway of the QPP, ASN is concerned that many MIPS-eligible clinicians have not checked their data in the QPP portal (https://qpp.cms.gov/) and will be unprepared for the change. Although many clinicians have reported that they previously performed well in MIPS, some are going to receive Medicare penalties, which may be as high as the maximum of 9%, starting January 1, 2024.

There are multiple reasons that physicians did not do as well during the 2022 performance year:

1) During the beginning of the pandemic, CMS automatically applied a hardship exemption for MIPS. In 2022, the hardship exemption was no longer automatic, and physicians had to apply.
2) CMS increased the MIPS performance threshold.
3) For the first time since 2019, CMS is counting the MIPS cost category. The cost category has numerous problems, and it is worth 30% of the MIPS score for the 2022 performance year.

Although the MIPS cost category accounted for 30% of eligible professionals' MIPS final scores and significantly contributed to physicians' 2024 MIPS payment adjustments, physicians had no way to anticipate, monitor, and improve their cost category performance because CMS did not share any data about its attributed measures, attributed patients, and observed costs until August 2023—more than 8 months after the conclusion of the performance period.

Prior to August 2023, there had been no information about this category since 2020 based on 2019 performance when only a few episode-based cost measures and the now-retired versions of the Total Per Capita Cost and Medicare Spending Per Beneficiary were in use.

Last fall, the American Medical Association, of which ASN is a member, strongly urged CMS to extend the targeted review or appeal deadline of October 9, 2023, and also to allow physicians to apply for a COVID-19 Extreme and Uncontrollable Circumstances (EUC) hardship exception. CMS declined to extend the deadline or allow EUC applications to be submitted during this time; however, ASN continues to urge CMS to reweight the 2022 cost performance category to zero to minimize the penalties that some physicians will experience this year.

ASN will continue to monitor this situation. Please feel free to share your concerns or experiences with ASN at policy@asn-online.org. ■

*David L. White is the regulatory and quality officer at ASN.*

# Banff Working Group Defines Pathologic Diagnostic Criteria for Thrombotic Microangiopathy in the Renal Allograft

By Rose Mary Attieh, Rimda Wanchoo, and Anuja Java

Thrombotic microangiopathy (TMA) is a clinicopathologic entity characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury occurring due to endothelial damage and microthrombi formation in small vessels. Kidney transplantation poses a challenging setting due to multiple potential triggers or mimickers (drugs, infections, and/or immunological factors) of TMA. Prompt recognition and timely treatment are critical to prevent allograft loss.

Post-transplant TMA (Tx-TMA) can be recurrent or de novo. Although recurrent TMA is almost always complement-mediated, de novo Tx-TMA may be complement-mediated or secondary to one of the above triggers. To overcome the challenges of a clinical diagnosis in the presence of multiple triggers, a kidney transplant biopsy is sometimes performed to establish a more definitive diagnosis. Moreover, de novo TMA can often be renal-limited and only identified on a biopsy. Histologically, the hallmark finding of TMA is the presence of thrombi, which can affect glomerular capillaries, arterioles, or arteries, although the absence of thrombi may be due to a sampling issue and should not lead to the exclusion of a TMA diagnosis. Similarly, there are a multitude of other histological parameters that vary in extent and frequency and rely on the interpretation by the pathologist.

To address this issue and standardize the histological diagnostic criteria, the TMA Banff Working Group convened a panel of 23 expert nephropathologists and used a modified Delphi method (1). Delphi is a structured process that involves a series of rounds during which an expert panel shares its opinion on specific questions with controlled feedback from a facilitator. The panelists remain anonymous during surveys to ensure that their interactions remain unbiased. The process continues through multiple iterations until a reliable consensus is reached. This method does not require a physical meeting for the participants, and all interactions are designed to be online (2). Out of the 338 diagnostic criteria initially proposed, following 9 rounds of deliberation, the panelists reached a consensus on 24 diagnostic criteria, including 18 pathologic, 2 clinical, and 4 laboratory criteria (see those with the highest level of agreement among nephropathologists in Table 1).

The work, undertaken by the TMA Banff Working Group, constitutes a significant step forward in defining the characteristics of Tx-TMA. The authors note the first-time use of Delphi method for Banff classification. Other strengths of the study include use of real-world clinical cases in an attempt to establish differential diagnoses and define acute and chronic features. A major challenge, however, was the lack of consensus on whether antibody-mediated rejection is a trigger or mimicker or falls in the spectrum of TMA differential diagnosis. The authors acknowledge this as an area of controversy and note that a follow-up study that will seek consensus among nephrologists is ongoing to help clarify this conflict and to further refine the laboratory and clinical criteria that may be specific for Tx-TMA.

This study was focused on establishing uniform diagnostic criteria for Tx-TMA, since the authors point out several differences in TMA between native and transplanted kidneys. However, it is important to note that TMA can occur as a manifestation of a systemic disease (such as complement-mediated TMA or lupus) in both the native kidney and after a transplant. Tx-TMA can manifest signs of systemic hemolysis, and TMA in the native kidney is not always a manifestation of a single disease (3). Therefore, the results may also be largely applied to the native kidney. Other minor aspects that need further clarification include the use of terms "acquired HUS [hemolytic uremic syndrome]" and "donor-related TMA," as acquired HUS may refer to complement-mediated TMA from acquired factors (such as factor H autoantibodies). Personal communication between the authors and panelists (A.J. with M. Afrouzian) helped to clarify that donor-related TMA refers to donor-derived, renal-limited TMA seen in the allograft, particularly when the kidney is procured from donors who died of head trauma or had a history of cocaine or other drug use. Such patients may present with delayed graft function, and biopsy performed in the first 1 to 4 weeks after transplant demonstrates a TMA.

Overall, the TMA Banff Working Group should be applauded for this massive undertaking and its efforts to address critical knowledge gaps in this evolving area. Perhaps the use of newer pathology tools, such as digital and computational pathology, or spatial transcriptomics will be helpful in achieving this goal in the near future. Meanwhile, results from the follow-up study are enthusiastically anticipated. ■

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Drs. Attieh and Wanchoo report no conflicts of interest. Dr. Java serves on the scientific advisory boards for Alexion, AstraZeneca Rare Disease, and Novartis Pharmaceuticals and also serves as a consultant for Aurinia Pharmaceuticals and Dianthus Therapeutics.

**References**

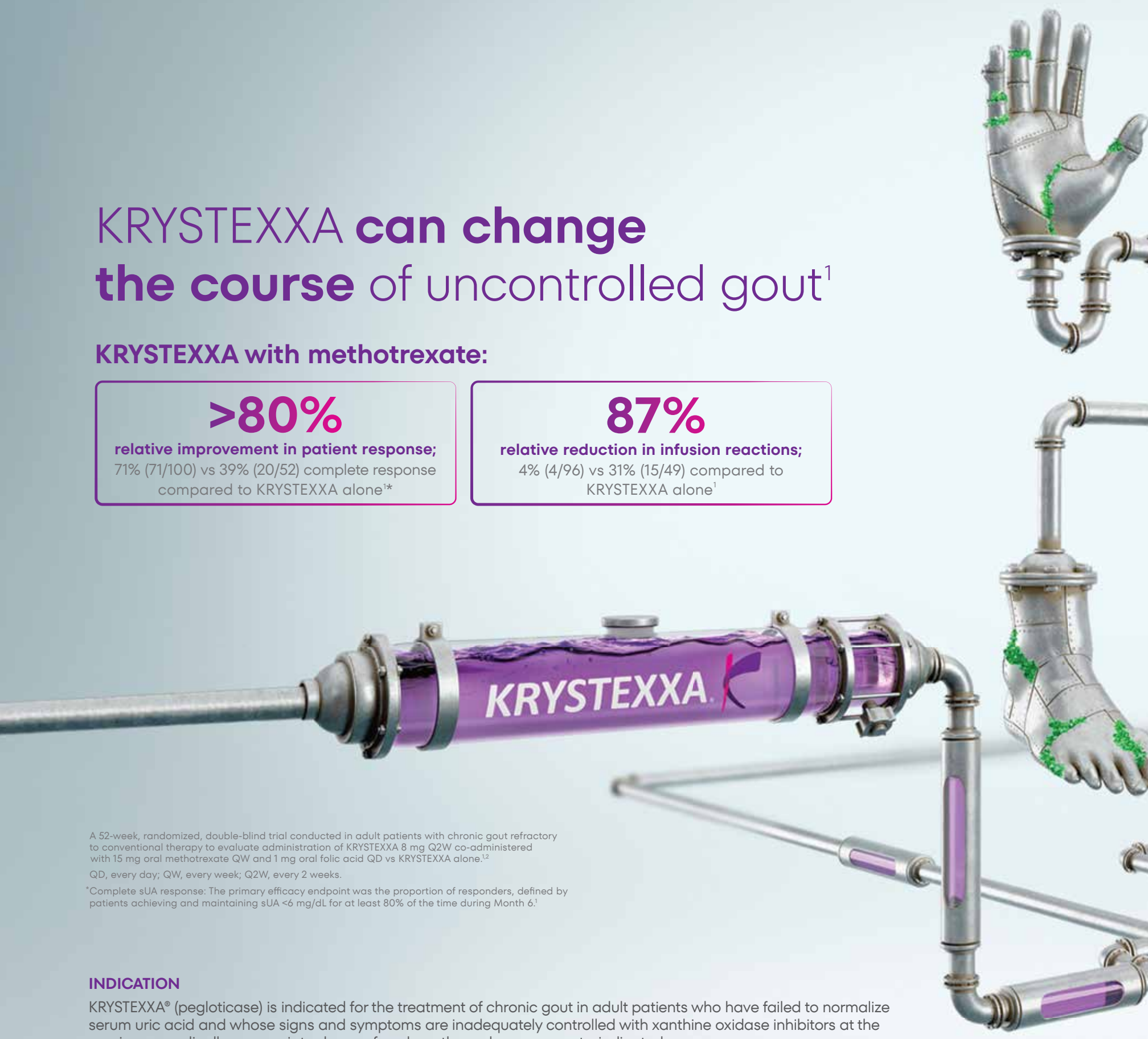
1. Afrouzian M, et al. Corrigendum: Thrombotic microangiopathy in the renal allograft: Results of the TMA Banff Working Group consensus on pathologic diagnostic criteria. *Transpl Int* 2023; 36:12047. doi: 10.3389/ti.2023.12047
2. Dalkey, N. An experimental study of group opinion: The Delphi method. *Futures* 1969; 1:408–426. doi: 10.1016/s0016-3287(69)80025-x
3. Ren Z, et al. Clinicopathologic implications of complement genetic variants in kidney transplantation. *Front Med* (*Lausanne*) 2021; 8:775280. doi: 10.3389/fmed.2021.775280

**Table 1. Diagnostic criteria and differential diagnoses with the highest level of agreement among nephropathologists**

| | |
|---|---|
| **Pathologic criteria** | Light microscopy:<br>• Fibrin thrombi in arterioles/small arteries or glomerular capillaries<br>• Arterial or arteriolar intimal edema/mucoid changes<br>• Mesangiolysis<br>• Glomerular endothelial swelling<br><br>Immunofluorescence:<br>• Glomerular intraluminal staining with fibrin-related antigens<br><br>Electron microscopy:<br>• Subendothelial widening/rarefaction with accumulation of "fluff"<br>• Fibrin tactoids in the lumen/widened subendothelial space<br>• Glomerular endothelial swelling with loss of fenestration<br>• Glomerular basement membrane duplication/lamination/multilayering with mesangial interposition |
| **Clinical criteria** | • History of pre-eclampsia/eclampsia or HELLP syndrome during pregnancy or postpartum<br>• Prior history of TMA/HUS/aHUS/TTP |
| **Laboratory criteria** | • Elevated LDH<br>• Reduced haptoglobin<br>• Worsening anemia<br>• Thrombocytopenia |
| **Differential diagnoses** | • TTP<br>• Acquired HUS<br>• aHUS<br>• Donor-related TMA<br>• Chronic transplant glomerulopathy<br>• Antibody-mediated rejection |

aHUS, atypical HUS; HELLP, hemolysis, elevated liver enzymes, and low platelets; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

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




## KRYSTEXXA with methotrexate:

**>80%**
**relative improvement in patient response;**
71% (71/100) vs 39% (20/52) complete response compared to KRYSTEXXA alone[1]*

**87%**
**relative reduction in infusion reactions;**
4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]

A 52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1,2]

QD, every day; QW, every week; Q2W, every 2 weeks.

