ASN American Society of Nephrology

Kidney News

January 2025 | Vol. 17, Number 1

CMMI Streamlines Final Transplant Payment Model, Boosts Upside Reimbursement

By Bridget M. Kuehn

https://doi.org/10.62716/kn.000432024

The final version of a new payment model designed to increase kidney transplant rates and transparency is more streamlined than the initially proposed model, has easier goals to achieve for growth, and incorporates larger payments for transplant centers that meet the model's goals.

The release of the final Increasing Organ Transplant Access (IOTA) Model (1) is the latest step toward meeting the goals of the 2019 Advancing American Kidney Health Initiative (2), which aims to reduce the number of patients on dialysis by increasing prevention and transplants.

The Center for Medicare and Medicaid Innovation (CMMI) first released a draft of the IOTA Model in May 2024 and requested public comments. The final model, released in November 2024, reflects compromises intended to address stakeholders' concerns about the model while still achieving the goal of boosting transplant access. Currently, approximately 1 in 13 patients on the kidney transplant waiting list dies before receiving a transplant, and as many as one-third of donated kidneys are discarded due to system inefficiencies.

"Kidney transplantation is the optimal therapy for most people with kidney failure," said ASN Past President Deidra C. Crews, MD, ScM, FASN, in a press release from ASN about the final model (3). "I am optimistic that IOTA's focus on increasing transplant rates will mean that more of the 550,000 Americans on dialysis can benefit, given the known survival and quality of life advantages that kidney transplantation confers."

Crews and other ASN leaders applauded the final model for its emphasis on increasing transplant rates, expanding the use of donor organs, increasing transparency in the process for patients and referring

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Show Me the Money: 2024 Nephrology Fellow Survey and Trends in Starting Salary

By Suzanne M. Boyle and Kurtis A. Pivert

https://doi.org/10.62716/kn.000362024

In 2020, the COVID-19 pandemic took the world by storm, causing significant and acute changes to the global economy. It caused near-immediate reductions in product supply chains as well as in human capital, including nurses and physicians. Work-related hazards and caregiver challenges (precipitated by lockdowns and virtual education) caused many health care professionals to leave the workforce. Meanwhile, market forces led to a tremendous spike in inflation, sending consumer prices soaring over the next several years. How might these events have impacted the economy for new nephrology graduates, including their salaries, job descriptions, and perspectives on the job market? We turned to the 2024 ASN Nephrology Fellow Survey Report to hear what story it tells (1).

Incoming workforce

The 2024 survey was distributed in May 2024 to 962 current adult, pediatric, and adult-pediatric fellows in Accreditation Council for Graduate Medical Education (ACGME)-accredited US nephrology training programs. The response rate was 46% (n = 447), which was on par with previous years. Respondent demographics were generally consistent with those reported by

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INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

ardelyx®

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

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

Most Common Adverse Reaction

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

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

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

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

7.2 Sodium Polystyrene Sulfonate

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Risk Summary

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

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

Juvenile Animal Toxicity Data

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

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

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

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

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

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

Administration and Handling Instructions

Instruct Patients:

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

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US-XPH-0162 11/23

ASN American Society of Nephrology

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ASN *Kidney News* is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to ASN *Kidney News*, c/o Customer Service, American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074.

ASN *Kidney News* (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $20 for ASN *Kidney News* subscription.

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nephrologists, and focusing more on improving longer-term transplant outcomes.

A model approach

The 6-year mandatory IOTA payment model pilot is designed as a randomized trial to test the model's ability to increase transplant rates. Eligible transplant programs in about half of the transplant service areas—approximately 230 in total—will be required to participate, and the other half of transplant centers will serve as a control group.

The model incentivizes transplant centers to increase the number of organs that they transplant annually and complements previous Centers for Medicare & Medicaid Services (CMS) payment models, like the 2021 End-Stage Renal Disease Treatment Choices (ETC) Model and the 2022 Kidney Care Choices (KCC) Model, which incentivize nephrologists and dialysis centers to refer patients for transplant.

"With the creation of the IOTA Model, CMMI is aiming to create value-based care models that support the continuum of kidney disease care, from KCC for patients with advanced chronic kidney disease to ETC for end-stage renal disease and now for patients who could receive a kidney transplant," said Mallika Mendu, MD, MBA, FASN, a nephrologist and vice president of Clinical Operations and Care Continuum at Brigham and Women's Hospital in Boston, MA, in an emailed statement. "Overall, the focus on creating value for patients with kidney [diseases] (improving quality while reducing cost) is positive, and related to IOTA, the opportunity to increase the number of transplants performed is potentially transformational."

The final IOTA model represents a more streamlined version. "It's an excellent model with some important changes from the proposed rule that are reasons for significant enthusiasm," said Sumit Mohan, MD, MPH, FASN, professor of medicine and epidemiology at Columbia University in New York City. He explained that the revised goals for increased transplant rates are more realistic, and achieving the criteria needed to earn the incentive payments is easier.

Eugene Lin, MD, MS, FASN, a health economics researcher and assistant professor of medicine at the University of Southern California in Los Angeles, also liked CMMI's steps to simplify the model. He noted that overly complex models can be confusing for clinicians and may set goals that are hard to achieve. It can also be difficult for patients to understand the goals of more complicated models. "It seems like CMMI has been moving toward more simplicity on these models, which I also think is a good thing for [practitioners]," he said. "They are literally just being incentivized to do more transplants."

Positive developments

Changes that ASN championed that were contained in the final model included pushing back the program's start date from January 1 to July 1, 2025, to give participating programs more time to prepare.

Another ASN-backed change was an increase in the Medicare fee-for-service beneficiary upside payments for centers that meet the model's goals from $8000 to $15,000. Many comments on the initial model raised concerns that the originally proposed $8000-plus side payment would not be enough to cover additional staff or services needed, particularly for the care of patients who have medical complexities.

Mendu, Mohan, and Lin were all appreciative of the decision to increase the reimbursement. "To succeed in this model, hospitals and [transplant centers] will need to make investments in infrastructure and staffing, particularly to support more complex patients," Mendu explained.

Centers that fail to meet the program goals must pay CMS $2000 per patient—the same as in the original proposal. Lin noted that centers have quite a bit of latitude; a center does not need to be performing at the highest level to avoid the penalty, and moderate performance is enough to avoid penalties.

Programs will be assessed on various factors, including growth in their overall transplant rate, donor organ acceptance rate, shared decision-making, and longer-term patient outcomes. Lin noted that the goals for growth were adjusted in the final proposal to be more sustainable and to rely on a 3-year average performance. He said that having a 3-year average is important because it will prevent centers from being penalized if something beyond their control happens, which temporarily lowers their annual transplant rate. "[Transplant centers] are not being held accountable to statistical noise," he said. "They're being held accountable to something that's more long-term and sustainable."

The IOTA Model also includes several measures to increase transparency in the transplant system. For example, transplant centers will be required to publicize their waitlist criteria, which may help patients find the right program. "One of the most challenging aspects of helping the patients [who] I have the privilege of serving get a kidney transplant is determining which program is the best fit for them," Crews added. "Being able to publicly access the criteria [that] each program uses when determining whether or not to add a patient to the kidney transplant waitlist will help me and the people with kidney failure that I care for navigate the system more efficiently and effectively."

The model also incentivizes centers to discard fewer organs. "There is a clear focus on improving efficiency and a center's organ offer acceptance rate," Mohan said. "As a result of the focus on organ acceptance rate, the model should help improve organ utilization and lower discard rates."

Room for future improvement

Although CMMI included many of the changes that ASN and individual nephrologists recommended in the model, there were a few notable omissions.

The final model did not include a requirement that centers inform patients if an organ declined on their behalf is successfully transplanted into someone else. On average, patients who die while on the waitlist have had 17 kidneys declined on their behalf that were successfully transplanted into someone else (4). Mohan called the omission unfortunate. The American Society of Transplant Surgeons recommended the change because it argued that the notifications would create an administrative burden (5).

Mohan and Lin agreed that adding patient notifications about declined kidney offers in the future might be beneficial. Lin noted that clinicians want to avoid overloading patients with information and carefully consider how to share information about declined offers. "We need to be moving in that direction long term but recognize that it may not be that simple to get there," he said. Mohan also hoped that tracking 6-year transplant outcomes, an exclusion in the revised model, may be added in later years to help bolster the emphasis on improving longer-term outcomes.

A health equity payment adjustment was also not included in the final model, and a requirement that centers create a health equity plan was made voluntary. "I am concerned that the health equity requirements were dropped from this proposed model, as that was a novel and important aspect of the initial proposed model," Mendu said. "The challenge is that there are already significant, long-standing disparities among under-represented minorities with respect to receiving kidney transplantation. A model like this that [strives] to increase kidney transplantation, without addressing the drivers of inequity, could exacerbate existing disparities."

Still, Mendu was optimistic that the model would help improve transplant quality, efficiency, and rates. However, she noted that it would be essential to track patient outcomes, including those related to disparities; monitor the effects on clinicians and centers; and provide feedback to CMMI. ■

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ACGME with a few minor exceptions: over-representation of adult US medical graduates (USMGs [43% versus 37%]), adult White fellows (34% versus 26%), and pediatric White fellows (55% versus 47%) and under-representation of adult international medical graduates (IMGs [57% versus 63%]) and pediatric Asian fellows (18% versus 28%) (2). Fifty-seven percent of adult respondents were US citizens, and 24% were J-1 visa holders. Notably, these demographics—including trends in over- and under-responses—have been relatively static for several years.

Base salaries

How might salaries have been impacted by the economic milieu? In 2021, the annual median reported base salary for new fellowship graduates was $200,000. One year later, it was $219,500, before rising to $231,000 in 2023 and to $240,000 in 2024—a 20% rise over 3 years. For comparison, base salaries only rose from $162,500 to $190,000 over the preceding 5 years (17% rise).

What contributed to the rise in base salary from 2021 to 2024? The most obvious explanation is inflation. The United States experienced one of its highest annual inflation rates in history between 2021 and 2022, at 7%. (Higher rates were only seen during World War II and the post-Vietnam/oil crisis economy of the late 1970s [3].) But it seems that salaries rose more than the inflation rate (Figure). Closer observation shows that the primary drivers of the rise in median base salary were IMG salaries. Between 2021 and 2022, IMG base salaries increased 13.9% (compared with only a 0.3% rise among USMGs). The inflation rates were 7.0% and 6.5% in 2021 and 2022, respectively. USMGs experienced a 12.2% base salary increase in 2022 (likely, in part, a response to the previous year's inflation), and IMGs still had a 4.3% increase in 2022.