*Complete sUA response: 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]

## 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.

**Dissolve years of urate deposition[3]**
**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 J, et al. *J Clin Rheumatol*. 2022;28:e129-e134. **3.** Data on File. Horizon, March 2022.

HORIZON.



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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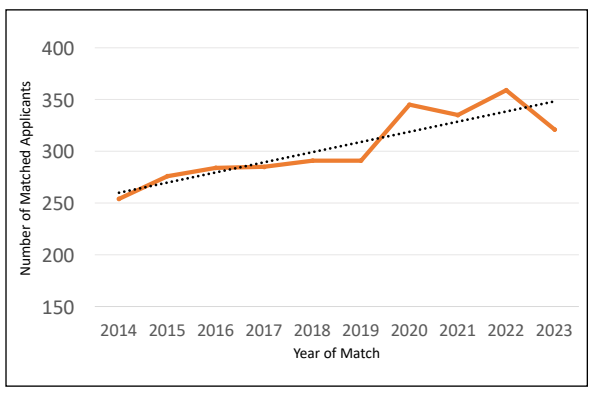
# Moving Forward: Innovation in Science and Continuing to Foster Interest in Nephrology

By Kenar D. Jhaveri and Matthew A. Sparks

The year 2023 continued to be optimistic for nephrology. We witnessed exciting advances in our field: Treatment options for immunoglobulin A (IgA) nephropathy are increasing, with the US Food and Drug Administration (FDA) granting accelerated pathway approval of endothelin antagonists and budesonide (1). In 2024, we may see inhibitors of complement (2) and anti-APRIL (a proliferation-inducing ligand) inhibitors emerging (3) for the treatment of IgA nephropathy. We are starting to see the four pillars of care for patients with diabetes and chronic kidney disease (CKD) treatment come to fruition, and we may finally see a major decline in the incidence of kidney failure (4). In the field of hypertension, aldosterone synthase inhibitors are emerging as potential therapeutic options (5), along with FDA approval of renal denervation (6). Lupus nephritis treatments are on the rise, and we may see more to come in 2024 as obinutuzumab may make a big splash (7). Finally, kidney xenotransplantation continues to take steps forward (8). This year will be remembered for nephrology.

In November 2023, Match Day for nephrology fellowships arrived, and the trend of unfilled positions in the United States persisted (9). However, although the number of applicants is down compared with the last few years, the trend has continued to rise over the past 10 years (Figure 1). Recruitment to a field is a long game, and we will see ebbs and flows from year to year. It is important that we keep pushing to innovate and improve advances in kidney care and how we deliver this care. As devoted nephrologists who are passionate about our field, how can we continue to push the envelope?

**Figure 1. Trend in nephrology fellowships based on matched applicants**




Number of matched applicants from 2014 to 2023. Solid line, numbers of matched applicants; dotted line, trend. Data are from the National Resident Matching Program.

The field of nephrology continues to be filled with excitement. CKD care is seeing novel treatments, and glomerular disease randomized clinical trials are rising. The Kidney Health Initiative has led to a new, accelerated drug-approval pathway by the FDA. It has already resulted in novel drugs in the hands of prescribers. Which aspects of nephrology should we continue advocating for?

Approximately a decade ago, we completed a survey of 714 fellows across all disciplines of internal medicine, except nephrology, about why they did not choose nephrology. This survey revealed some eye-opening findings (10). Of the respondents, 31% indicated that nephrology was the most difficult physiology course taught in medical school, and 26% considered nephrology a career choice. Nearly one-fourth of the respondents said they would have considered nephrology if the field generated higher incomes or if the subject was taught more thoroughly during medical school and residency. The top reasons for not choosing nephrology were the belief that patients with end stage kidney disease were too complicated, the lack of a mentor, and insufficient procedures in nephrology. Have those factors changed now with the current applicant pool? There is a perception that demand for non-procedural fields like endocrinology and rheumatology is greater than nephrology.

In 2023, the matching process for medical specialties saw different levels of applicant success: Endocrinology accepted 350 fellows; infectious disease, 303; and rheumatology, 273, whereas nephrology filled 321 positions. Endocrinology and rheumatology have lower total spots than nephrology. Although not all nephrology fellowship spots are filled during the match, most are filled post-match. This situation may be undesirable for both the program and the candidates.

Are patients with kidney diseases too complex? A study from Canada confirmed our assumption (11). This study was a population-based retrospective cohort study of 2,597,127 residents of the Canadian province of Alberta, aged 18 years or older, with at least one physician visit in 2014 through 2015. Data were analyzed in September 2018. When types of physicians were ranked according to patient complexity across all nine markers, the order from most to least complex was nephrologist, infectious disease, neurologist, pulmonologist, hematologist, rheumatologist, gastroenterologist, cardiologist, general internist, endocrinologist, allergist/immunologist, dermatologist, and family physician. Regarding the mean number of comorbid conditions that a specialist treats, nephrologists were the highest followed by infectious diseases physicians. More often, nephrologists (followed by infectious disease physicians and neurologists) supported patients with chronic conditions, often involving emotional concerns—not a surprise to most of us. Nephrologists also treated patients who were prescribed the most medications (not just by nephrologists but by all of their treating physicians). As a result, medication discrepancies are not uncommon in patients with kidney diseases. Most patients who were referred to renal specialists were also more often treated by other physicians, a close second to those treated by infectious diseases specialists. Strikingly, nephrology also included patients with the highest mortality (significantly higher than in other fields). What is more important is not where nephrologists stand in the ranking but that there is such a wide variation in the degree of complexity of patients with kidney diseases compared with those in other specialties. As the authors suggest, this impacts educational and health policy.

Complexity and curiosity drove us to nephrology, but for some physicians exploring the field, it might push them away. In addition, physician or facility reimbursement in the United States does not reflect the complexity of the patient. There is no question that patient complexity requires time (including the time required to communicate with multiple other physicians), expertise, and resources to optimize management. However, reimbursement of physicians and facilities in the United States is most commonly based on fee-for-service compensation. The complexity of medical decision-making is addressed by assessing the number of diagnoses and management options considered, the medical risks, and the amount of data to be reviewed. Adjusting payments to encourage physicians to spend more time and resources caring for patients at the highest risk of complications makes sense from a health care payer's perspective. However, how do nephrologists do this and discourage those who may take advantage of the system by overbilling? This reimbursement dilemma is crucial in nephrology, given the declining interest in this field. Changes in reimbursement could potentially reverse this trend.

Nephrologists are at the center of a complex field of medicine, with high regard from many medical disciplines, and should take pride in this. As a result, improvements in negotiations with policymakers who decide dollar amounts for work relative value units (wRVUs) should be initiated. According to a recent study, compensation rates assumed in wRVU valuations are small contributors to differences in physician compensation (12). It is actually the factors outside of the wRVU system, such as payer mix and work hours, that can be targeted if narrowing the difference in compensation across specialties is desired. The commonly used benchmarking surveys do not capture the essence of the work done by a nephrologist and join the call for national nephrology societies to lead efforts to clarify the scope of the problem and identify the non-patient encounter activities for which value has yet to be recognized. We need to educate the payers that complexity takes time, and treating patients with complex conditions is equally as hard as undertaking an interventional procedure. As mentioned in a 2021 *Kidney News* issue (13), a survey of patient care activities occurring outside of patient encounters would be of tremendous benefit to the nephrology community and provide a more realistic basis for applying wRVU targets. This would provide both academic and private nephrology practices with benchmarks and points of comparison through which value for currently uncompensated work could be determined. Meanwhile, we may consider other ideas to overhaul and adapt the field of nephrology to the new generation of learners and physicians.

**Table 1. Potential ideas to change the way we view nephrology**

| | |
|---|---|
| 1 | Compensation restructuring to value outpatient nephrology and subspecialities of nephrology (glomerulonephritis, onconephrology, stone disease, cardionephrology, etc.), similar to inpatient and dialysis, is essential. |
| 2 | Split nephrologists to perform only inpatient or outpatient treatment to enhance work–life balance. |
| 3 | Cultivate more co-existence of advanced practitioner-based care with fellowship and fellowship training-related activities. |
| 4 | The average wRVU rate needs to increase for nephrology and transplantation so it is comparable to perhaps an intensive unit level of care to allow for better compensation. |
| 5 | New models of fellowship training should be instituted—combined 4 years of internal medicine and nephrology as an example. |
| 6 | Most practices need to ensure lifestyle changes are implemented in their schedules: on-call, number of weeks in the hospital, and splitting of inpatient and outpatient weeks (minimizing "windshield" time). |
| 7 | Infusion centers should be owned by nephrologists, as new therapies continue to evolve to allow for more control of infusions for large practices and academic centers. |

We need to identify what the true problem is. Repeating the original survey of non-nephrology fellows (10) after 10 years may help identify current obstacles before we consider drastic changes.