Figure. Percent change in base starting nephrology salaries and annual US inflation, 2021–2024

Sources: ASN Fellow Surveys and Bureau of Labor Statistics

Why was there such a dramatic increase in the salary of IMGs relative to USMGs? Perhaps this is because IMGs may be more likely to accept employment in underserved (typically, rural) areas, where salaries are higher due to a low supply and a high demand for nephrologists. Approximately 25% of IMGs are J-1 visa holders, which means that to continue to practice in the United States without first returning to their home country, they must complete a waiver in a state-designated underserved area. Pandemic-induced workforce shortages may have further exacerbated the already-existing shortages in these areas, leading to increases in salaries. Also, loss of revenue by health systems during the early stages of the pandemic may have caused budgetary restrictions in more populous areas (where USMGs might be more likely to seek employment). Median base salaries were comparable between private practices (n = 67 respondents, 50% of responses) and academic practices (n = 42 respondents, 32% of responses). However, employees of nonacademic health systems reported substantially higher base salaries (and bonus/incentive pay) than private or academic practices, although there were fewer graduates who took such positions (n = 19 respondents, 14% of responses). Of note, base starting salaries do not reflect the differences in long-term earning potential between private practice and academic positions because it can take several years to become vested as a partner in a private practice and share in the full range of revenue income.

Important factors

Despite rising consumer prices, a competitive housing market, higher interest rates, and significant educational debt (disproportionately burdening USMGs, who have a median $250,000 in educational debt), new nephrology graduates valued lifestyle factors over financial compensation when searching for employment. However, compared with previous fellow surveys, compensation broke into the top five job-related attributes (ranked 5 out of 20) that are "extremely important" to new graduates. It only made the top five by a margin, but this could still potentially be a side-effect of the economy.

Future directions

In 2024, the ASN Data Subcommittee piloted a dedicated transplant nephrology fellow survey with nine current transplant fellows participating. Results from the survey can be found in the 2024 ASN Nephrology Fellow Survey Report (1). This research instrument will continue to expand to ensure that all facets of the incoming nephrology workforce are accounted for. ■

Suzanne M. Boyle, MD, MSCE, is the chair of the ASN Data Subcommittee. She is an associate professor of medicine and nephrology training program director at the Temple University Lewis Katz School of Medicine in Philadelphia, PA. Kurtis A. Pivert, MS, CAP, is ASN's Director of Data Science.

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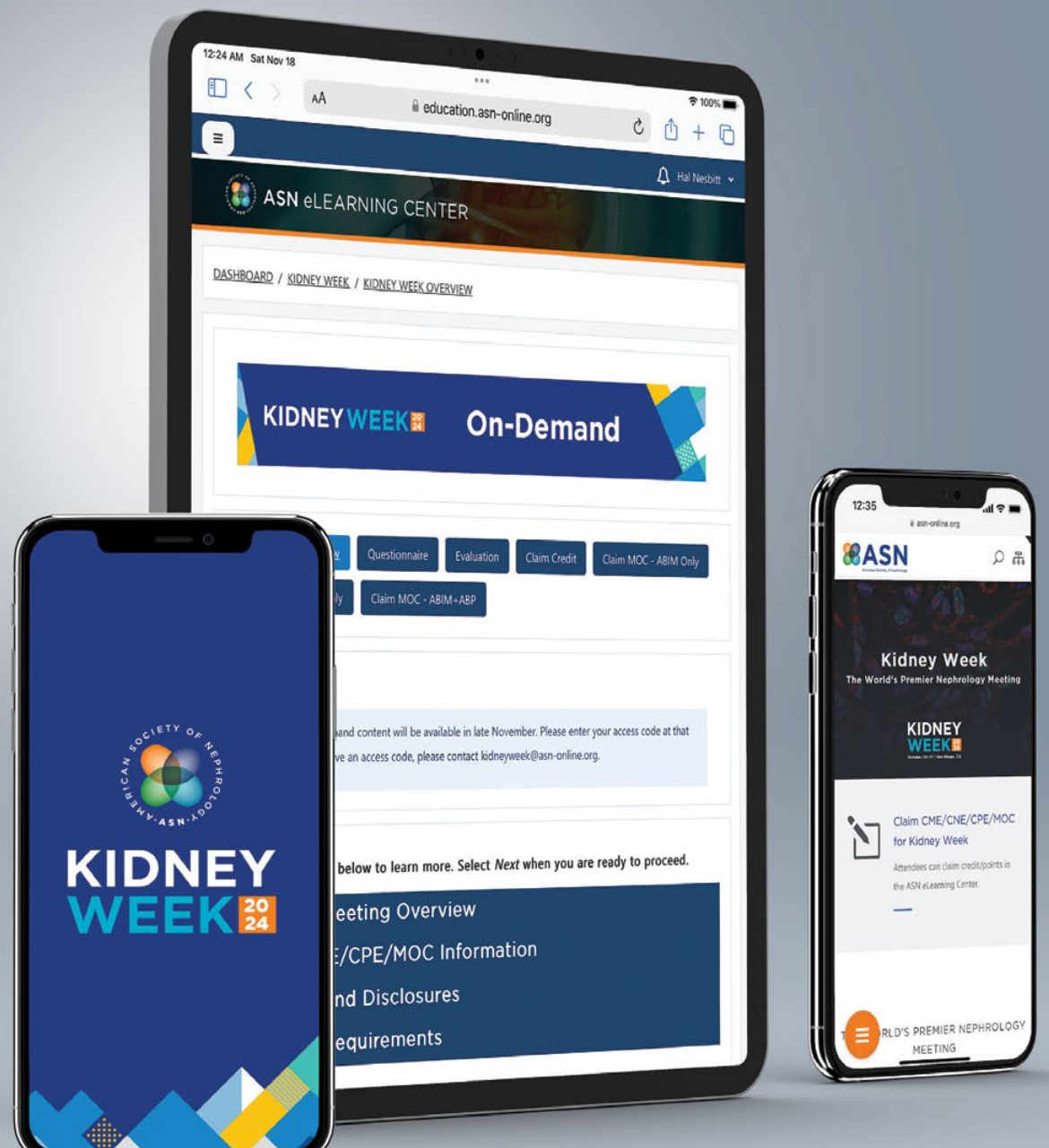

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ASN President's Update

Be a Part of the Change

By Prabir Roy-Chaudhury

https://doi.org/10.62716/kn.000312024

January 2025 marks a pivotal and exciting time for kidney care, research, and education. For the first time in my career as a nephrologist, we are witnessing an influx of new therapies in the kidney disease field, expanding treatment options beyond angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; the Advancing American Kidney Health Initiative has resulted in policy changes in which incentives are, for the first time, being aligned with value; and kidney health is now a key component of the cardiovascular-kidney-metabolic triad of chronic diseases.

True change in kidney care, however, will only reach our patients when all of us—as members of ASN—and the broader kidney community are a part of the change; when we all participate in creating a new future for people living with kidney diseases; and when we can truly cure kidney diseases and promote kidney health for all.

And while I will come back to the importance of all of us being a part of the change later in this piece, I want to start by telling you a little about myself—my story, if you will.

I was born in Ottawa, Canada, and grew up mainly in India. However, I had the good fortune to also go to school in Switzerland and Thailand and to spend a lot of time in Sri Lanka, Egypt, and Burma because my father worked with the United Nations for many years. After graduating from the Armed Forces Medical College in Pune, India, I spent almost 8 years in Aberdeen, Scotland, where I completed a master's degree in clinical pharmacology, became a Member of the Royal College of Physicians of the United Kingdom (internal medicine residency equivalent), and earned a PhD on "Adhesion Molecules in Glomerulonephritis."

Aberdeen will always be special to me, not only because I married my wife Ashwini and had our first child there but also because it is where an amazing mentor, Professor James Petrie, guided and inspired me to become the best version of myself. I then moved to the United States for a nephrology fellowship at Beth Israel Hospital in Boston, MA, which included 2 years of research in a transplant immunology laboratory.

The next 5 years of my life involved a period of great uncertainty, not uncommon for international medical graduates, as I repeated a part of my internal medicine training in Cincinnati, OH, followed by a J-1 visa waiver position at the Cincinnati Veterans Affairs Medical Center. I was successful in being able to cross these barriers and stay in the United States, only because of the support and guidance of three inspiring role models and mentors: Terry Strom, MD, and Vikas Sukhatme, MD, PhD, in Boston and Roy First, MD, in Cincinnati.

Cincinnati was home for 19 years, during which time I worked as a transplant nephrologist, developed a translational program in dialysis vascular access, and most importantly, saw my three children grow up as Cincinnati Bengals fans in a wonderful midwestern environment. It was also during my time in Cincinnati that I came into contact with yet another mentor who shaped me midcareer. Past ASN President Ronald J. Falk, MD, FASN, introduced me to the world of ASN, in which I served as the founding cochair of the Kidney Health Initiative (KHI).

A public-private partnership between the US Food and Drug Administration (FDA) and ASN, KHI started with the goal of creating an innovation substrate that would facilitate the development of drugs, devices, and biologics for kidney diseases. KHI is now a mature organization and, just as Dr. Falk envisaged, has played a key role in the resurgence of new therapies for kidney diseases by validating new surrogate endpoints. For example, KHI's efforts to identify surrogate endpoints for immunoglobulin A nephropathy has resulted in a deluge of new drugs for this condition.

On a more personal level, KHI allowed me to interact with and learn from a diverse group of talented and dedicated people from federal agencies, patient organizations, industry partners, and other health professional organizations. It allowed me to grow my mind, to become a much more holistic person, and most importantly, to understand the significance of the patient perspective in every aspect of health care. For that, I will always be grateful to Dr. Falk, Patrick Archdeacon, MD (FDA cochair of KHI), and Melissa West (now senior director of Strategic Relations and Patient Engagement at ASN).

...true progress will only come if each and every ASN member commits to grab this opportunity and, in some small way, be a part of this change.

I am currently the codirector of the University of North Carolina Kidney Center at Chapel Hill. I am privileged to lead a wonderful group of physicians, scientists, staff, and trainees as we work together to leverage research, advocacy, innovation, clinical care, and public policy to improve kidney health. Within this larger vision, we have been able to create a vibrant kidney technology incubator within an academic institution so that our patients can actually benefit from the advances in biology, cell therapies, and material sciences that have revolutionized other specialties. We are excited about a host of potential technologies that we are developing, including microfluidic devices to risk stratify patients with kidney diseases, as well as a variety of instruments for the creation and maintenance of vascular access, including nitric oxide-releasing catheter locks and bioengineered vessels, new membranes for kidney replacement therapy, and novel perfusion technologies to preserve and use less-than-ideal kidneys.

As I reflect back upon my story, two things jump out at me:

First, I am extremely proud of having trained and worked in three countries on three continents. And although at times I feel a bit lost when people ask me where I am from, I also feel good about being able to say that I am a global citizen.

The second is that more than the science and more than the patient care, my story is really a story about people; a story about the mentors who opened opportunity doors for me and imparted wisdom about what to do as I walked through those doors; a story about all of my colleagues and trainees who influenced my thinking; a story about the patients who I cared for, who taught me about so much more than medicine; and a story about people at ASN and KHI who gave me the opportunity to grow my mind holistically.

And this is where my story and the story of kidney health intersect with each other….

Just as my journey reflects a global perspective, kidney diseases are also a global problem. Although there are nuances of kidney care in different countries for the 850 million people living with kidney diseases, the basic issues are the same:

- We need more education and awareness.
- We need better therapies to prevent and treat kidney diseases.
- We need better implementation of the new therapies that are changing kidney care across the globe.
- We need to address the disparities in access to kidney care as a result of socioeconomic factors, geography, education, race, and ethnicity.

Since I have gained so much from the opportunities provided through ASN and KHI, a key focus of my work at ASN will be ensuring that the society nurtures its members, provides professional growth opportunities for its members, and continues to support the larger kidney community. And by ASN members, I truly mean *all* of its more than 21,000 members in 142 countries, especially community nephrologists, early-career nephrologists, PhD researchers, and other health professionals like nephrology nurses, mid-level practitioners, and PharmDs. ASN must continue to mentor and enhance growth in people who will enable change in kidney care, research, and education.

Building on these themes of global kidney care and professional development of ASN members, I plan to focus on three important initiatives during my year as ASN president:

1. **Demonstrate the value of nephrology**. We need to leverage the incredible advances in new diagnostics, drugs, devices, and biologics in kidney care to demonstrate the value of nephrology to the health care system as a whole. To do this, we must break out of our small nephrology bubble and demonstrate the importance of kidney care within the larger bubble of the global health care system. This step is essential to ensure that there are well-defined reimbursement pathways for new therapies to continue to enter the kidney field; that these advances reach the most vulnerable of our patients; and that nephrologists are compensated appropriately for the immense value that they bring to health care as a whole.

For example, an initiative on leadership, economics, and access to quality care in nephrology is needed to promote professional growth and to provide nephrologists with the necessary skill sets in health care policy, quality improvement, advocacy, health economics, and data analytics. This effort should actively engage constituencies such as community nephrologists, division directors, dialysis organizations, and value-based care companies, as well as expand on ongoing initiatives and partnerships, such as ASN's Data Science Program, the ASN-Columbia University Nephro-Economics symposium, and the Nephrology Business Leadership University. Finally, it should leverage the common linkages in the context of cardiovascular-kidney-metabolic disease through ASN's focus on "saving kidneys, hearts, and lives."

2. **Address the linked ssues of the impact of climate change on kidney health and sustainable innovation in nephrology**. When combined with ASN's Emergency Partnership Initiative, this focus should support patients with kidney diseases who are living in disaster settings, champion innovative ways to reduce power and water use in dialysis, and partner with other members of the kidney community and beyond to confront the reality of conditions like chronic kidney disease of unknown origin.

   For example, KidneyX (Kidney Innovation Accelerator)—a partnership between the US Department of Health and Human Services and ASN—initiated a sustainability prize last fall to recognize cutting-edge innovative approaches that can reduce water use and power consumption for dialysis.

3. **Highlight ASN's international footprint**. As countries across the planet address the same challenges of education, advocacy, health economics, implementation, and access to care, I believe that there are lots of opportunities for ASN and its members to both partner with and learn from countries across the globe. I, therefore, plan to advance the already strong partnerships that we have with the European Renal Association and the International Society of Nephrology, while at the same time, develop direct country-to-country partnerships with the Japanese Society of Nephrology and the Indian Society of Nephrology.

   For example, ASN should strengthen its overseas symposia, continue to identify country ambassadors at Kidney Week, and develop opportunities for early-career professionals to fulfill electives in other countries and vice versa. Similar to internal medicine as a whole, there are a large number of international medical graduates practicing nephrology in the United States who could be a conduit for connections and partnerships with other countries. Nephrology's diversity is a unique strength in this setting.

Serving as ASN president is by far the greatest honor of my professional career and a testament to this amazing country, in which I arrived 31 years ago. In particular, I consider myself truly lucky to be leading this amazing organization at a time of incredible positive change in kidney health. We are at a unique inflection point in kidney care with a plethora of new therapies and policy changes, but true progress will only come if each and every ASN member commits to grab this opportunity and, in some small way, be a part of this change. And if we can do that, then I believe that we will be able to cure kidney diseases, embrace kidney health, and achieve our dream of a world without kidney diseases. ■

Prabir Roy-Chaudhury, MD, PhD, FASN, is the Drs. Ronald and Katherine Falk Eminent Professor in Nephrology and codirector of the University of North Carolina Kidney Center at Chapel Hill, and ASN president.

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

Kidney Transplant Policy: 2024 Progress, 2025 Priorities and Predictions

By Rachel Nell Meyer

https://doi.org/10.62716/kn.000402024

At the time of writing, holiday decor is going up, snow is falling, and the US Congress is attempting to determine how it will extend government funding when it runs out on December 20, 2024.

You, of course, are reading this piece well after its deadline in early December 2024. At this time, it remains to be seen how and for how long Congress will fund the government and what other legislation of interest to kidney advocates Congress might pass in the waning days of 2024.

Despite this temporary uncertainty, the 118th Congress (2023–2024) proved to be a banner year for progress on kidney transplant policy, and it is reasonable to predict that 2025 will bring even more focus on how to help Americans with kidney failure access the optimal therapy. ASN worked hard to tee up several bills for inclusion in an end-of-year legislative package, actively engaging with policymakers on Capitol Hill to advance any priorities to President Biden's desk for signature in the 118th Congress. The odds of a large package filled with any bills that are not strictly essential seem slim, but any single piece of transplant legislation enacted in 2024 would be a welcome holiday present from Capitol Hill!

Looking ahead to 2025, with Republicans sweeping both chambers of Congress as well as the White House, we can expect to see coordination on priorities, including health care priorities. Given the robust focus on kidney care during the last Trump administration, including the sweeping Executive Order on Advancing American Kidney Health, kidney health will hopefully again be a top priority for the incoming Trump-Vance administration and their allies. The robust bipartisan support for improving kidney health, including the past three presidential administrations and more than a decade of congressional collaboration across the aisle, positions the kidney and transplant communities well for continued momentum—despite many current unknowns about agency appointments, congressional committee assignments, and White House health care priorities.

The number of bills to improve support for living donors and to make the donation process less burdensome reached an all-time high in the 118th Congress. ASN has played an active role in shaping and championing many of these bills, in partnership with congressional sponsors and other advocates.

Living Donor Protection Act

This bill would remove barriers to living donation by prohibiting insurance companies from denying or limiting life, disability, or long-term care insurance to living donors. It also bars insurance companies from charging living donors higher premiums. Crucially, the bill codifies that living organ donors may use time off of work under the Family and Medical Leave Act to recover from donation.

This legislation, introduced on a bipartisan basis for roughly 1 decade, reached a peak of 43 bipartisan Senate cosponsors and over 200 House cosponsors. At the time of writing, ASN and other advocates are working to elevate this bill for inclusion in a 2024 end-of-year legislative package.

Honor Our Living Donors (HOLD) Act

Broad consensus exists that living donors should not face out-of-pocket costs for donation, and a government-funded program exists to support Americans who are socioeconomically disadvantaged through reimbursement for donation-related costs. However, that program determines eligibility for reimbursement not based on the living donor's income but rather on the recipient's income. This approach, which is defined in statute, likely dates back to when most living organ donors were immediate family members of recipients. Therefore, this bill revises the statute to determine eligibility for reimbursement for living donation-related costs on the living donor's income. ASN worked closely on the original shaping of this legislation, championed it throughout the year, and has been advocating for its inclusion in a 2024 year-end package.

Two major 11th-hour advances position the bill advantageously for this goal: On December 13, Senator Ben Ray Lujan (D-NM) and Senator John Boozman (R-AR) introduced a Senate companion bill, and on December 16, the HOLD Act passed the House. These twin power moves at the end of the session bode well, and at press time, hopes are high that the HOLD Act will be a gift in the end-of-year legislative package.

Expanding Support for Living Donors Act

ASN was instrumental in helping Congressional Kidney Caucus Cochairs Representatives Suzan DelBene (D-WA) and Larry Bucshon, MD (R-IN) and other lead bipartisan sponsors to craft a bill to significantly expand financial support for living donors as well as to reauthorize the government program that provides reimbursement for donation-related costs, commonly known as the National Living Donor Assistance Center. The overall goal of the bill is to make living donation cost-neutral for most Americans who donate. Specifically, it would reauthorize the program through 2035 and increase the amount of funds that Congress can allocate to it, as well as increase the maximum reimbursement amount to $10,000 (pegged to inflation) and double the income eligibility to about $100,000 per year for a single person. Advocating for the enactment of this bill will be a top ASN legislative goal in the 119th Congress.

Organ Donation Referral Improvement Act

Living donation is not the only opportunity for improvement in transplantation on Congress' radar. Bipartisan legislation led by Representative Rob Wittman (R-VA) and endorsed by ASN would study how automated software can increase efficiency in the organ donation referral process.

The goal is to harness technology to ensure that every potential organ donor is automatically referred, while reducing the time and effort that hospital staff spend on making referrals through telephone calls and other manual means. Early hospital and organ procurement organization adopters of automated referral technology relay that it allows hospital staff to focus more on patient care, minimizes the risk of human error or bias, and has increased procurement rates. ASN looks forward to continuing to support this legislation and support other opportunities for greater efficiency in organ procurement.

Funding for ongoing transplant initiatives

In addition to advocating for statutory changes, ASN continues to advocate for full funding for the Health Resources and Services Administration to continue to provide reimbursement through the National Living Donor Assistance Center as well as to implement the reforms and technologic modernization efforts called for in the 2023 Securing the US Organ Procurement and Transplantation Network Act, a top ASN policy victory in the first year of the 118th Congress.

Other action

In addition to all of the action on Capitol Hill, at least three major regulatory milestones took place in the last weeks of 2024:

- **Finalization of the Increasing Organ Transplant Access Model.** A simplified, streamlined mandatory model from the Centers for Medicare & Medicaid Services Innovation Center will enroll roughly half of adult kidney transplant programs with the aim of increasing access to kidney transplant and increasing patient transparency. ASN helped shape the model and, as a strong proponent, will continue to support its advancement under the incoming administration. The model is slated to begin July 1, 2025, and to last 6 years.
- **Full implementation of the HIV Organ Policy Equity Act.** More than 1 decade after legislation that ASN helped champion, the act allows HIV-positive organ transplant to recipients who are HIV positive. After numerous studies to ensure the safety of the procedure in the United States, HIV-positive-to-HIV-positive kidney transplantation is now legal outside of the research realm. This advancement will increase the overall organ supply as well as speed wait times for vulnerable populations.
- **Proposal to collect pre-waitlisting data.** A recent proposal aims to shed light on the opaque process between a patient's referral and a waitlisting decision. Gathering these data would allow policymakers and health care professionals to understand and develop interventions to address the barriers to referral, evaluation, and waitlisting—the gateways to transplantation. This top ASN policy goal will be considered in a series of two proposed rules, with a final decision likely reached in 2025.