What can we do in 2024 to improve nephrology? Table 1 discusses some potential ideas, and we welcome other potential ways to improve and move nephrology forward. Let's start a dialogue to change nephrology for the better and improve our patients' and practitioners' lives. ■

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**References**

1. Noor SM, et al. IgA nephropathy: A review of existing and emerging therapies. *Front Nephrol* 2023; 3:1175088. doi: 10.3389/fneph.2023.1175088
2. Rizk DV, et al. Targeting the alternative complement pathway with iptacopan to treat IgA nephropathy: Design and rationale of the APPLAUSE-IgAN study. *Kidney Int Rep* 2023; 8:968–979. doi: 10.1016/j.ekir.2023.01.041
3. Mathur M, et al.; ENVISION Trial Investigators Group. A phase 2 trial of sibeprenlimab in patients with IgA nephropathy. *N Engl J Med* (published online November 2, 2023). doi: 10.1056/NEJMoa2305635
4. Agarwal R, Fouque D. The foundation and the four pillars of treatment for cardiorenal protection in people with chronic kidney disease and type 2 diabetes. *Nephrol Dial Transplant* 2023; 38:253–257. doi: 10.1093/ndt/gfac331
5. Mullen N, et al. Treating primary aldosteronism-induced hypertension: Novel approaches and future outlooks. *Endocr Rev* (published online August 9, 2023). doi: 10.1210/endrev/bnad026
6. Schaffer R. FDA approves first renal denervation device to treat hypertension. *Cardiology Today*, Healio. November 8, 2023. https://www.healio.com/news/cardiac-vascular-intervention/20231108/fda-approves-first-renal-denervation-device-to-treat-hypertension
7. Furie RA, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: A randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2022; 81:100–107. doi: 10.1136/annrheumdis-2021-220920
8. Montgomery RA, et al. Results of two cases of pig-to-human kidney xenotransplantation. *N Engl J Med* 2022; 386:1889–1898. doi: 10.1056/NEJMoa2120238
9. Pivert KA. First look: AY 2024 match. ASN Data. November 29, 2023. https://data.asn-online.org/posts/ay_2024_match/
10. Jhaveri KD, et al. Why not nephrology? A survey of US internal medicine subspecialty fellows. *Am J Kidney Dis* 2013; 61:540–546. doi: 10.1053/j.ajkd.2012.10.025
11. Tonelli M, et al. Comparison of the complexity of patients seen by different medical subspecialists in a universal health care system. *JAMA Netw Open* 2018; 1:e184852. doi: 10.1001/jamanetworkopen.2018.4852
12. Childers CP, Maggard-Gibbons M. Assessment of the contribution of the work relative value unit scale to differences in physician compensation across medical and surgical specialties. *JAMA Surg* 2020; 155:493–501. doi: 10.1001/jamasurg.2020.0422
13. Pflederer TA. Nephrologists' value exceeds RVU calculations. *Kidney News*, September 2021; 13(9):19. https://www.kidneynews.org/view/journals/kidney-news/13/9/article-p19_8.xml

# Emerging Trends in Onconephrology: 2024 Edition

By Paul E. Hanna and Prakash Gudsoorkar

In the ever-evolving field of onconephrology, 2024 should witness some notable emerging trends that may hold promise for kidney function assessment in patients with cancer and mitigating drug-induced injury.

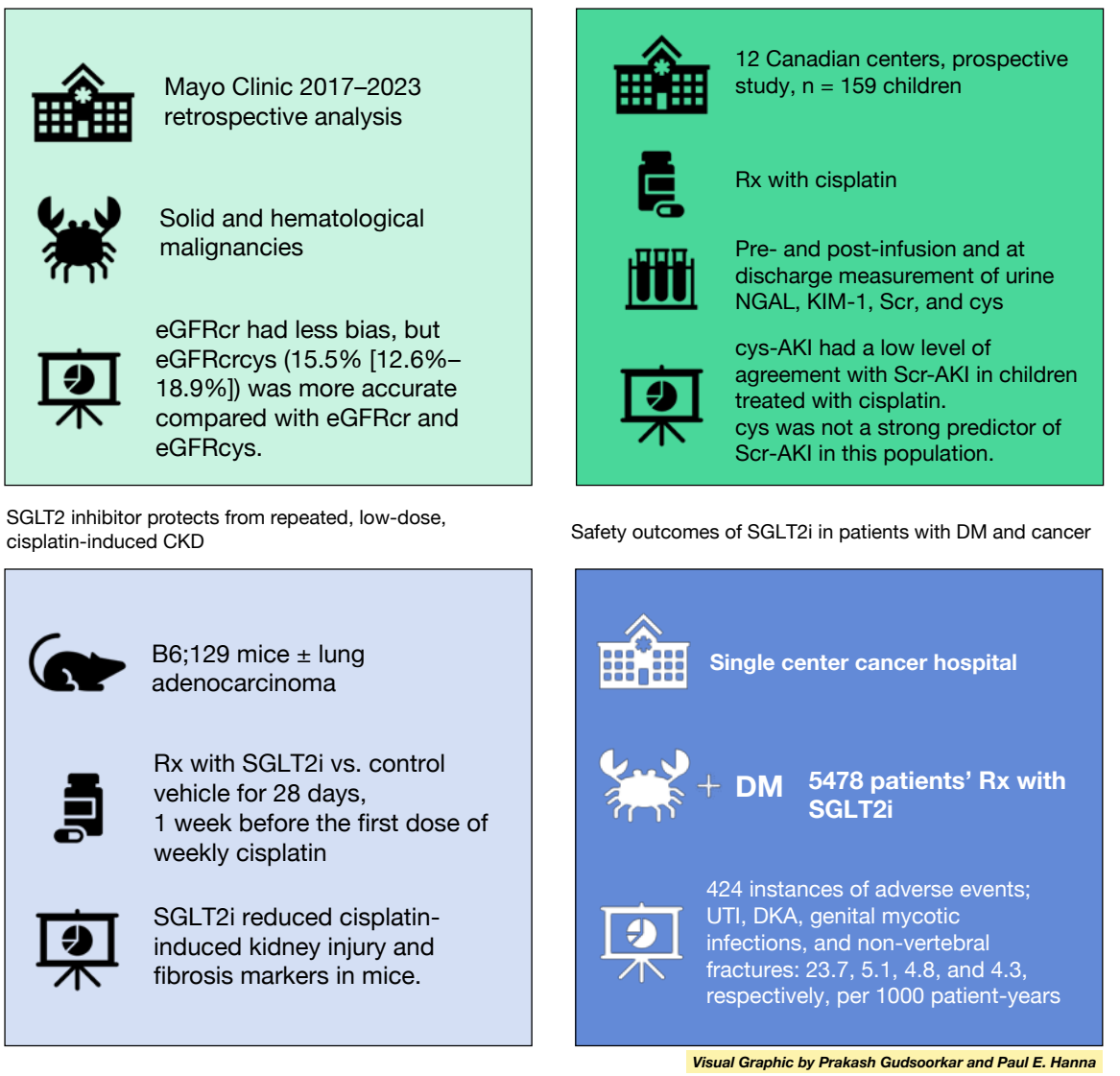
## The role of cystatin C in eGFR

Accurate evaluation of kidney function in patients with cancer is crucial, as it can significantly impact decisions regarding the initiation or discontinuation of advanced therapies, including chemotherapy and immunotherapy. Recent trends, as highlighted in the oral onconephrology presentations at Kidney Week 2023, indicate a notable shift toward incorporating cystatin C (cys) for estimated glomerular filtration rates (eGFRs) in patients with cancer. This approach, reflected in two significant abstracts (1, 2), underscores the importance of establishing baseline kidney function and defining acute kidney injury (AKI) in this vulnerable population.

The first abstract explores the performance of creatinine (cr)-based eGFR equations in patients with malignancy, revealing potential limitations compared with the general population (1). The study, conducted retrospectively at the Mayo Clinic from 2017 to 2023, involved patients with neoplasia, excluding in situ and benign lesions. The analysis incorporated a urinary iothalamate clearance measured GFR (mGFR) and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes for neoplasia up to 1 year prior to the mGFR date. Results demonstrated that median bias aligned with existing literature among 3719 patients with eGFR based on cr alone. However, among the subset of 522 patients with both cr and cys measurements, eGFRcrcys exhibited superior accuracy (15.5%) compared with eGFRcr (26.7%) and eGFRcys (25.5%). This improvement was consistent across different cancer types. The study concludes that, particularly in patients with solid or hematological malignancies, the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) eGFRcrcys better reflects mGFR, suggesting its potential superiority for clinical decision-making.

The second abstract focuses on cisplatin-induced AKI in children, aiming to detect and mitigate AKI early to prevent long-term consequences (2). Serum cys was investigated as a potential, early biomarker compared with serum cr, particularly as it is largely unaffected by muscle mass. The prospective study involving 159 children treated with cisplatin reveals

*Continued on page 20* >




DM, diabetes mellitus; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin; Scr, serum cr; SGLT2i, SGLT2 inhibitor; UTI, urinary tract infection.

# Emerging Trends in Onconephrology

*Continued from page 19*

that cys-AKI and serum cr-AKI had only an 83% agreement, indicating a low level of concordance between the two definitions. Furthermore, cys was not a strong predictor of serum cr-AKI in this pediatric population. The study suggests the need for future investigations with more measurement time points to ascertain whether the observed differences result from the earlier rise of cys compared with cr.

## SGLT2 inhibitors in drug-induced AKI

Other significant presentations at Kidney Week 2023 have shone a spotlight on the potential for sodium-glucose cotransporter-2 (SGLT2) inhibitors to ameliorate the side-effects of cisplatin chemotherapy on the kidney, a notorious cause of AKI that afflicts approximately one-third of recipients and often progresses to CKD. Given the absence of US Food and Drug Administration-approved preventative treatments for drug-induced kidney damage, the findings could herald a new era in onconephrology.

In a mouse model designed to replicate clinical conditions—repeated low-dose cisplatin administration in the presence of lung adenocarcinoma—daily treatment with SGLT2 inhibitors, specifically empagliflozin or dapagliflozin, was initiated 1 week before the first cisplatin dose and continued for 28 days (3). The results were promising: SGLT2 inhibitors mitigated the alterations in kidney function and injury typically induced by cisplatin. Markers of kidney fibrosis, such as transforming growth factor-β, α-smooth muscle actin, fibronectin, and collagen, were notably reduced in the treatment group versus the control without any adverse impact on tumor growth or cisplatin response.

These preclinical findings, however, must be juxtaposed with real-world clinical data to appreciate the full scope of the impact of SGLT2 inhibitors. In a retrospective analysis of 5478 patients with diabetes and cancer, those prescribed SGLT2 inhibitors experienced higher rates of adverse events (4). The cohort accumulated 11,175 patient-years on these medications, within which 424 adverse events were documented, translating to a higher-than-expected incidence of diabetic ketoacidosis (DKA) at 5.1 per 1000 patient-years—surpassing the 0–2.2 range reported in recent meta-analyses and observational studies. Rates of urinary tract infections, genital mycotic infections, and non-vertebral fractures were also elevated.

The dichotomy of these findings underscores the complexity of translating promising animal model results into clinical practice, particularly for a patient population that has been historically excluded from large clinical trials due to their cancer diagnosis. While the renoprotective effects observed in the mouse model are undeniably significant, the higher incidence of adverse events in the human study prompts a reassessment of the risk-benefit ratio for SGLT2 inhibitor use in oncologic settings.