Stay tuned for more updates by following coverage in *Kidney News* and the ASN podcast feed, and visit ASN's policy webpage (https://www.asn-online.org/policy/). For real-time updates from ASN Policy, follow @ASNAdvocacy on X. ■

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The Overlooked Inequality: How Severe Mental Illness and Chronic Kidney Disease Intersect

By Claire Carswell and Rebecca Nisbet

https://doi.org/10.62716/kn.000062024

Severe mental illness is a term used to refer to mental health conditions that can present with psychosis, such as schizophrenia, bipolar disorder, and schizoaffective disorder (1). People living with severe mental illness experience significant physical health inequities and die, on average, 15–20 years earlier than people without severe mental illness. This phenomenon is known as the mortality gap (1). Although some reasons for this disparity are suicide or accidental death, the main contributors to the mortality gap are higher rates and poorer outcomes of long-term conditions, including chronic kidney disease (CKD) (2).

The relationship between severe mental illness and CKD is under-researched (3). Yet, there are a multitude of factors that could potentially contribute to the increased risk. People with severe mental illness require long-term treatment with antipsychotics and/or mood stabilizers, which have significant side-effect profiles. Many antipsychotics are associated with an increased risk of type 2 diabetes (2), a leading cause of CKD (4). Additionally, lithium, a mood stabilizer used to treat bipolar disorder and schizoaffective disorder, has a narrow therapeutic range and is nephrotoxic at high blood concentrations. Lithium has been linked to a 6.5-fold higher risk of CKD (5). Other aspects of living with and managing severe mental illness likely contribute to this increased CKD risk, including higher rates of smoking, substance use, and socioeconomic deprivation, as well as lower rates of physical activity and health care access (2).

Individuals with severe mental illness also experience inequalities in access to care, from factors such as diagnostic overshadowing, whereby physical symptoms may be dismissed as psychosomatic or otherwise psychological. Additionally, this patient group is less likely to receive specialist kidney care or to be waitlisted for kidney transplants (6). Among some decision-makers, severe mental illness may be seen as a contraindication to receiving a transplant, due to perceptions of noncompliance with post-transplant care (7). However, there are limited data to support these assumptions, as the evidence suggests that transplant outcomes are similar between those with severe mental illness and those without (6). Considering access to care, clinical outcomes—along with other factors of which we do not yet fully know the role (3)—should be researched further to explain the higher mortality rates and suboptimal care for those with severe mental illness and CKD (6).

This combination of increased risk of CKD and experiences of inferior outcomes of care for those with severe mental illness and CKD suggests a need for targeted support and intervention. However, this is a significantly under-researched area. With further research and deeper understanding, health care professionals can more effectively meet this population's needs and improve health outcomes (6). ■

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The authors report no conflicts of interest.

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What's Next for Onconephrology? Key Takeaways From Kidney Week 2024

By Prakash Gudsoorkar

https://doi.org/10.62716/kn.000342024

The interplay between nephrology and oncology continues to evolve as advanced cancer therapies highlight the delicate balance of safeguarding kidney health while optimizing therapeutic outcomes. ASN Kidney Week 2024 showcased key findings that shed light on nephrotoxic risks and advancements in biomarker-based diagnostics. Seven groundbreaking studies presented at the meeting underscore the need for multidisciplinary approaches and innovative strategies to enhance patient outcomes in this intersectional field.

Infliximab in steroid-dependent immune checkpoint inhibitor-acute interstitial nephritis

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy but carry a 3%–5% risk of acute interstitial nephritis (ICI-AIN), with some cases exhibiting steroid dependence. A study presented at Kidney Week (1) detailed three patients with biopsy-confirmed ICI-AIN treated with infliximab as a steroid-sparing agent. All patients initially showed elevated biomarkers, including urine CXCL9, tumor necrosis factor-α, RNA-binding protein, serum interleukin-2 receptor, and C-reactive protein, which decreased following therapy. Infliximab enabled steroid tapering while preventing significant serum creatinine rise in all cases. The relapse-associated rise in biomarkers underscores their potential as indicators for monitoring disease activity. These findings highlight the promise of infliximab in managing steroid-dependent ICI-AIN, although larger studies are needed to validate these biomarkers and therapeutic strategies.

Risk stratification for chronic kidney disease postnephrectomy

Nephrectomy for renal cell carcinoma increases the risk of chronic kidney disease (CKD), and risk stratification tools are critical for early intervention. The Australian risk stratification score for CKD (ARSC) was assessed in a Brazilian cohort of 349 patients with renal cell carcinoma undergoing nephrectomy (2). While ARSC demonstrated satisfactory discrimination (area under the concentration time curve, 0.70), it overestimated CKD risk in higher-risk categories. These findings emphasize the need for external validation of risk scores across diverse populations. Tailored follow-up strategies for patients at risk for CKD can mitigate CKD progression, making accurate risk-stratification tools an indispensable part of postnephrectomy care.

Glucagon-like peptide-1 receptor agonists and acute kidney injury in oncology

The safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with cancer has been debated due to reports of acute kidney injury (AKI). A retrospective analysis of over 14,000 patients treated with anticancer therapies revealed no significant association between GLP-1RA use and increased AKI risk (3). Despite exposure to nephrotoxic chemotherapies, patients treated with GLP-1RAs showed similar AKI rates compared with those not receiving these agents. These findings reassure clinicians about the safety of GLP-1RAs on the kidneys and suggest that their potential cardiovascular and metabolic benefits can be safely extended to patients with cancer.

Magnesium's role in preventing cisplatin-induced AKI

Cisplatin, a cornerstone in cancer treatment, poses a significant risk of nephrotoxicity. A multicenter cohort study evaluated the effect of intravenous magnesium (Mg) administration in over 13,000 patients receiving cisplatin (4). Mg administration was associated with a significant reduction in the risk of moderate to severe cisplatin-associated AKI (adjusted odds ratio, 0.73). These findings align with preclinical evidence suggesting that Mg reduces cisplatin uptake by renal tubular cells. With no currently established standard of care to prevent cisplatin nephrotoxicity, these results lay the groundwork for prospective trials to confirm the nephroprotective role of Mg.

The role of sodium-glucose cotransporter-2 inhibitors during cisplatin therapy

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are well known for their nephroprotective benefits in CKD and heart failure, but their role in acute settings remains unclear. A retrospective study of 300 patients assessed the safety of SGLT2i use during cisplatin therapy (5). Over 1 year, SGLT2i users and nonusers experienced similar declines in kidney function, and no significant differences were observed in AKI or major adverse kidney events, including mortality or dialysis initiation. While these findings are promising, they emphasize the need for prospective studies to explore whether SGLT2is can offer protective benefits during cisplatin therapy.

Advancing biomarker-based diagnostics for ICI-AIN

The limitations of kidney biopsy in diagnosing immune-related kidney injuries have fueled efforts to develop noninvasive biomarkers. Researchers used Nucleic Acid Linked Immuno-Sandwich Assay (NULISA) to assess 203 proteins in urine and plasma from patients treated with ICI (6). A novel two-protein urine signature emerged as a highly accurate tool for diagnosing ICI-AIN, achieving an area under the concentration time curve of 0.94. This represents a significant improvement over traditional biomarkers such as CXCL9. By enabling an earlier and a less-invasive diagnosis, these findings could revolutionize the management of ICI-AIN, improving outcomes for patients receiving life-saving ICIs.

Single-cell analysis illuminates ICI-AIN pathogenesis

Building on the biomarker findings, another study used single-cell RNA sequencing to map the cellular landscape of ICI-AIN (7). The study identified $CD8^+$ T cells as key mediators of disease by analyzing kidney and urine samples from patients with biopsy-confirmed ICI-AIN. These cells, conserved across kidney tissue and urine, exhibited gene-expression patterns consistent with interferon-gamma signaling. The findings provide mechanistic insights into ICI-AIN and reinforce the feasibility of using urine samples for noninvasive diagnostic testing. This innovative approach paves the way for targeted therapies and improved diagnostic tools in immune-mediated kidney injuries.

Implications for clinical practice and research

Together, these studies highlight the growing complexity of nephrology in oncology. The potential of infliximab to manage steroid-dependent ICI-AIN, the promise of Mg and SGLT2is in mitigating chemotherapy-associated AKI, and the development of cutting-edge biomarkers all underscore the importance of nephrologists in cancer care. At the same time, the limitations of existing tools like ARSC emphasize the need for robust, externally validated strategies to guide clinical decision-making.

ASN Kidney Week has once again demonstrated the power of multidisciplinary collaboration in advancing patient care. The intersection of oncology and nephrology is a challenging yet promising field, in which innovative approaches are essential to address nephrotoxicity risks while preserving the efficacy of cancer therapies. As research continues to evolve, nephrologists are uniquely positioned to lead these efforts, improving the lives of patients navigating both cancer and kidney diseases. ■

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The author reports no conflicts of interest.

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Complement Inhibitors for the Treatment of C3G: The Dawn of a New Era

By Kirsten Martin and Matthew A. Sparks

https://doi.org/10.62716/kn.000262024

C3 glomerulopathy (C3G) is a rare form of glomerulonephritis, comprising two main subtypes: dense deposit disease and C3 glomerulonephritis. The pathogenesis of C3G centers on the dysregulation of the alternative complement pathway, often due to autoantibodies known as C3, C4, or C5 nephritic factors, or genetic mutations in key complement regulatory proteins. On kidney biopsy, C3G can sometimes resemble postinfectious glomerulonephritis or, rarely, be associated with monoclonal gammopathies; both conditions should be considered but were excluded in the clinical trials discussed in this article.

C3G primarily affects pediatric and young adult populations and, at present, lacks any US Food and Drug Administration (FDA)-approved therapies. As a result, patients frequently experience progressive kidney disease and intense proteinuria, often culminating in kidney failure requiring dialysis. Even for those who undergo kidney transplantation, the disease has a high recurrence rate, significantly impacting long-term outcomes. Within a decade of diagnosis, 30%–50% of individuals with C3G progress to kidney failure (1). Guidelines recommend initial treatment with steroids and mycophenolate mofetil, although there are no randomized controlled trial data to support this practice. Observational studies assessing the efficacy of this approach have been small and have demonstrated only modest improvements in clinical remission (2–4). Eculizumab, a C5 inhibitor, has been proposed as a more targeted treatment but has not been shown to be effective, leaving patients and practitioners with a dearth of therapeutic options (5).

New targeted factor B, C3, and C3b inhibitors are under investigation as therapeutic agents for C3G and have the potential to change the landscape of treatment for patients with this rare disease. The VALIANT trial (Phase III Study Assessing the Efficacy and Safety of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis), reported as a late-breaking clinical trial at ASN Kidney Week 2024, is a double-blind, randomized, placebo-controlled phase 3 trial investigating proteinuria reduction from pegcetacoplan, one such C3 and C3b inhibitor (6). This trial enrolled 124 patients aged 12 years or older with a diagnosis of C3G, including both native cases and post kidney transplant recurrences. Patients were randomized to receive twice-weekly subcutaneous pegcetacoplan infusions at home or placebo. The primary outcome measured was the change in the log-transformed urine protein-to-creatinine ratio (UPCR) from baseline to 26 weeks. Impressively, the pegcetacoplan group achieved a 68% relative reduction in proteinuria compared with the placebo group after just 6 months of treatment.