As we stand on the cusp of potentially integrating SGLT2 inhibitors into the therapeutic regimen for patients with cancer at risk of cisplatin-induced AKI, these studies collectively advocate for a tempered approach. They call for rigorous clinical trials to elucidate the safety and efficacy of SGLT2 inhibitors in this unique cohort, emphasizing vigilant monitoring for adverse events. Only with such due diligence can we protect our patients' kidney health without compromising their oncological outcomes.

In conclusion, these emerging trends in onconephrology for 2024 could show potential in evaluating kidney function in individuals with cancer and reducing injury caused by drug administration. The integration of cys in eGFR holds promise but requires further refinement, whereas the potential use of SGLT2 inhibitors demands cautious exploration through rigorous clinical trials. As the field progresses, a balanced approach that considers both the advancements and challenges will be pivotal for improving outcomes in patients with cancer and related adverse effects on the kidney. ■

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The authors report no conflicts of interest.

**References**

1. Titan S, et al. Performance of creatinine and cystatin C-based equations among patients with hematological or solid cancers: Real-world data from a clinical cohort [Abstract]. *J Am Soc Nephrol* 2023; 34:28. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3944821
2. Hessey E, et al. Cystatin C-defined AKI in children treated with cisplatin [Abstract]. *J Am Soc Nephrol* 2023; 34:29. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3938500
3. Sanchez Vega D, et al. SGLT2 inhibitor protects from repeated low-dose cisplatin-induced chronic kidney damage [Abstract]. *J Am Soc Nephrol* 2023; 34:29. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3946126
4. Shaikh A, et al. Safety outcomes of sodium-glucose cotransporter-2 inhibitors in patients with diabetes mellitus and cancer [Abstract]. *J Am Soc Nephrol* 2023; 34:31. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3940988

# The Future of Acute Kidney Injury Research: Key Trends in 2024

By Jia H. Ng

Acute kidney injury (AKI) is a critical health issue globally. Heading into 2024, research in this field offers promising avenues for understanding and managing AKI. This article outlines three key research areas set to advance AKI knowledge and treatment.

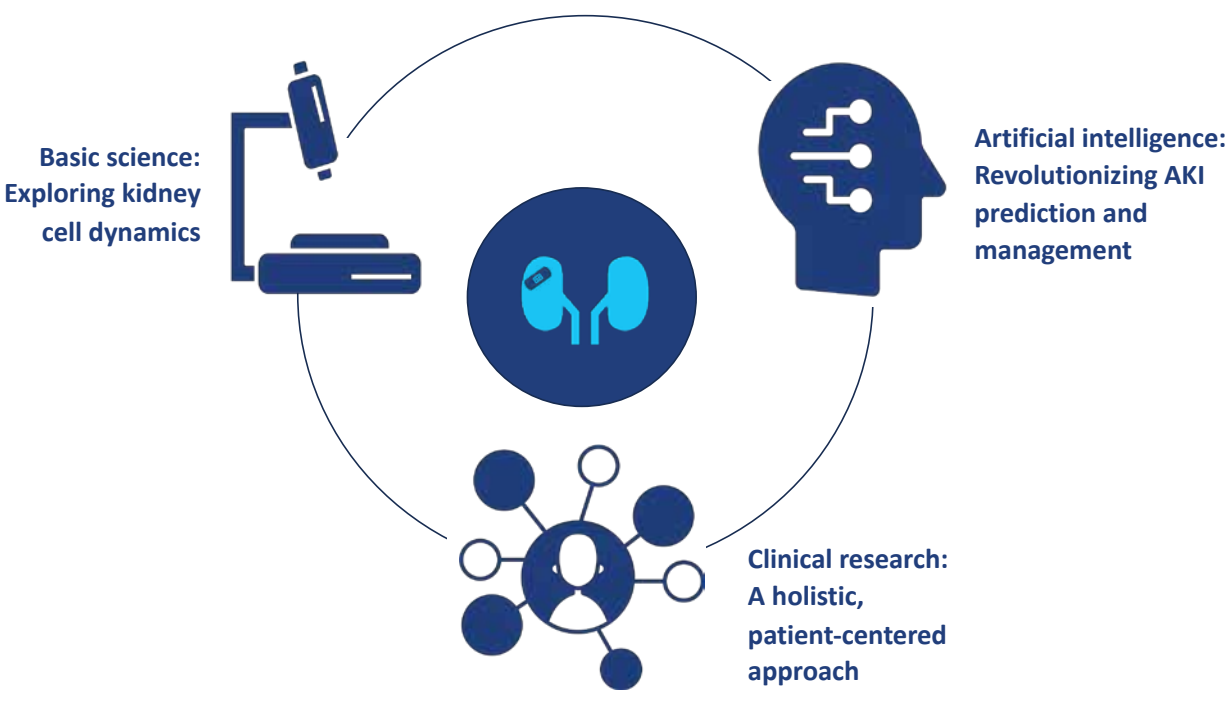
## Basic science: Exploring kidney cell dynamics

In 2024, scientists are focusing on the cellular and molecular dynamics of kidney cell death and recovery (1–4). Breakthroughs in this domain could revolutionize how we approach AKI treatment. Key focuses include kidney fibrosis and the processes of adaptive repair and maladaptive repair—the body's response to AKI. These insights have the potential for groundbreaking treatments that prevent cell death or enhance repair post-injury.

## Artificial intelligence: Revolutionizing AKI prediction and management

Building on the work presented at ASN Kidney Week 2023, artificial intelligence (AI) and machine learning are redefining AKI research (5–7). We saw researchers developing predictive models through different stages of AKI, from detecting AKI to managing AKI. Specific examples include models that are designed to identify high-risk individuals early, complex algorithms for analyzing vast data sets, personalized diuretic strategies, dynamic risk assessment, and AI-guided dosing in AKI treatment. Such advancements could lead to earlier interventions, reducing AKI severity or preventing it.

**Figure 1. AKI research: What to watch for in 2024**



## Clinical research: A holistic, patient-centered approach

Current AKI research is adopting a holistic, patient-centered perspective, focusing on physical, emotional, and cognitive impacts (8). This approach recognizes AKI's broader effects on quality of life and explores interventions targeting the entire health spectrum of patients. A significant study in this domain is the IMPROVE AKI Cluster-Randomized Trial (9), which investigated the sustainability of team-based coaching in patient care. The AKINow Recovery Workgroup (https://epc.asn-online.org/projects/akinow/akinow-recovery-post-aki-workgroup/) is working on projects to improve post-AKI transition of care.

AKI research in 2024 will span basic science, AI, and clinical research (Figure 1). This synergy will result in more effective prevention and treatment strategies, improving outcomes for patients with AKI. ■

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The author reports no conflicts of interest.

**References**


1. American Society of Nephrology. ASN Kidney Week 2023 On-Demand. Developments in AKI and repair mechanisms. November 2, 2023. Available for purchase via https://education.asn-online.org/local/catalog/view/product.php?productid=118
2. Cao S, et al. The epidermal growth factor receptor is an essential mediator of interstitial fibrosis development following AKI [Abstract]. *J Am Soc Nephrol* 2023; 34:1. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3939238
3. Li C, Anders HJ. Differential roles of Regnase3 in resident macrophages vs. renal tubular epithelial cells in kidney injury [Abstract]. *J Am Soc Nephrol* 2023; 34:2. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3937469
4. Chen Y, et al. Novel anti-inflammatory effects of IL-1 receptor in kidney myeloid cells following AKI [Abstract]. *J Am Soc Nephrol* 2023; 34:2. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3941800
5. American Society of Nephrology. ASN Kidney Week 2023 On-Demand. Artificial intelligence and its promise to complement AKI care. November 2, 2023. Available for purchase via https://education.asn-online.org/local/catalog/view/product.php?productid=118
6. Griffin BR, et al. Use of a recurrent neural network to predict development of nephrotoxic AKI in adults [Abstract]. *J Am Soc Nephrol* 2023; 34:30. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3945632
7. Oh W, et al. Machine learning-guided novel subphenotypes of sepsis-associated persistent AKI [Abstract]. *J Am Soc Nephrol* 2023; 34:30. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3945752
8. Bhatraju PK, et al. AKI is associated with long-term decline in cognitive function at 3 years: ASSESS-AKI study [Abstract]. *J Am Soc Nephrol* 2023; 34:29. https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3940530
9. Brown JR, et al. Team-based coaching intervention to improve contrast-associated acute kidney injury: A cluster-randomized trial. *Clin J Am Soc Nephrol* 2023; 18:315–326. doi: 10.2215/CJN.0000000000000067


# A Different RTA Causing Headaches for Nephrologists in Value-Based Care

By Katherine Kwon

As 2023 wound to a close, nephrologists and their value-based care partners participating in the Comprehensive Kidney Care Contracting (CKCC) model found themselves anxiously awaiting an announcement from the Center for Medicare and Medicaid Innovation (CMMI) about the Retrospective Trend Adjustment (RTA). Having set their budgets well over 1 year ago, based on their population's benchmark cost of care, nephrologists may find their margins significantly smaller than anticipated. This could turn an expected profit into a loss, and since the CKCC is a multi-year model, participants could choose to exit if they do not see a path to financial success.

A value-based care program starts with the assumption that Medicare can project how much it expects to spend for a given patient, based on a patient's past claims. This estimate forms the benchmark for a CKCC model's patient population. If the CKCC can deliver care for less than the benchmark, while preserving clinical quality, CKCC partners can keep a portion of the savings that they generated. They also need to cover their operating expenses from their savings share—the salaries and infrastructure investments that are not directly compensated by claims. Shared savings are delivered approximately 10 months after year's close, so the CKCC partners must invest capital for many months in anticipation of receiving shared savings.

The CKCC benchmark was set based on claims from 2017 to 2019. To account for market changes between then and 2022, the first year of the CKCC model, the Centers for Medicare & Medicaid Services (CMS) used the US per capita cost model to forecast changes in health care expenditures. However, if the forecast is inaccurate, the benchmark may be set either too high or too low. To cover this possibility, there is a look back after the end of each model year. This look back is the RTA, which compares the actual cost of care with the predicted cost of care (Figure 1).

Health care expenditures for 2022 came in lower than forecasted, so the RTA is expected to reduce the benchmark. This shrinks the margin of performance and reduces the money available as shared savings. It is a hard pill to swallow alongside the rising costs of labor and capital financing that have been a challenge over the past year.