Investigators also observed significant improvements in key secondary endpoints, including stabilization of the estimated glomerular filtration rate (eGFR) at 26 weeks, with a reduced eGFR decline of 6.3 mL/min/1.73 m² compared with the placebo group. Kidney biopsies taken after 26 weeks of treatment revealed clinically and statistically significant reductions in C3c (protein fragment of C3) staining, with an impressive 71% of patients treated with pegcetacoplan achieving zero-intensity staining. Notably, there was no indication of increased adverse events in the treatment groups. These findings highlight a promising new therapeutic option for patients with C3G, with the potential to prevent kidney failure entirely in this population.

Another inhibitor of alternative complement activation, iptacopan, a factor B inhibitor, has also shown promising results in treating patients with C3G. In the APPEAR-C3G trial (Study of Efficacy and Safety of Iptacopan in Patients With C3 Glomerulopathy), patients receiving iptacopan, an oral therapy, achieved a 35% reduction in proteinuria at 6 months, with this effect sustained through 12 months of treatment. Additionally, iptacopan stabilized eGFR and significantly decreased C3 deposition scores on biopsy compared with placebo (7, 8).

These promising advances bring new hope that we may soon have effective, targeted treatments for individuals affected by this rare but serious disease. However, with pegcetacoplan projected to cost nearly $500,000 per year (it is FDA-approved for geographic atrophy and paroxysmal nocturnal hemoglobinuria), securing insurance or pharmaceutical coverage will be essential for accessibility. It is also likely that these treatments would be lifelong, and the effects of discontinuation on disease progression remain unknown—a critical factor to discuss with all patients, especially women of childbearing age, who may prefer to avoid these medications during pregnancy due to limited safety data. Additionally, these complement inhibitors necessitate vaccination against encapsulated organisms, such as those causing meningococcal infections. However, the long-term infectious risks associated with these treatments remain uncertain.

In the coming year, we may see FDA approval of two new therapies specifically demonstrated to improve meaningful clinical outcomes in patients with C3G—something we have never had before. ■

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The authors report no conflicts of interest.

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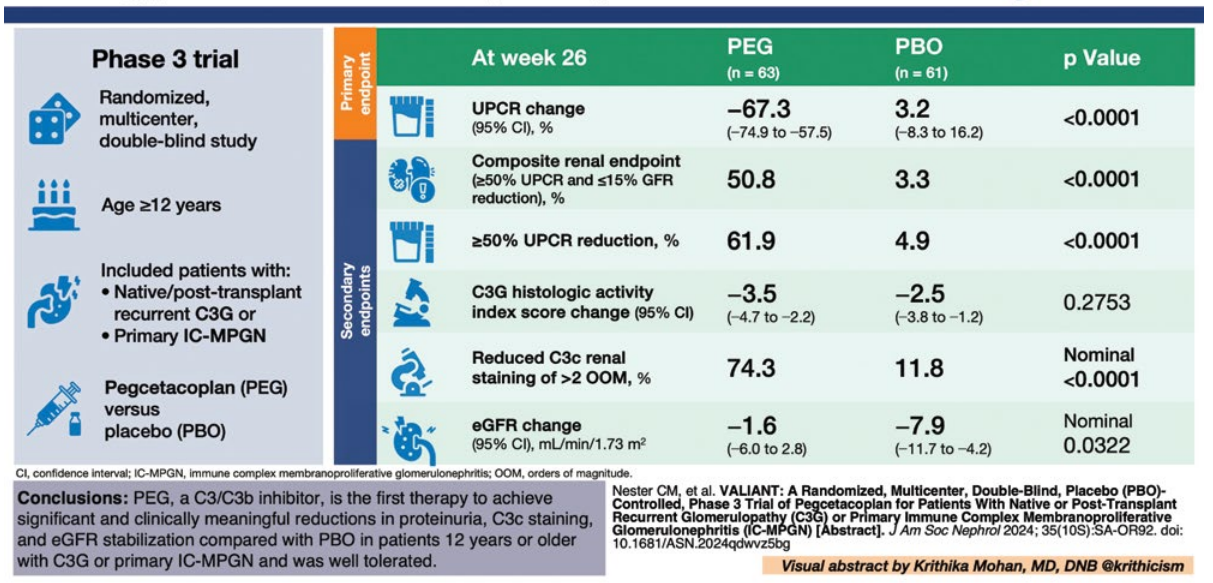

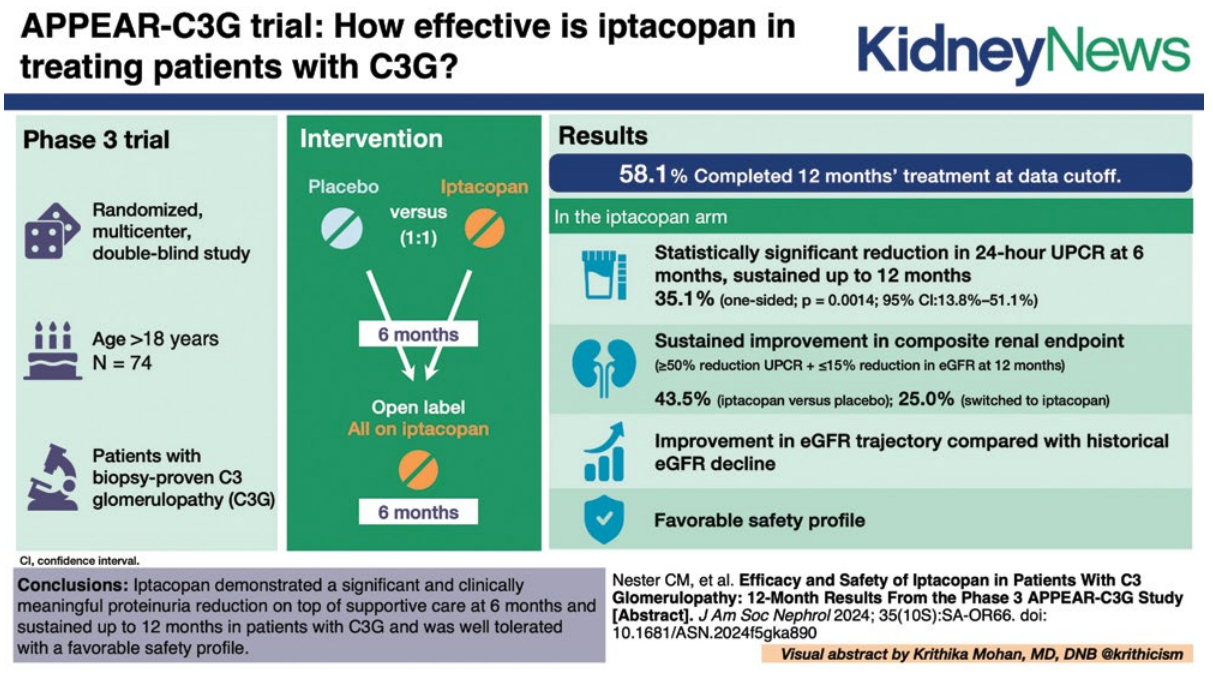

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Finerenone: Completing the Cardiorenal Guideline-Directed Medical Therapy?

By Zahra Khosravi, Muneeb Iqbal, and Sam Kant

https://doi.org/10.62716/kn.000332024

Heart failure (HF) and chronic kidney disease (CKD) are often a concurrent diagnosis; almost 50% of patients with HF experience kidney dysfunction, and HF is prevalent in 17%–50% of patients with CKD (1). Kidney function is an independent predictor for inpatient mortality of patients with acute HF, length of hospital stay, and readmission rate (2). Finerenone, a nonsteroidal mineralocorticoid antagonist (MRA), has proven efficacy in reducing kidney disease progression, albuminuria, and cardiovascular events (including hospitalization for HF) in patients with CKD and type 2 diabetes, whereas steroidal MRAs reduce morbidity and mortality among patients with HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (3, 4). Given significant overlap of HF and CKD along with therapeutic benefits of MRAs in these individual diseases, two recent studies in *The New England Journal of Medicine* (5) and the *Journal of the American College of Cardiology* (6) explored cardiac and renal outcomes associated with finerenone in patients with HFpEF and HF with moderately reduced EF (HFmrEF).

In *The New England Journal of Medicine*, Solomon et al. (5) conducted an international, double-blind study that evaluated composite outcomes of worsening HF events, including hospitalizations and mortality, in patients treated with finerenone versus placebo (FINEARTS-HF). Their results showed a significant reduction in primary outcome events for the finerenone group compared with placebo (relative risk, 0.84; 95% confidence interval [CI], 0.74–0.95), although improvement in New York Heart Association classification scores at 12 months was not statistically significant (odds ratio, 1.01; 95% CI, 0.88–1.15). They also assessed kidney composite outcomes, including a more than 50% decline in the estimated glomerular filtration rate (eGFR), initiation of long-term dialysis, or kidney transplantation. Finerenone was not associated with an improvement in kidney composite outcome, although it is pertinent to note that these patients were at low risk for kidney disease progression given low prevalence of albuminuria. The trial had the following limitations:

- Low enrollment of Black patients was attributed to global distribution, although the authors state that it was proportional to the population percentage on a regional basis.
- The prespecified subgroups were underpowered, so the results of the subgroup analysis should be interpreted with caution.
- It cannot be deduced that benefits could be redemonstrated with other MRAs.

A study ascertaining kidney outcomes in the FINEARTS-HF cohort was simultaneously published in the *Journal of the American College of Cardiology* and specifically addressed sustained ≥50% eGFR decline or kidney failure (sustained eGFR decline, <15 mL/min/1.73 m^2); initiation of maintenance dialysis; renal transplant; eGFR slope; and changes in the urine albumin/creatinine ratio (6). Albuminuria was a predictor of adverse cardiovascular and kidney outcomes in HFmrEF and HFpEF (7). The authors found that those assigned to finerenone had an initial acute decline in eGFR from baseline to month 3, although it did not alter the eGFR slope chronically. Finerenone reduced urine albumin/creatinine ratio by 30% (95% CI, 25%–34%) over 6 months versus placebo, an effect that persisted throughout follow-up—a pertinent finding that likely has long-term implications for the development of kidney failure. In addition, it reduced the risk of new onset of microalbuminuria by 24% (hazard ratio, 0.76; 95% CI, 0.68–0.83) and macroalbuminuria by 38% (hazard ratio, 0.62; 95% CI, 0.53–0.73). The long-term effect of this reduction in onset of albuminuria and levels could not be assessed due to short-term follow-up associated with the study.

Although both studies report hyperkalemia as an adverse effect of finerenone, neither assessed it in depth. There is lack of robust guidelines on the frequency of a potassium measurement postdrug commencement and characteristics that portend a higher risk of hyperkalemia.

In light of the above findings, finerenone has the potential to become an essential component of the cardiorenal goal-directed medical therapy in populations that have a high proportion of overlap of CKD and HF, especially after the success of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists (2). A few questions remain:

- When is the ideal time to commence finerenone, and where does it stand in the sequence of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists?
- Is finerenone going to be beneficial when treating patients established on the aforementioned drugs?
- Is the reduction in onset of albuminuria and levels in patients with established HFmrEF and HFpEF (and therefore preventing development of CKD) going to correlate with optimal long-term cardiac and renal outcomes? Although the answer to this is intuitively positive, follow-up data from these trials are required.