Large swings in the performance margin make it more difficult to succeed financially in CKCC. CMMI is charged with developing new payment models that reduce costs to taxpayers while preserving health care quality. However, since many doctors operate in a for-profit environment, the payment models must also be viable from a business standpoint. CKCC is nephrology's second attempt to execute value-based care addressing the unique needs of our patient population. Hopefully, we can partner with the CMMI to develop a better way to care for people living with kidney diseases. ■

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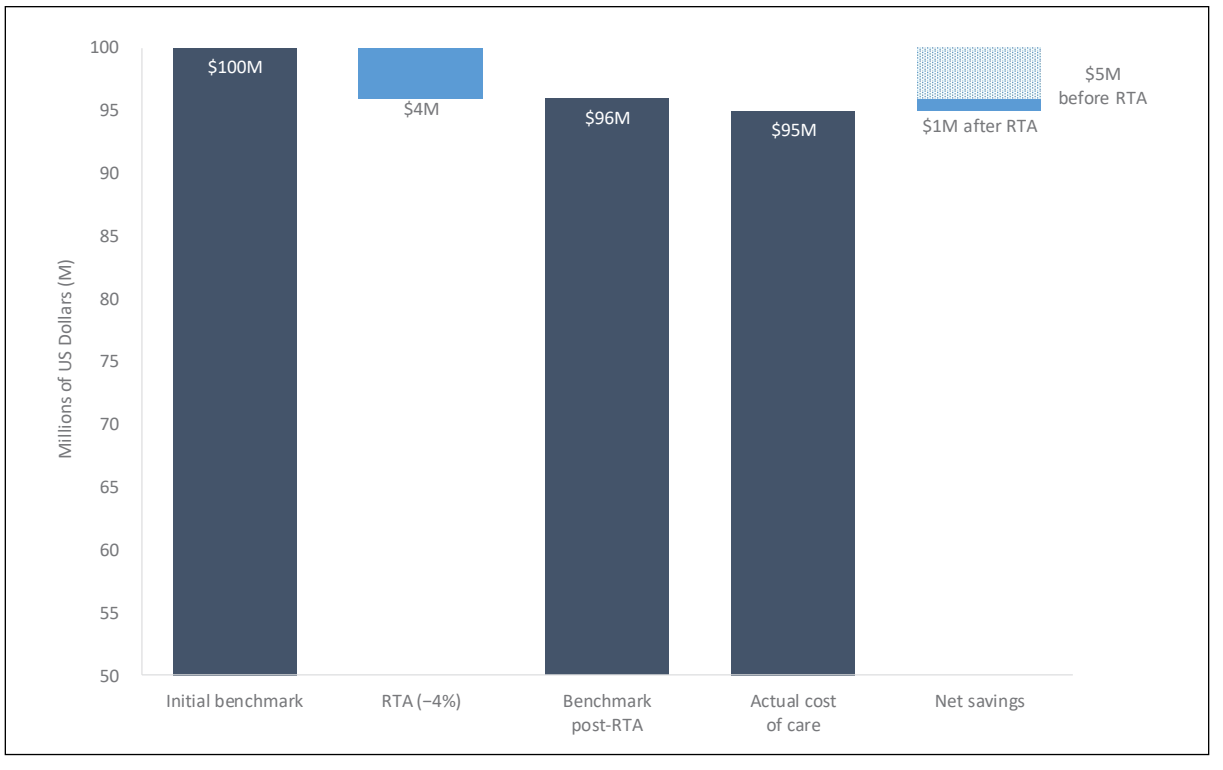
Opinions expressed in this article are those of Dr. Kwon alone.

**Figure 1. Shared savings fall by 80% following RTA**




In an example scenario under the CKCC model in which the initial benchmark is $100 million, the RTA results in an adjustment of a 4% decrease from the initial benchmark. Before RTA, shared net savings are $5 million. Following RTA, savings are $1 million, an 80% reduction. CKCC partners are subject to a quality withhold based on their performance on the quality measures, a portion or all of which can be earned back. The quality withhold and earn-back have been omitted from this chart for simplicity.

# The Steady Beat: Maintaining Nephrology's March toward Kidney Health Equity

By Ray Bignall

The last several years have seen efforts to advance health equity surge in popularity and attention. Across the United States, governments, corporations, and health care institutions have pledged their support to initiatives aimed at eliminating disparities in health outcomes and improving access to care, especially for historically marginalized and vulnerable populations. This focus took on a fierce urgency following the murder of George Floyd, the Movement for Black Lives, and the COVID-19 pandemic, which seemed to galvanize international attention on the matter. The kidney health community has led the way in many of these efforts—both in our progress and in acknowledgement of the work we have yet to do. Even our World Kidney Days have been dedicated to this work, with themes entitled "Kidney Health for All" since 2022 (1).

Time to celebrate? Not so fast! In fact, these nascent kidney health equity efforts have never faced more headwinds than they face today.

Increasingly, kidney health equity efforts must contend with the politics of cultural grievance. Sentiment in many communities against diversity, equity, and inclusion (DEI) has driven more than two dozen states' legislatures to introduce bills that would target efforts to promote equity and diversity at public institutions, including state-affiliated academic hospitals (2). In Texas, the passage of recent laws to eliminate publicly funded DEI offices and to disrupt the delivery of gender-affirming care to youths has left health care practitioners deeply worried about their ability to ensure best outcomes for some of the state's sickest patients (3) and have resulted in institutions struggling to recruit diverse faculty (4). In Florida, passage of laws that overhaul DEI programs and immigration policy have many immigrants fearful to seek care at all (5). The US Supreme Court decision to strike down affirmative action in higher education (6) has likewise left many advocates for an inclusive and excellent kidney health workforce scrambling to adapt existing programming designed to maintain progress in workforce diversity that has resulted in nephrology being one of the most diverse subspecialties in the country (7). In addition to these legislative challenges, the post-pandemic and DEI-related "fatigue," which threatens the organizational resolve to meet the challenges kidney health inequities pose for our patients, is matched only by the threat of complacency in the space, pushing the falsehood that "our work is done."

Now more than ever, the kidney health community must commit itself to advancing equity and justice in kidney care. I propose we commit ourselves to two key areas in 2024:

1. **Diversify the impact:** Initiatives that promote a diverse and inclusive workforce improve the working experience and work product of everyone in the field. Kidney health is advanced when the field is opened to minoritized and marginalized groups, "centering at the margins" the experiences of others. **We should also broaden our appreciation of what diversity means. Remember: Dimensions of diversity are found in everyone.** This may mean racial and ethnic diversity but also includes the experiences of other historically excluded groups, such as LGBTQ folks, women, immigrants, people with disabilities, and people from rural or indigenous communities. As colleagues and kidney health professionals, we all must work together to celebrate our differences and dismantle systems that marginalize some of us because of our differences.
2. **Demonstrate the progress:** A PubMed search of the term "health equity" reveals tens of thousands of articles, with exponential growth in the last decade. However, although most of these articles provide an accounting of health equity challenges and propose potential solutions, fewer are dedicated to documenting progress toward health equity. **If we do not celebrate our health equity success stories, we risk losing the motivation to make more progress!** Successful kidney health equity efforts have enabled the elimination of race in estimating equations for the glomerular filtration rate (8) and have helped to close some pediatric kidney transplant disparities (9). Our field has maintained almost unrivaled workforce diversity (7), and advocacy efforts have led to novel public–private partnerships that champion innovation (10). Let us share these success stories widely in 2024 and challenge ourselves to reach even higher.

I am proud of who I am: a nephrologist, a pediatrician, a Black man in medicine, a first-generation American of immigrant parents, and an advocate for the broad and beautiful spectrum of patients and colleagues with whom I work. In 2024, I am looking forward to us continuing our important work together, championing one another, centering those who have been marginalized, and advancing the field. I hope you are too. ■

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The author reports no conflicts of interest.

**References**

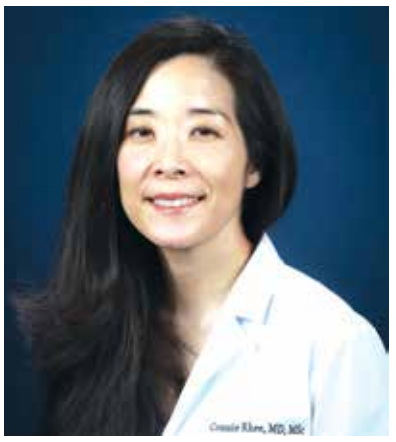
1. World Kidney Day. Kidney health for all. https://www.worldkidneyday.org/2024-campaign/2024-wkd-theme/
2. Bryant J, Appleby C. These states' anti-DEI legislation may impact higher education. Best Colleges. June 21, 2023. https://www.bestcolleges.com/news/anti-dei-legislation-tracker/
3. Gaffney T. Texas wants to wean trans youth off meds in a 'safe and medically appropriate' way. Doctors say that's impossible. *STAT*, May 26, 2023. https://www.statnews.com/2023/05/26/trans-youth-hormones/
4. Dey S. New anti-DEI law for public Texas colleges presents hiring challenges. *The Texas Tribune*, September 22, 2023. https://www.texastribune.org/2023/09/22/texas-universities-chancellors-diversity/
5. Pedersen JM. Undocumented fear: How Florida's new law affects migrants & hospitals. WMFE, August 9, 2023. https://www.wmfe.org/health/2023-08-09/undocumented-fear-how-floridas-new-law-affects-migrants-hospitals
6. Ehrenfeld JM. SCOTUS affirmative action ruling "undermines the health of our nation." American Medical Association. June 29, 2023. https://www.ama-assn.org/press-center/press-releases/scotus-affirmative-action-ruling-undermines-health-our-nation
7. Agarwal A. Nephrology—taking the lead. *Clin J Am Soc Nephrol* 2021; 16:1113–1116. doi: 10.2215/CJN.20061220
8. Inker LA, et al.; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021; 385:1737–1749. doi: 10.1056/NEJMoa2102953
9. Krissberg JR, et al. Racial disparities in pediatric kidney transplantation under the new kidney allocation system in the United States. *Clin J Am Soc Nephrol* 2021; 16:1862-1871. doi: 10.2215/CJN.06740521
10. Fowler KJ, Conway PT. The new HHS Kidney Innovation Accelerator: When innovation stalls, HHS says floor it! *Clin J Am Soc Nephrol* 2018; 13:1747-1749. doi: 10.2215/CJN.04800418

# Rhee Named *CJASN* Editor-in-Chief

By Karen Blum

**Connie Rhee, MD, MSc, assumed the editor-in-chief role for the *Clinical Journal of the American Society of Nephrology* (*CJASN*) this month, becoming the first female editor of one of the most widely read nephrology journals in the United States.**

**Rhee, chief of nephrology at the VA Greater Los Angeles Healthcare System and professor of medicine at the David Geffen School of Medicine at the University of California Los Angeles, served on the journal's editorial board since 2018 and had been an ad hoc reviewer since 2013. She spoke with *Kidney News* (*KN*) about her vision and goals.**



***KN*: What interested you in becoming editor of this journal?**

**Rhee:** Throughout my career, ASN and our kidney community have had a major positive impact in shaping my career in academic nephrology and motivating my path in clinical research. As a trainee, I "grew up" studying and consuming both *CJASN* and the *Journal of the American Society of Nephrology* (*JASN*) and their rich research and clinical content, which served as a critical source of my curriculum as I developed into a physician-scientist and clinical nephrologist.