In conclusion, we are progressively entering an era in which two diseases (CKD and HF) can be treated with multiple agents. Whereas nephrology was a bit late to the concept of guideline-directed medical therapy, it has certainly arrived and will be carrying the baton going forward. ■

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The authors report no conflicts of interest.

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Shaping the Future of AKI: Trends to Watch in 2025

By Jia Hwei Ng

https://doi.org/10.62716/kn.000372024

As we move into 2025, the field of acute kidney injury (AKI) research continues to evolve, promising exciting advances in science, technology, and patient care. Based on recent developments and presentations, the following are key trends to watch:

1 Interorgan communication in AKI

Emerging research is shedding light on the critical interplay between organs during AKI. The Kidney Week 2024 presentation "Interorgan Cross-Talk: Kidney Injury and More" emphasized the systemic effects of AKI, moving beyond kidney-centric models to study crosstalk among the kidney, gut, heart, brain, lungs, and other organs (1). Understanding these connections could unlock new therapeutic approaches targeting systemic inflammation and organ protection.

2 Advancements in prognostication and management in AKI

Oral abstracts presented at Kidney Week last year highlighted key advancements in predicting and managing AKI. Researchers are improving risk stratification using biomarkers and uncovering new insights into AKI subtypes through precision medicine. Innovative tools, such as ultrasound-guided diuretic therapy and muscle ultrasonography, are being studied to predict fluid responsiveness and aid in patient management. These approaches aim to enhance care for patients who are critically ill by streamlining care transitions and improving recovery predictions. Together, these studies offer practical strategies to personalize and optimize AKI treatment.

3 Novel therapeutic pathways

Emerging therapies are paving the way for transformative AKI treatment through metabolic reprogramming and regenerative medicine. The LiMiT AKI trial, for example, is investigating metformin as a treatment for sepsis-associated AKI (2). By activating kidney tubular adenosine monophosphate-activated protein kinase, metformin has shown potential to reduce AKI severity and mortality in animal models (3). At the same time, regenerative medicine is advancing with mesenchymal stem cell (MSC) therapies. MSCs provide anti-inflammatory and tissue-regenerative benefits, and early trials confirm their safety (4). Future innovations, such as engineered extracellular vesicles derived from MSCs, hold promise for even greater therapeutic efficacy. These therapies reflect a multifaceted approach to addressing AKI's systemic and localized impacts.

This year promises to be a transformative year for AKI research, driven by breakthroughs in interorgan communication, prognostication tools, and therapeutic innovations. By combining systemic insights, advanced management strategies, and cutting-edge therapies, researchers and clinicians are redefining the future of AKI care. ■

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Dr. Ng reports receiving funding support from the National Institutes of Health and the Breslin Family Foundation and has received consultancy fees from George Clinical and Vifor Pharmaceuticals. She is the founder of PublishedMD Consulting, LLC.

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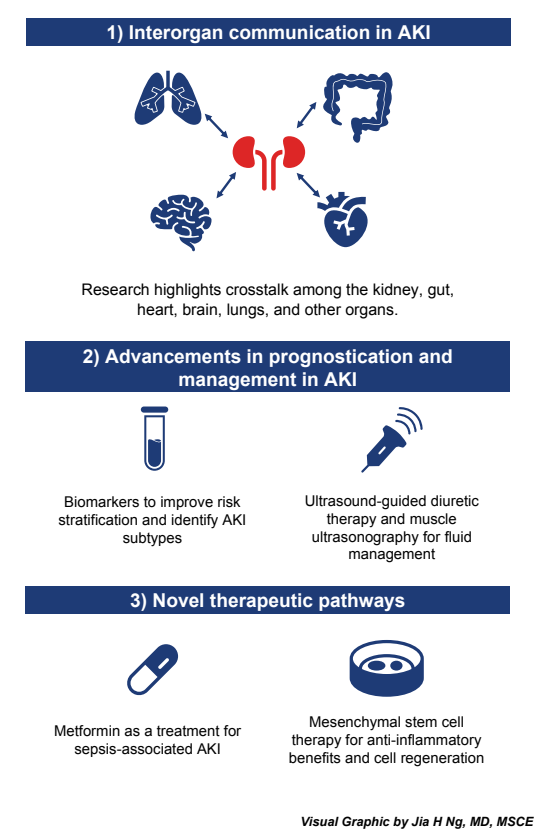

What Role Should Nephrologists Play in the Care of Patients With Kidney Diseases?

By Katherine Kwon

https://doi.org/10.62716/kn.000292024

Patients with advanced kidney diseases usually see their nephrologists far more often than the other members of their care team. This has worked well for nephrologists in a fee-for-service environment, for whom these patients represent a reliable income stream for the practice due to their frequent visits. However, when patients are shifted to value-based care (VBC) models, financial success is uncoupled from visit volume and instead comes from reduction in care costs, especially hospitalizations. A particular focus of VBC efforts includes patients with multiple comorbid illnesses, since they are hospitalized frequently and are at high risk for care gaps because they are seen by multiple specialists. Nephrologists risk being sidelined in the care of patients with kidney diseases if they do not embrace updated clinical guidelines, polychronic care, and efforts to address care fragmentation.

Cardiovascular-kidney-metabolic (CKM) syndrome is common in the population of patients living with chronic kidney disease (CKD). Therapies for CKM syndrome, including angiotensin-converting enzyme inhibitors (ACEis), sodium-glucose cotransporter-2 inhibitors (SGLT2is), and glucagon-like peptide-1 receptor agonists (GLP-1RAs), now have multiple indications and can be reasonably prescribed by primary care physicians, cardiologists, endocrinologists, and nephrologists. The prevalence of CKM syndrome and the high cost of care inspired St. Luke's Mid America Heart Institute to create the Cardiometabolic Center Alliance, a network of clinical centers of excellence. Most of the founding clinics are run by cardiologists, with scant representation from nephrologists. Earlier this year, the alliance published its results in improving use of guideline-directed medical therapy (1). The rate of SGLT2i use in patients with diabetes and CKD improved from 33.3% to 82.3% over 6 months. This is substantially better than the 13% reported nationwide in patients with diabetic kidney disease (2).

The Advancing American Kidney Health Initiative VBC programs focus on patients with stages 4–5 CKD and kidney failure. Many of the companies that partner with nephrologists in these programs are choosing to hire their own clinical staff to implement their interventions. One company describes the fragmented care that patients can experience and notes, "Nephrologists are focused on dialysis and care within their centers." They tout their "multispecialty teams of employed physicians and nurse practitioners" to provide complex, coordinated care (3). Another company lists the tasks its nurse practitioners perform, including "deliver[ing] the best care" and "break[ing] communication [silos]" (4).

Where, then, are the nephrologists in the care of these patients with kidney diseases? For now, they may be happy that someone else is taking on the load. Gaining experience with new medications such as GLP-1RAs takes effort, and fee-for-service visits pay the same, whether or not updated

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What Role Should Nephrologists Play?

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standards of care are applied. Coordinating care with other physicians is time consuming and poorly reimbursed. However, the Centers for Medicare & Medicaid Services has a stated goal of 100% of Medicare beneficiaries to be in a VBC arrangement by 2030 (5). If nephrologists remain focused on dialysis rounds and defer the implementation of new therapies to the primary care physicians and cardiologists, they will find themselves on the outside of newer care models and clinics.

As we head into 2025, it should be just as unthinkable for a nephrologist to defer treatment of heart failure with an SGLT2i or obesity with a GLP1-RA as it would be to pass on prescribing an ACEi for hypertension. Nephrologists should be actively involved in treating all aspects of CKM syndrome. Practices should be building analytic capabilities to monitor their performance and embracing partnerships that rely on their active participation in improving outcomes. By doing so, they will help ensure that our specialty remains centered in the care of patients with kidney diseases. ■

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The author reports no conflicts of interest.

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A Closer Look at Sparsentan

By Edgar V. Lerma

https://doi.org/10.62716/kn.000422024

Scientific posters presented at ASN Kidney Week 2024 highlighted significant advancements in nephrology. Notably, there has been an explosion of data pertaining to diabetic kidney disease and immunoglobulin A nephropathy (IgAN). Three years ago, in the Kidney Watch 2022 edition of *Kidney News*, we explored the four pillars of diabetic kidney disease management, which provided a comprehensive framework for treatment (1). As we consider topics to watch in 2025, the focus shifts to IgAN, reflecting the growing attention and research in this area.

One of these novel agents is sparsentan, a nonimmunosuppressive dual endothelin angiotensin receptor antagonist that was recently approved by the US Food and Drug Administration with an indication to slow kidney function decline in adults with IgAN who are at risk of disease progression. Several posters at Kidney Week 2024 focused on sparsentan, with four standing out as particularly noteworthy, as described below.

For context, PROTECT (A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy) is a large, international, double-blind, active phase 3 randomized controlled trial designed to evaluate the efficacy and safety of sparsentan compared with irbesartan in patients with IgAN (2). The study demonstrated in 2-year results that sparsentan effectively reduced proteinuria and increased the proportion of patients achieving complete remission (CR) compared with the maximum-labeled dose of irbesartan.

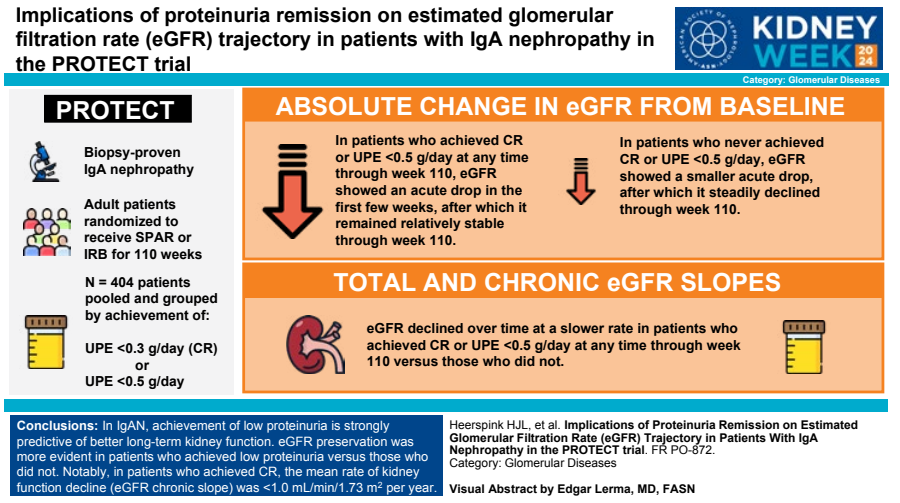
It has also been demonstrated in other studies that in IgAN, proteinuria is significantly associated with worse kidney outcomes, and reduction has been shown to predict slower disease progression and lower risk of kidney failure (3, 4).

Implications of Proteinuria Remission on Estimated Glomerular Filtration Rate (eGFR) Trajectory in Patients With IgA Nephropathy in the PROTECT Trial

Proteinuria is currently the only validated biomarker in IgAN, making its reduction a critical therapeutic goal. A post hoc analysis of the 110-week PROTECT trial evaluated the eGFR trajectories in patients achieving CR of proteinuria (<0.3 g/day) or urinary protein excretion (UPE) <0.5 g/day at any time compared with those who did not.

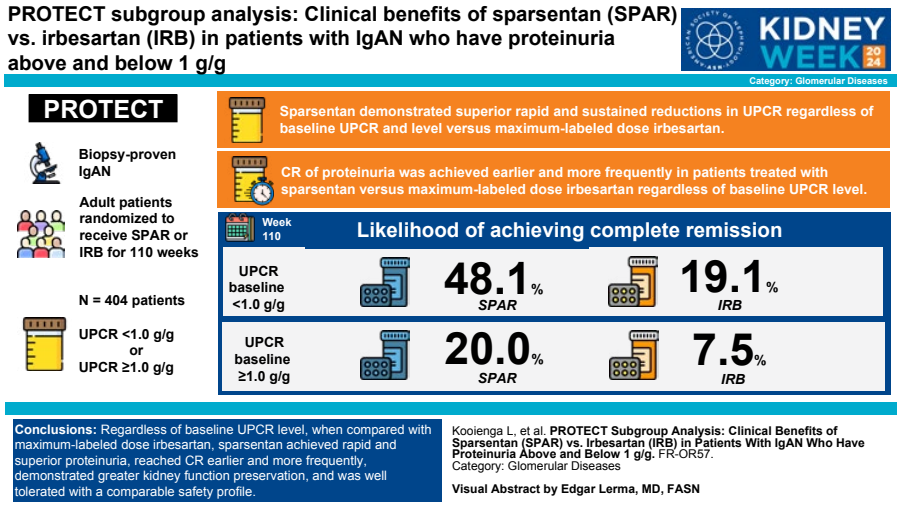
The findings reinforced the relationship between proteinuria reduction and kidney function preservation, highlighting sparsentan's long-term benefits. Achieving CR (UPE <0.3 g/day) or UPE <0.5 g/day regardless of treatment was associated with better preservation of kidney function compared with patients who did not achieve these targets. This aligns with the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines draft, emphasizing the importance of maintaining UPE <0.5 g/day (ideally, <0.3 g/day) to mitigate disease progression in IgAN.

Sparsentan demonstrated greater proteinuria reduction and a higher likelihood of achieving CR compared with irbesartan. Additionally, sparsentan slowed the rate of GFR decline more effectively. Among patients achieving CR, the mean rate of kidney function decline (eGFR total slope) was below the therapeutic goal of <1.0 mL/min/1.73 m² per year. Treatment-emergent adverse events were reported in 93% of patients achieving CR versus 89% of those who did not.



PROTECT Subgroup Analysis: Clinical Benefits of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients With IgAN Who Have Proteinuria Above and Below 1 g/g

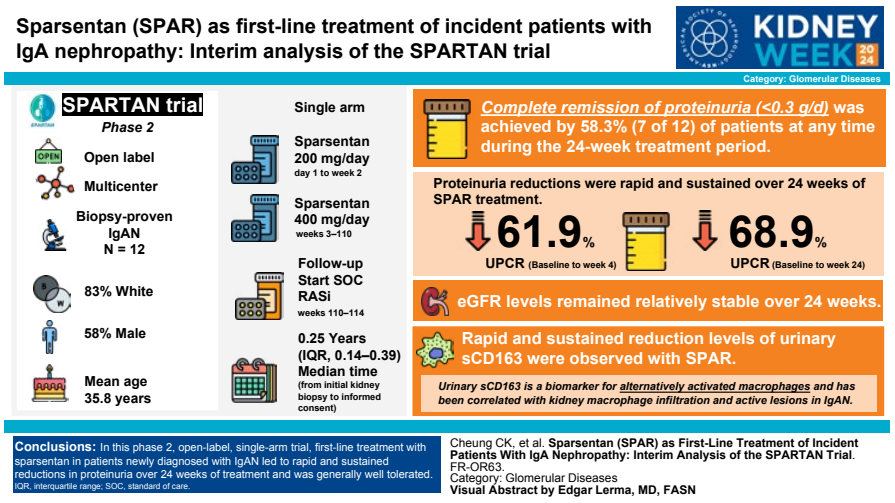
Although those who were randomized to sparsentan had a greater proteinuria reduction and smaller change in eGFR from baseline to week 110, regardless of the baseline urine protein-to-creatinine ratio (UPCR), this study showed that those with baseline proteinuria <1 g/g were more likely to achieve CR (48.1% sparsentan versus 19.1% irbesartan) compared with those with baseline proteinuria ≥1 g/g (20.0% sparsentan versus 7.5% irbesartan).



Sparsentan (SPAR) as First-Line Treatment of Incident Patients With IgA Nephropathy: Interim Analysis of the SPARTAN Trial

A fascinating study presented at Kidney Week 2024, this is a single-arm study, in which the authors attempted to determine the safety, efficacy, and mechanistic action of sparsentan as first-line therapy in patients newly diagnosed with IgAN. Note that eligibility criteria for this study did not allow renin-angiotensin system inhibitor (RASi) use within ≤12 months or systemic immunosuppressive therapy within ≤6 months.

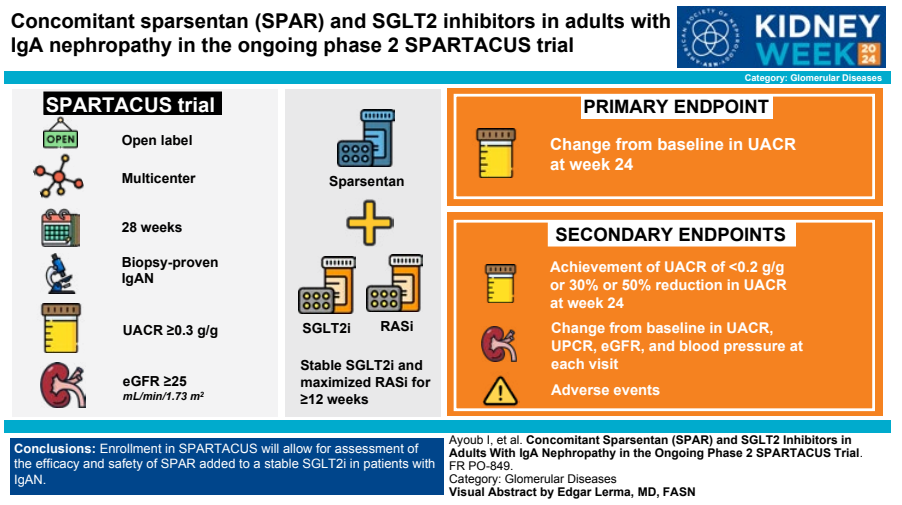
As a first-line treatment, sparsentan led to a rapid and sustained reduction in proteinuria (≈68.9% at week 24). After 24 weeks, 60% of patients achieved CR. Most interestingly, there was also a rapid and sustained reduction in the levels of urinary soluble CD163 (sCD163)—a marker for alternatively activated macrophages that has been correlated with kidney macrophage infiltration and active lesions in IgAN. For reference, in the TESTING (Therapeutic Evaluation of Steroids in IgA Nephropathy Global) trial (5), a ≥50% reduction of urinary sCD163 was associated with a reduced risk of the composite kidney endpoints. This is particularly significant because this is the first demonstration of sparsentan's anti-inflammatory effect in humans.



Concomitant Sparsentan (SPAR) and SGLT2 Inhibitors in Adults With IgA Nephropathy in the Ongoing Phase 2 SPARTACUS Trial

Several clinical studies have demonstrated that sodium-glucose cotransporter-2 inhibitors (SGLT2is) have reduced proteinuria and the risk of progression to kidney failure in patients with IgAN (6, 7). One can therefore assume that combining sparsentan with an SGLT2i may provide therapeutic benefits. This is the premise of the ongoing SPARTACUS trial (a 24-week phase 2, exploratory, open-label, single-arm, multicenter study), which will evaluate the efficacy and safety of sparsentan added to stable SGLT2i treatment in adults with IgAN.

In this study, patients on a stable regimen of RASi and SGLT2i were transitioned to a combination of sparsentan and SGLT2i. Interim analysis revealed that this combination achieved substantial additional reductions in the urine albumin-to-creatinine ratio (UACR) in patients with IgAN, with reductions of ≥30% observed in nearly two-thirds of patients and ≥50% in approximately one-third. The study is ongoing, and future analyses will include data from a larger patient cohort.



Conclusion

Preliminary findings from these studies underscore the significant benefits of sparsentan for patients with IgAN. The most commonly reported adverse events included COVID-19, headache, hyperkalemia, peripheral edema, dizziness, hypotension, and hypertension. Further updates from this research in IgAN are anticipated. The nephrology community should stay tuned into this research area in 2025. ■

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Dr. Lerma reports serving as a member of the speaker/advisory boards for Amgen, AstraZeneca, Bayer, Calliditas, Novartis, Novo Nordisk, Opko, Otsuka, scPharmaceuticals, Travere, and Vertex.

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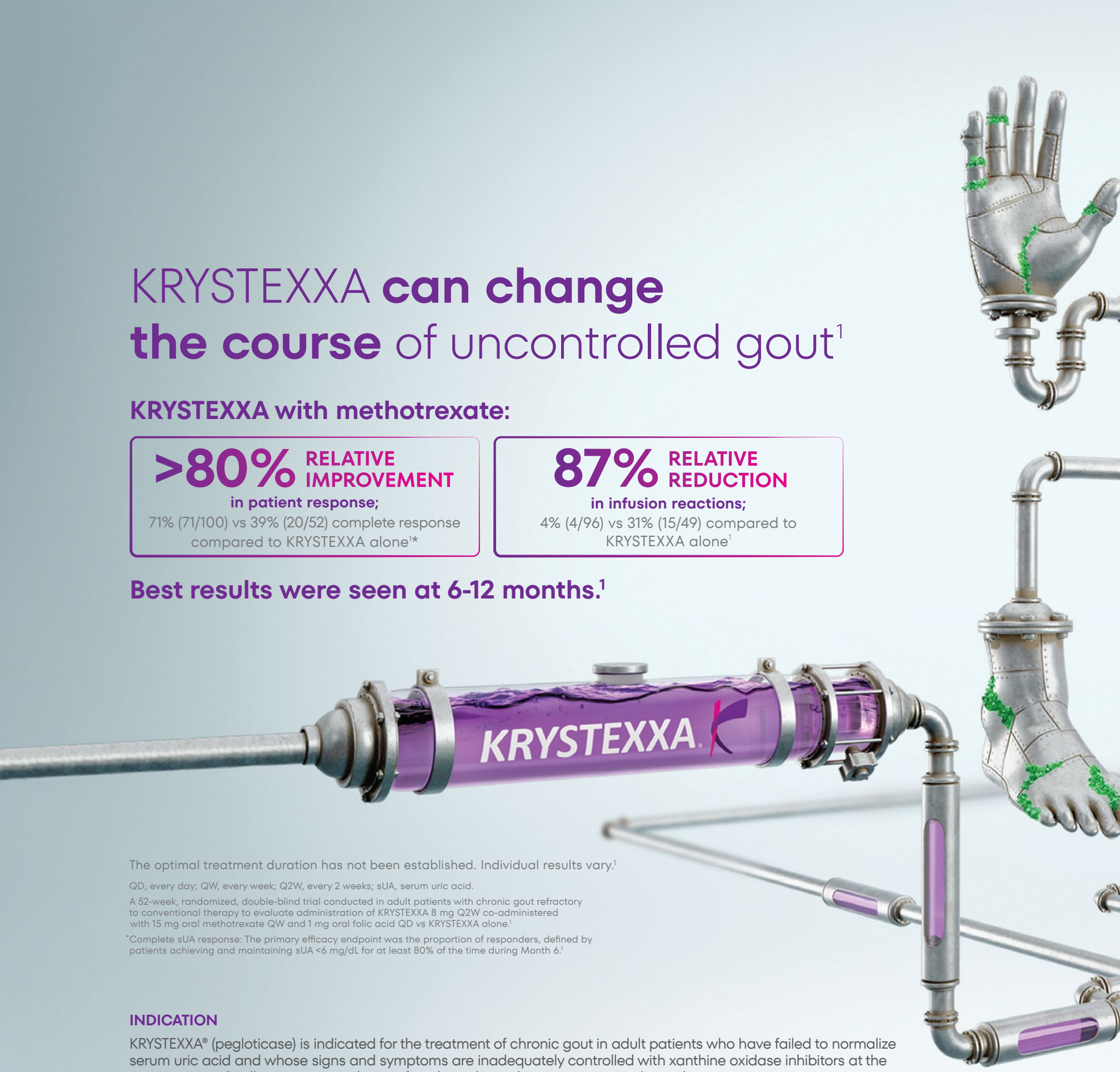
KRYSTEXXA **can change the course** of uncontrolled gout[1]