Over the years, I have served in various leadership positions in the administrative, clinical, and research arenas. The roles that I most value are caring for patients and their care partners, conducting and disseminating clinical research that can directly improve the health and well-being of our patients, and mentoring trainees and early-career investigators who aspire to pursue careers in clinical medicine or research.

The current and previous *CJASN* editors-in-chief and editorial teams have been inspirational role models in promoting high-quality, clinically relevant research and in their dedication to elevating the next generation of clinicians and scientists. Given that *CJASN* is one of the most widely read journals among all clinicians, researchers, trainees, and patients in nephrology, I was eager to pursue the editor-in-chief role in which I could potentially make a positive, meaningful, and enduring impact on our community.

***KN*: What are some of *CJASN*'s strengths?**

**Rhee:** There are numerous strengths, including its very broad reach and inclusivity across our kidney community. One of the most popular areas of content is the "Patient Voice" articles, which were inaugurated by the most recent *CJASN* editorial team to ensure that patients' voices are being heard and prioritized. Another major strength is *CJASN*'s dissemination of rigorous, high-quality science. The previous editorial teams have established high standards for publishing research that is internally and externally valid and that can directly inform clinical decision-making or catalyze patient-centered research. *CJASN* also has innovatively expanded its modes of communication via exciting visual abstracts, podcasts, and social media channels to connect with a wider audience.

***KN*: What are some of your designs for the journal?**

**Rhee:** There are seven major goals that our new *CJASN* editorial team and I will be pursuing over this next term:

1. We will continue to expand the global reach of the journal. I am honored to work alongside a diverse, world-class team of editors and kidney advocates who represent a large geographic catchment area. It is a privilege to partner with these renowned experts and leaders as we engage with our international readership in the pursuit of the highest-quality clinical medicine and science and to influence positive change in our field.
2. We want to ensure that the voices from the most vulnerable populations in the kidney community are being heard, both within and outside of the United States.
3. We aim to augment cross-disciplinary content, given that we are increasingly collaborating with non-nephrology colleagues in primary care, endocrinology, cardiology, and other specialties in both the clinical and research spheres using a team-based and team-science approach, respectively.
4. Having greatly benefited from *CJASN*'s didactic material and ASN's educational programs through the years, I am passionate about expanding trainee-focused topics and material.
5. We aim to expand our interdisciplinary content that encompasses the interests of the diverse workforce of advanced practitioners, physician assistants, nurses, pharmacists, dietitians, social workers, and technicians who are also on the front lines serving kidney patients.
6. We plan to develop and highlight more research with an upstream focus on kidney health that emphasizes the primary and secondary prevention of kidney diseases using lifestyle medicine and holistic approaches.
7. Finally, we will work in close collaboration with the other ASN journal portfolio editors-in-chief—Rajnish Mehrotra, MD, MS, FASN, of *JASN* and senior editor-in-chief of the ASN journal portfolio and Michael Allon, MD, of *Kidney360*—and their editorial teams to strategically align the content, format, and best practices across the three journals.

***KN*: How do you plan to work with the other ASN journals?**

**Rhee:** I am truly grateful to Dr. Mehrotra, Dr. Allon, the most recent *CJASN* editorial team, the ASN journal portfolio team, and ASN staff, who have strongly supported me and our new editorial team in making a smooth transition to the journal. Since the announcement of my position, we have had multiple meetings to brainstorm and discuss how we can synchronize the three ASN journals to enhance the authors' and readership's experiences and to inspire the best research that will have a positive and long-lasting influence on our field.

I am deeply honored and excited to serve our kidney community to the best of my abilities as the *CJASN* editor-in-chief. While there is a vast amount of work that lies ahead, I am truly excited for what the future holds for the journal, the ASN journal portfolio, and our field! I am ready to roll up my sleeves, dive in, and work hard to serve our kidney community.

**Do you have an opinion about a story published in *Kidney News*?**

**Email kidneynews@asn-online.org to submit a brief Letter to the Editor. Letters will be considered for publication in an upcoming issue.**

# Serving the Underserved

The following article is the first of a five-issue series focused on improving care for patients in underserved populations. Inspired by several sessions at Kidney Week 2023, this series will feature unique patient and physician perspectives, explain legal protections and limitations, and seek to identify opportunities to improve kidney care for these communities.

# **Reframing Disability:** Shifting Perspective to Better Care for Patients with Disabilities

By Bridget M. Kuehn

Ken Sutha, MD, PhD, a pediatric nephrologist at Stanford University School of Medicine in Palo Alto, CA, was diagnosed with focal segmental glomerulosclerosis at aged 10 years.

In his second year of medical school, he received a kidney allograft from his father. The treatment came with its ups and downs, Sutha said. Ten years later, he experienced loss of function of the kidney allograft and underwent 2 years of peritoneal dialysis as he started his fellowship, before receiving a second kidney allograft. "Through all of that, I never thought about myself as being someone with a disability, and that hindered me from reaching out for help and asking for accommodations I would have benefited from," he said. "I was fortunate that I worked with people who were very understanding and able to work with me through my difficulties."

Sutha now identifies as a member of the community of people with disabilities, and he shared his experience, the legal frameworks that protect individuals with disabilities, and the diverse perspectives of members of his community during the "When the Patient Becomes the Teacher: Exploring the Intersections of Disability and Kidney Diseases" session at Kidney Week 2023 in Philadelphia, PA. He challenged attendees to rethink how they view disability in patients and in their practices.

"Although my journey with kidney disease has been difficult, there are many wonderful and beautiful things that have come to me because of [it]," Sutha said, "Experiences that I'm able to bring to bear in the care of my patients by sharing my lived experience and how that impacts the way that I view their care."

## Disability 101

One in four adults, or 61 million people in the United States, live with a disability (1). Sutha explained that the Americans with Disabilities Act (ADA) (2) defines disability as a physical or mental impairment substantially limiting one or more major life activities. However, he noted that people under this legal umbrella may have diverse views of their condition, identity, and experiences.

Some disabilities are apparent, such as with those who use a wheelchair, whereas other disabilities may be invisible, such as living with a chronic disease or mental illness, Sutha said. Some are temporary, whereas others may be long-term. People with apparent disabilities may not have a choice whether or when to disclose their condition; however, those with less-visible disabilities can decide with whom to share the information. Both have their challenges, he said. People with apparent disabilities may face preconceived notions about them, whereas those with invisible disabilities may face stigma or disbelief, he noted. Some people with disabilities prefer person-first language describing their condition (i.e., "a person with a disability"). In contrast, others identify as a "disabled person" because they feel it is central to their identity and experience, Sutha explained.

The ADA requires accommodations for people with disabilities at work, school, and in other areas of public life. However, not everyone with a disability may choose to request accommodations. Sutha said he was lucky to have support from his fellowship program despite not requesting formal accommodations and could work full-time while undergoing peritoneal dialysis. However, he has spoken to many trainees and fellows who experienced challenges because they did not seek formal accommodations under the ADA.

Intersectional identities, such as being a member of racial or ethnic minoritized groups or identifying with a sexual or gender minority, may also affect an individual's experience with disability, Sutha said. Some groups have higher rates of disability, whereas others may be less likely to identify as having a disability, he added. For example, 3 in 10 American Indian or Alaska Native individuals have a disability, compared with 1 in 4 who are Black, 1 in 5 who are White, 1 in 6 who are Hispanic or Native Hawaiian or Pacific Islander, and 1 in 10 who are Asian American (3). These individuals may also experience discrimination, or "ableism," based on their disability, as well as racism, sexism, or discrimination based on their sexual orientation or their gender identity.

People's experience with disability may also vary based on their circumstances or resources, such as social support, socioeconomic status, employment, or access to assistive technology or accommodations, Sutha said. For example, he noted that some individuals may have the same need for dialysis that he did during his fellowship but not have the resources or space for supplies required for home dialysis. As a result, they may require in-center dialysis multiple times each week, which could impact their ability to work or care for their family.

Physicians tend to view disability through a medical model as an impairment to be fixed, Sutha said. "This takes away decision-making capacity from them, making them an

object of charity, someone to pity," he explained. "It's only the ones who rise above whose stories get lifted up."

However, an alternate perspective considers disability as a part of human diversity and people with disabilities as deserving of equal rights. "This focuses on autonomy, choice and freedom, and consent for disabled individuals," he said. "It says society should be doing the work to support disabled people, and the community should be adjusting to make things accessible."

## Patient priorities

More than one-half of physicians say they welcome patients with disabilities in their practices. Still, fewer than one-half feel confident caring for them, and only 20% strongly agree that people with disabilities are treated unfairly in the medical system (4). Sutha cited evidence that people with disabilities view their quality of life as much higher than physicians do. For example, a study of emergency care professionals also found that only 18% imagined they would be glad to survive a spinal cord injury, and 41% felt resuscitation efforts for people with spinal cord injuries were too aggressive, whereas 92% of people with spinal cord injuries were glad to be alive (5).

"This is one of the big reasons many patients with disabilities face health inequities," Sutha said. He noted that one in three patients with disabilities does not have a usual care physician. The same proportion has unmet health care needs because of cost, often linked to low incomes or challenges with employment. Patients with kidney diseases often face low employment rates. For example, although 84% of the general population are employed, 38% of patients with kidney diseases are employed 6 months before initiating dialysis, and after starting dialysis, that number drops to 24% (6). Black and Hispanic patients with kidney diseases are disproportionately affected by unemployment, Sutha noted, adding to these burdens. "This is a population of people that have missed opportunities. If properly accommodated, they could be employed, be contributing, and that could be beneficial to their health and well-being," he said.

Unemployment can contribute to food insecurity and housing instability, which both may drive the development of disability, said Cynthia Delgado, MD, FASN, a professor of medicine at the University of California, San Francisco, and associate chief of nephrology for clinical operations and the director of the dialysis program at the San Francisco Veterans Affairs Health Care System. These factors contribute to higher rates of obesity, smoking, heart disease, and diabetes for people with disabilities, Sutha noted.

Dialysis may contribute to frailty, particularly in older patients, and many patients with chronic kidney disease (CKD) also report difficulties with activities of daily living, Delgado said. She added that many patients lose mobility and the ability to do things independently.

"If you asked on your rounds what patients did on their non-dialysis day, they will tell you they didn't do anything," she said.

Delgado noted growing awareness among nephrologists about the importance of patient experience and that the Standardised Outcomes in Nephrology (SONG) initiative developed core outcomes for nephrology research, many of which include focusing on patient quality of life (7). For example, SONG issues include fatigue, the ability to travel or work, dialysis-free time, pain, stress, anxiety, sexual function, financial impacts, and the effects of their condition on their family and friends. "How are we going to help our patients re-engage with life?" she asked. "One way of doing it is having the awareness to ask the right questions."

She noted that the Centers for Medicare & Medicaid Services has also recently created the End-Stage Renal Disease Quality Incentive Program (8), which includes quality of life as a metric in the dialysis unit. She said the goal is to remove burdens from patients so "they're just individuals thriving, living with CKD."

Delgado added that this may take new and creative approaches. For example, she cited a pilot study by Deidra C. Crews, MD, MS, FASN, Johns Hopkins University School of Medicine, Baltimore, MD, which identified patients' challenges at home and deployed a team—including a maintenance person, an occupational therapist, and a nurse—to their homes to complete up to $1300 in repair, modifications, or device installations to help patients overcome physical barriers (9).

Delgado also highlighted the interactions between exercise and physical functioning. She cited evidence that interventions to gradually increase patients' physical activity, such as wearable physical activity monitors (10), can help patients with CKD improve their physical function. "If we address it early, we may be able to reverse it," Delgado said. "[Physical] limitations lead to loss of independence, financial stress, and social isolation, stressors that we don't want our patients to also experience with the burden of CKD."

## Healthcare humility

Despite the high rates of disability in the US population, people with disabilities are underrepresented in health care, accounting for 5% or less of the workforce (11), Sutha noted, which may also contribute to poor care. A survey at Stanford University found that 5% of medical students and just 3% of practicing physicians identify as disabled, Sutha said. He noted that fear of repercussions from disclosure may cause some not to disclose. "We need to be superhuman to work in medicine," Sutha said. "We celebrate doing 24-hour calls and the amount work we do while we are sick and never having to ask for help. That is a detriment to us as health care [professionals] and ultimately to our patients."

He noted that health care practitioners with disabilities bring valuable, lived experience with the challenges of living with disabilities and managing appointments and medications that may benefit patients. Colleagues working with clinicians with disabilities may also help by getting to know them and their capabilities. "Disability doesn't mean inability; when we are properly accommodated, we can accomplish as much if not more," he said.

Sutha emphasized the importance of physicians exercising humility when caring for patients with disabilities, listening to them, and believing them. He also said health care must embrace universal design to make spaces accessible to everyone and be mindful of language. He noted that often universal accommodations may benefit everyone. For example, curb cuts created to accommodate people using wheelchairs help many people, such as those with rolling bags or strollers. "We need to recognize the authority of people with disabilities as experts on their own lives and elevate their voices," he said at Kidney Week 2023. "ASN has been doing a great job elevating patient voices, and I'm glad to see that at this conference." ■

### References


1. Centers for Disease Control and Prevention. Disability and Health Promotion. Disability impacts all of us. May 15, 2023. Accessed November 10, 2023. https://www.cdc.gov/ncbddd/disabilityandhealth/infographic-disability-impacts-all.html
2. US Department of Justice Civil Rights Division. The Americans with Disabilities Act (ADA) protects people with disabilities from discrimination. October 31, 2023. Accessed November 10, 2023. https://www.ada.gov/
3. Centers for Disease Control and Prevention. Disability and Health Promotion. Adults with disabilities: Ethnicity and race. September 16, 2020. Accessed November 10, 2023. https://www.cdc.gov/ncbddd/disabilityandhealth/materials/infographic-disabilities-ethnicity-race.html
4. Iezzoni LI, et al. Physicians' perceptions of people with disability and their health care. *Health Aff (Millwood)* 2021; 40:297–306. doi: 10.1377/hlthaff.2020.01452
5. Gerhart KA, et al. Quality of life following spinal cord injury: Knowledge and attitudes of emergency care providers. *Ann Emerg Med* 1994; 23:807–812. doi: 10.1016/s0196-0644(94)70318-3
6. Hallab A, Wish JB. Employment among patients on dialysis: An unfulfilled promise. *Clin J Am Soc Nephrol* 2018; 13:203–204. doi: 10.2215/CJN.13491217
7. Standardised Outcomes in Nephrology (SONG). The SONG initiative. Accessed November 10, 2023. https://songinitiative.org/
8. Centers for Medicare & Medicaid Services. ESRD Quality Incentive Program. Accessed November 10, 2023. https://www.cms.gov/medicare/quality/end-stage-renal-disease-esrd-quality-incentive-program
9. Crews DC, et al. Pilot intervention addressing social support and functioning of low socioeconomic status older adults with ESRD: The Seniors Optimizing Community Integration to Advance Better Living with ESRD (SOCIABLE) study. *Kidney Med* 2019; 1:13–20. doi: 10.1016/j.xkme.2018.12.001
10. Malhotra R, et al. The impact of a wearable activity tracker and structured feedback program on physical activity in hemodialysis patients: The Step4Life pilot randomized controlled trial. *Am J Kidney Dis* 2023; 82:75–83. doi: 10.1053/j.ajkd.2022.12.011
11. Bureau of Labor Statistics, US Department of Labor. Persons with a disability: Labor force characteristics—2022. February 23, 2023. Accessed November 10, 2023. https://www.bls.gov/news.release/pdf/disabl.pdf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# Addressing Social Determinants of Health in Blood Pressure Control and Cardiovascular Risk in Patients with CKD

By Karen Blum

Social determinants of health (SDOH) and structural racism are key drivers of disparities in blood pressure control and cardiovascular risk in patients with chronic kidney disease (CKD), said Dinushika Mohottige, MD, MPH, assistant professor in the Institute for Health Equity Research at the Icahn School of Medicine at Mount Sinai in New York City, at Kidney Week 2023. In an effort to improve kidney care for those in underserved communities, Mohottige introduced a session reviewing how SDOH contribute to inequities in cardiovascular disease (CVD) prevention in patients with CKD.

The conditions in which people live, work, play, and pray shape their experience in terms of health outcomes, said Anika Hines, PhD, MPH, assistant professor of health behavior and policy at Virginia Commonwealth University School of Medicine in Richmond. This includes factors such as the wealth of local communities and related quality of schools, availability of healthy food and green spaces, noise, stress, and access to health care.

In one example, a recent study (1) found that factors such physician environment, safety and social cohesion of neighborhoods, plus perceived stress and discrimination on cardiovascular health all had influence on the difference in cardiovascular health factors like blood pressure and on behavior like cigarette smoking between Black and White participants, Hines said.

There are several steps clinicians can take to work to address SDOH, Hines posited:

- **Acknowledge the role of structural factors.** Remember that the patient you see represents not just themself but the broad, lived experience of their family or community. "These societal structures may impact the way that they make decisions…or their health behaviors," Hines said. "We should not treat behaviors as just individuals' 'moral defects' but think about broader levers that can impact an individual's health or their healthy decision-making."
- **Engage with patients in equipoised discussions about navigating barriers.** Strive to engage with patients in a way that allows them to tell their lived experiences that could illuminate opportunities as well as barriers to implementing changes you might ask them to make in terms of their health.
- **Provide proper referral to resources.** Be aware of organizations and agencies providing accessible services for patients in need in your area, so you can direct patients appropriately.

## SDOH in the Hispanic community

Hispanic individuals represent the largest ethnic minority in the United States, with approximately 63.6 million people recorded in 2022 census data (2), said Tali Elfassy, MSPH, PhD, a research assistant professor at the University of Miami Leonard M. Miller School of Medicine, FL. Hispanic individuals have a lower prevalence of hypertension (34%) than do those who are non-Hispanic Asian, non-Hispanic Black, and non-Hispanic White, according to data from the National Health and Nutrition Examination Survey used in a 2018 study (3). However, that study sampled predominantly people of Mexican origin, Elfassy said.

"The Hispanic population has actually been very heterogeneous so it's not necessarily reflective of the health of all US Hispanics," she said. Data from the Hispanic Community Health Study/Study of Latinos (4), which recruited over 16,000 Hispanic individuals from diverse backgrounds, found prevalence of hypertension to be 25% across the board but varied by country of origin, with people from Cuba, the Dominican Republic, and Puerto Rico having higher rates (5).

SDOH impact changes in blood pressure among US Hispanic individuals, Elfassy said. For example:

- **Economic stability.** Women earning above $30,000 had lower rates of hypertension; however, that effect was not statistically significant in men (5).
- **Education.** Having less than a high school education was associated with a lower rate of hypertension among men but a higher rate of hypertension among women (5).
- **Health care access.** Having health insurance was associated with a lower rate of hypertension but only in women (5).
- **Built environment.** Having 1 standard deviation of neighborhood socioeconomic deprivation was associated with 49% greater odds of having hypertension (6).

## The role of biomarkers

Black adults experience a higher burden of cardiovascular risk factors and are 32% more likely to die from CVD than members of other racial and ethnic groups (7), said Susanne Nicholas, MD, PhD, MPH, professor of medicine and hypertension specialist at University of California Los Angeles Health, citing data from the National Center for Health Statistics. They also have the highest incidence of kidney failure compared with other groups (8), she said.

However, there is a survival paradox in that Black patients on dialysis actually have lower mortality compared with White patients on dialysis, Nicholas added. Research looking to explain this phenomenon has found that Black patients have lower levels of C-reactive protein (9) and genetic variation in levels of apolipoprotein L1 (10). This survival advantage begins even before dialysis, research has found (11). "It begs the question: What's contributing to this, and also, are there markers that we can potentially identify in individuals?" Nicholas said.

Several major pathophysiological mechanisms link CKD and CVD outcomes, she said, such as anemia, inflammation, and increased oxidative stress and accumulation of uremic toxins (12). The two conditions also are impacted by many similar biomarkers as well as SDOH, she noted.

Studies from Nicholas' group confirmed that African American patients with diabetes had higher levels of C-reactive protein, whereas Hispanic patients had higher levels of urine albumin excretion (13). C-reaction protein levels could be detected in Black patients with metabolic syndrome even before the development of diabetes, she noted, and could predict the development of cardiovascular parameters (14).

Nicholas' group also studied levels of vitamin D (15), which is deficient in approximately 80% of African Americans and thought to contribute to CVD. In a clinical trial, they repleted patients with 100,000 units of vitamin D3 every 4 weeks for 12 weeks and found that it was significantly correlated with pulse wave velocity, a measure of arterial stiffness.

The identification and validation of additional race-specific biomarkers could allow clinicians to stratify patients based on risk to delay progression of CVD and CKD, identify strategies to provide precision-directed therapies based on biomarker values to potentially predict clinical outcomes, monitor response to therapy, and educate patients on potential risks for disease progression, Nicholas said.

**References**


1. Hines AL, et al. Neighborhood factors, individual stressors, and cardiovascular health among Black and White adults in the US: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *JAMA Netw Open* 2023; 6:e2336207. doi: 10.1001/jamanetworkopen.2023.36207
2. Krogstad JM, et al. Key facts about U.S. Latinos for National Hispanic Heritage Month. Pew Research Center. September 22, 2023. Accessed November 10, 2023. https://www.pewresearch.org/short-reads/2023/09/22/key-facts-about-us-latinos-for-national-hispanic-heritage-month/
3. Muntner P, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *J Am Coll Cardiol* 2018; 71:109–118. doi: 10.1161/CIRCULATIONAHA.117.032582
4. Sorlie PD, et al. Prevalence of hypertension, awareness, treatment, and control in the Hispanic Community Health Study/Study of Latinos. *Am J Hypertens* 2014; 27:793–800. doi: 10.1093/ajh/hpu003
5. Elfassy T, et al. Incidence of hypertension among US Hispanics/Latinos: The Hispanic Community Health Study/Study of Latinos, 2008 to 2017. *J Am Heart Assoc* 2020; 9:e015031. doi: 10.1161/JAHA.119.015031
6. Savin KL, et al. Social and built neighborhood environments and blood pressure 6 years later: Results from the Hispanic Community Health Study/Study of Latinos and the SOL CASAS ancillary study. *Soc Sci Med* 2022; 292:114496. doi: 10.1016/j.socscimed.2021.114496
7. American Heart Association. Heart Attack and Stroke Symptoms. Age-adjusted total CVD mortality rates by race/ethnicity. November 11, 2020. Accessed November 10, 2023. https://www.heart.org/en/about-us/2024-health-equity-impact-goal/age-adjusted-total-cvd-mortality-rates-by-race-ethnicity
8. Norton J, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephr* 2016; 27:2576–2595. doi: 10.1681/ASN.2016010027
9. Crews DC, et al. Inflammation and the paradox of racial differences in dialysis survival. *J Am Soc Nephr* 2011; 22:2279–2286. doi: 10.1681/ASN.2011030305
10. Lertdumrongluk P, et al. Survival advantage of African American dialysis patients with end-stage renal disease causes related to APOL1. *Cardiorenal Med* 2019; 9:212–221. doi: 10.1159/000496472
11. Newsome BB, et al. Survival advantage of Black patients with kidney disease after acute myocardial infarction. *Clin J Am Soc Nephr* 2006; 1:993–999. doi: 10.2215/CJN.01251005
12. Matsushita K, et al. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. *Nat Rev Nephrol* 2022; 18:696–707. doi: 10.1038/s41581-022-00616-6
13. Sinha SK, et al. Association of race/ethnicity, inflammation, and albuminuria in patients with diabetes and early chronic kidney disease. *Diabetes Care* 2014; 37:1060–1068. doi: 10.2337/dc13-0013
14. Sinha SK, et al. How clinically relevant is C-reactive protein for Blacks with metabolic syndrome to predict microalbuminuria? *Metab Syndr Relat Disord* 2021; 19:39–47. doi: 10.1089/met.2019.0121
15. Sinha SK, et al. Vitamin D3 repletion improves vascular function, as measured by cardiorenal biomarkers in a high-risk African American cohort. *Nutrients* 2022; 14:3331. doi: 10.3390/nu14163331

## Taurolidine and Heparin Lock Product Lowers CRBSI Risk

A newly approved taurolidine and heparin lock solution reduces the risk of catheter-related bloodstream infection (CRBSI) in patients undergoing hemodialysis with a central venous catheter (CVC), as demonstrated by a pivotal trial in *CJASN*.

The phase 3 "LOCK-IT-100" (Study Assessing Safety & Effectiveness of a Catheter Lock Solution in Dialysis Patients to Prevent Bloodstream Infection) trial included 795 adults receiving maintenance hemodialysis with a permanent CVC enrolled at 70 US centers. Patients were randomly assigned to receive a taurolidine (13.5 mg/mL) and heparin (1000 U/mL) solution or heparin only. Study solutions were instilled at the end of each hemodialysis session. Baseline characteristics were similar between groups. The primary outcome was the occurrence of CRBSI, assessed by blinded clinical adjudication. Catheter removal and loss of patency were evaluated as secondary outcomes.

Of 41 CRBSI events, 32 occurred in the heparin-only group: 2% of patients assigned to taurolidine and heparin versus 8% with heparin only. Event rates were 0.3 for heparin only versus 0.46 for taurolidine and heparin per 1000 catheter days. The hazard ratio for CRBSI was 0.28 in the taurolidine and heparin group. Based on this "highly statistically significant" result and the absence of safety issues, the study was terminated after a planned interim analysis.

Secondary outcomes were similar between groups. Most patients in both groups experienced treatment-emergent adverse events, mainly mild to moderate. In both groups, 5% of patients died, most commonly due to cardiac causes.

The LOCK-IT-100 results led to US Food and Drug Administration (FDA) approval of the proprietary taurolidine and heparin catheter lock solution, marketed as DefenCath. It is the third drug to be approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs and received both a fast-track and Qualified Infectious Disease Product designation, according to an FDA announcement.

By lowering the risk of CRBSIs, the new product is likely to reduce morbidity and mortality in the vulnerable group of in patients undergoing hemodialysis with CVCs. The investigators conclude: "Reducing CRBSIs in hemodialysis patients will likely increase the efficiency of care and reduce the number and duration of hospitalizations and overall costs" [Agarwal AK, et al. Taurolidine/heparin lock solution and catheter-related bloodstream infection in hemodialysis: A randomized, double-blind, active-control, phase 3 study. *Clin J Am Soc Nephrol* 2023; 18:1446–1455. doi: 10.2215/CJN.0000000000000278].

## Remote Monitoring Improves Hypertension Outcomes


Remote patient monitoring (RPM) can improve the outcomes of anti-hypertensive therapy in older adults, with some accompanying increases in costs, reports a study in *Annals of Internal Medicine*.

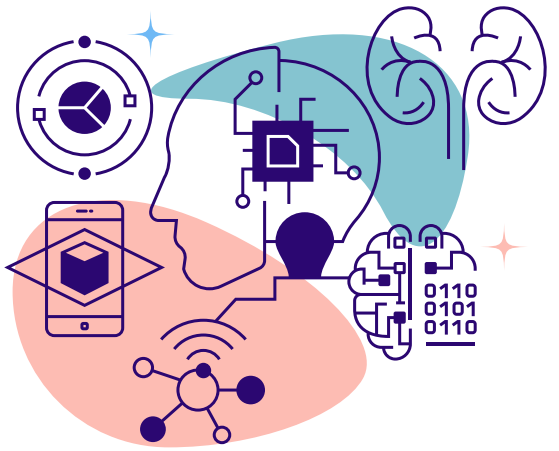
The researchers identified matched groups of traditional Medicare beneficiaries receiving treatment for hypertension at practices with high use of RPM (≥25% of patients) or low RPM use (<2.5% of patients). The analysis included 19,978 patients at 192 high-use RPM practices and 95,029 patients at 942 low-use RPM practices. Measures of anti-hypertensive medication use were compared, along with outpatient visits, use of tests and imaging, and hypertension-related spending.

Several measures of anti-hypertensive medication use were significantly improved in the high-use RPM group. Findings included relative increases of 3.3% in medication fills, 1.6% in days with medication supply, and 1.3% in unique medications prescribed. Hypertension-related acute care encounters decreased by 9.3% with high RPM use, whereas testing and imaging use decreased by 5.9%. Most of the reduction in testing was related to clinical chemistry tests. Patients treated at high-use RPM practices had a relative 7.2% increase in primary care office visits, with a $45 increase in spending, largely driven by increased use of telemedicine. The total increase in spending in the high-use RPM group was $274 per patient, for a relative increase of 7.4%.

In subgroup analyses, patients with low initial medication adherence had greater improvements in hypertension-related acute care visits and hospitalizations. These effects included not only emergency department visits but also hospitalizations for stroke and cardiovascular disease.

The authors define RPM as "remote transmission of physiologic measurements from patients to clinicians." Although the use of RPM for chronic disease management is growing rapidly, there are concerns that it may lead to increased spending without meaningful improvements in care.

The new study, designed to emulate a longitudinal cluster randomized trial, shows increased anti-hypertensive medication use for Medicare patients at high-use RPM practices. This and other improvements suggest "a more aggressive approach to hypertension control" at practices that use RPM. The findings also show "overall increased spending from direct RPM reimbursement and incremental PCP [primary care physician] visits," the researchers write. They discuss possible approaches to increase the value of RPM for patients with hypertension [Tang M, et al. Effects of remote patient monitoring use on care outcomes among Medicare patients with hypertension: An observational study. *Ann Intern Med* 2023; 176:1465–1475. doi: 10.7326/M23-1182].




## Can AI Predict Which Donor Kidneys Will Be Transplanted?

Machine-learning approaches show promise for use in identifying potential donor kidneys at high risk of organ nonuse or nonrecovery, according to a study in *JAMA Surgery*.

Using information from the United Network for Organ Sharing (UNOS), the researchers evaluated the use of artificial intelligence (AI) approaches to make predictions about the use versus nonuse of potential donor kidneys. The study evaluated machine learning (ML) models using structured data on donor characteristics, as well as natural language processing (NLP) models using unstructured, free-text donor narratives. The free-text data included comments from the UNOS admission course, medical and social history, as well as donor highlights.

The AI approaches were evaluated for their ability to classify donors regardless of recovery status versus those who had at least one kidney recovered for transplant. Performance was compared with that of a model using the Kidney Donor Profile Index (KDPI). A training and validation cohort consisted of 9555 donors offered to the study center between 2015 and 2020; a test cohort comprised 2481 donors from 2021.

Just 20% to 30% of potential donors had at least one kidney transplanted. The model using the KDPI had an area under the receiver operating characteristic curve of 0.69, with accuracy of 0.64. Performance was almost identical for two multivariable ML models based on structured donor data (logistic regression and random forest classifier models).

A classic "bag of words" NLP model showed the best performance with the random forest classifier: area under the curve, 0.70 and accuracy, 0.59. An advanced Bidirectional Encoder Representations from Transformers model met this level of performance only after the addition of basic donor information.

Models using free text were "slightly inferior" to models using structured data. Analysis of feature importance and Shapley additive explanation summaries provided information on conditions potentially affecting donor selection: Terms implying chronic disease tended to have negative effects, whereas terms implying trauma appeared positive.

The findings suggest that ML models can potentially predict donors with high-risk kidneys that are ultimately not used for kidney transplant. The researchers conclude: "The use of structured data is likely to expand the possibilities, but further exploration of new approaches...will be necessary to develop explainable models with high predictive metrics" [Sageshima J, et al. Prediction of high-risk donors for kidney discard and nonrecovery using structured donor characteristics and unstructured donor narratives. *JAMA Surg*, published online November 1, 2023. doi: 10.1001/jamasurg.2023.4679].

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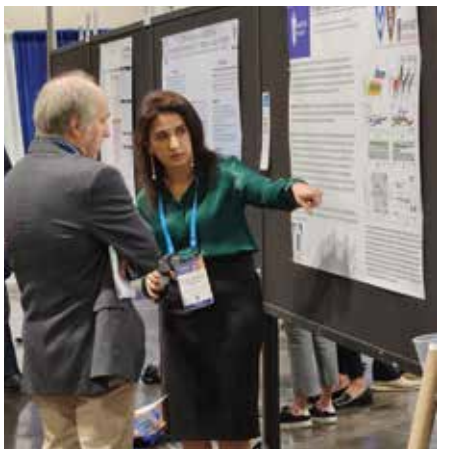

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