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]

Best results were seen at 6-12 months.[1]

The optimal treatment duration has not been established. Individual results vary.[1]

QD, every day; QW, every week; Q2W, every 2 weeks; sUA, serum uric acid.

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]

*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.

KRYSTEXXA has not been studied to reverse damage to the heart, kidneys, or any organ.

Dissolve years of systemic urate deposition **with KRYSTEXXA**[2,3]

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.** Sundy JS, et al. *JAMA.* 2011;306:711-720. **3.** Schlesinger N, et al. *Arthritis Rheumatol.* 2017;69(suppl 10):1-4426.

KRYSTEXXA® pegloticase

AMGEN Rare Disease

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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Supporting Pregnancy and Parenthood in Fellowship

By Sarah Rogal and Jessica Mace

https://doi.org/10.62716/kn.000212024

Sarah Rogal, MD, MPH

I gave birth to my daughter just 2 weeks before my pediatric nephrology fellowship was supposed to start. I still remember the anxiety I felt about telling the program about our daughter's due date. Luckily, everyone was supportive, however not fully informed of the new Accreditation Council for Graduate Medical Education (ACGME) leave policies that had recently been updated. Working closely with human resources, I was able to go back to work when my daughter was 10 weeks old.

I was doing a lot of firsts all at once—new city, new home, new job, and a new baby—while navigating parenting, breastfeeding, pumping, and childcare. My husband, also in medicine, was transitioning to a new job as well. In my first week back at work, one of my attendings lent me a breast pump and gave me a box of oat bars so I always had a snack at my desk. In that moment, in which everything else felt uncertain, this act of kindness and attention to the transformation I had just gone through helped me feel comfort among all these firsts.

Jessica Mace, MD

I, on the other hand, having already had a child while in residency, was aware of the ACGME and The American Board of Pediatrics (ABP) policies and knew that there was always uncertainty about how policies are enacted. Years in parenthood and medicine had made me more comfortable living in this world of uncertainty, but what I was not comfortable with were the risks associated with waiting until after fellowship to have my second child. I knew that with my increasing age, my fertility was declining. I also knew that the risk of infertility for women in medicine is higher than that of the general population. In a 2023 survey of 1056 women in medicine, 34% reported infertility, and half of those required in vitro fertilization (commonly known as IVF) compared with national data, in which only 6%–19% of women experience infertility (1). With all of this information, a calculated risk was taken, and I gave birth to my second child 1 month prior to the start date of my pediatric nephrology fellowship. I, too, have been lucky to find support during my training and my journey through motherhood in medicine.

Discussion

In the National Survey of Pregnancy and Parenthood Among Nephrology Trainees, recently published in *CJASN*, 79% of trainees did not want to have more children during fellowship (2). In addition, almost half of the respondents were unsure of their institutions' leave policies when asked about their knowledge of parental leave policies. As a reason for respondents to defer pregnancy, approximately 25% felt that there were perceived negative emotions from programs for taking parental leave. What seemed to be the strongest factor to defer pregnancy was that over 60% of respondents said it was because they did not want to extend training (2).

This conversation comes at a crucial time in pediatrics and pediatric nephrology, as there are mounting concerns about the present and future workforce. Thirty percent of pediatric residency slots went unfilled in 2023, and 62% of pediatric nephrology fellowship slots went unfilled in 2024 (3, 4). Within pediatric nephrology training programs, 22% of fellows do not complete their training, and of those who have completed training, 33% plan to reduce or stop clinical work (5). While parental leave is not the only factor contributing to these gaps, we feel it is of growing concern.

Tables 1 and 2 outline the most up-to-date policies from ACGME and ABP, respectively (6, 7). We call on our colleagues to start having a truly open and honest conversation regarding pregnancy, parenthood, and medical training. As a community of pediatric nephrologists, we are small. It is important that we learn how to support and uplift one another to ensure that our community continues to grow. How can we create systemic changes to help young physicians and their families? We dedicate our careers to the future of children, but to put our best foot forward, we also should be looking inward.

By shifting the mental framework to one in which building a family is celebrated, we can pursue systemic changes that provide better support and that nurture the development of strong and resilient physicians. Starting the conversation is where we can begin to make change and acknowledge that everyone's experience will be different and personal. We hope that by sharing our own experiences, we can holistically help trainees, not just in parenting but with any life event or significant change, supporting their mental, physical, and emotional well-being during a rigorous training period. ■

Table 1. ACGME leave policy

- Sponsoring institutions must "provide residents/fellows with a minimum of 6 weeks of approved medical, parental, and caregiver leave(s) of absence…starting the day they are required to report."
- The leave(s) of absence policy does not mandate vacation or sick leave to be used.
- Provide residents/fellows with at least the equivalent of 100% of their salary for the first 6 weeks of approved medical, parental, or caregiver leave(s) of absence taken.
- Provide residents/fellows with a minimum of 1 week of paid time off reserved for the use outside of the first 6 weeks of the first approved medical, parental, or caregiver leave(s) of absence taken.
- Ensure the continuation of health and disability insurance benefits for residents/fellows and their eligible dependents during their approved medical, parental, or caregiver leave(s) of absence.

Accreditation Council for Graduate Medical Education (6).

Table 2. Summary of the ABP "Absences from Training Policy"

- **Allowed absences**: 1 Month of absence per year for vacation, illness, or family leave
- **Additional leave**: 3-Year programs with up to 8 weeks of parental, medical, or caregiver leave over the entire training period; nonstandard/combined pathways with up to 6 weeks of additional leave over the training period
- **Conditions for extended leave**: Must be for parental, medical, or caregiver reasons. Competence must be verified by the program director and Clinical Competency Committee. All required training and scholarly activity (for fellows) must be completed, excluding elective or research time.
- **Training extensions**: Any absence beyond the allowed limits requires training extension. Interruptions exceeding 24 months (residency) or 12 months (fellowship) require an ABP petition to determine credit for prior training.
- **Vacation "banking" discouraged**: Trainees are encouraged to use vacation time yearly to support health and well-being.
- **Institutional variability**: Leave policies are subject to institutional discretion but must align with ABP guidelines.

The American Board of Pediatrics (7).

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The authors report no conflicts of interest.

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Highlighting Continued Achievements and Exploring Future Opportunities: Insights From the 2024 ASN Nephrology Fellow Survey

By Niralee Patel

https://doi.org/10.62716/kn.000352024

The annual 2024 ASN Nephrology Fellow Survey Report provides valuable insights into the current landscape of nephrology training (1). From 962 adult and pediatric fellows, 46% completed the survey. The demographics of survey respondents closely align to the data from the Accreditation Council for Graduate Medical Education, with 40% of participants identifying as women and 43% as US medical graduates (USMGs) (Figure).

Among the 189 surveyed fellows graduating from their programs, private practice remains the dominant career path. Fourteen fellows had plans to pursue critical care, whereas 12 expressed interest in transplant nephrology. Annual median starting base salaries after fellowship were up slightly ($240,000), at 3%, from the previous year; however, overall, they had improved compared with $219,500 reported in 2022. International medical graduates (IMGs) reported higher starting salaries than USMGs, with medians of $250,500 and $225,000, respectively. Notably though, USMGs often face significant educational debt, averaging four times as much compared with IMGs. It would be interesting to explore whether IMGs are obtaining employment in higher-paying rural areas, possibly driven by J-1 visa requirements, the availability of H-1B visa sponsorship with a pathway to residency, or simply the attainability of long-term opportunities.

Seventeen percent of fellows surveyed participated in ASN's Kidney Students and Residents (STARS) program, and 2% participated in ASN's Tutored Research and Education for Kidney Scholars (TREKS) program during their medical student years. These initiatives were created to inspire interest in nephrology, especially with current challenges in recruitment. It would be valuable to revisit these programs to identify and address gaps in which trainees may diverge and explore alternative career paths. Future surveys could also evaluate the impact of newer programs like the NephSim Nephrons mentorship initiative, launched in 2021, to understand their role in fostering lasting interest in the specialty.

One of the most encouraging findings from the 2024 survey is the consistent enthusiasm for nephrology, with 90% of fellows recommending it as a career. USMGs showed slightly higher enthusiasm (94%) compared with IMGs (88%), which has also been consistent over the years. Another consistent theme in the survey is the concerns about the financial and lifestyle challenges of nephrology. Although nephrology is viewed as a fulfilling field, the financial pressures, including higher educational loan debt, and work-life balance struggles can be a real source of stress for those just starting out in their careers.

One notable trend emerging from the survey is the growing role of nephrohospitalists—those who focus solely on inpatient care (2). The nephrohospitalist pathway, which appeals to fellows seeking a more structured schedule and acute-care work, may offer an attractive work-life balance compared with traditional nephrology roles. As the role continues to evolve, could the nephrohospitalist pathway offer a middle ground for those seeking critical care-style work? It may also present a more appealing alternative to hospitalist medicine, a field that many former nephrology candidates are now pursuing. This shift raises the question of whether nephrology can fill the gap for those desiring inpatient, acute-care roles while still providing opportunities for specialization and a fulfilling career path. The growing nephrohospitalist role offers potential aforementioned solutions for fellows, addressing concerns that are central to ongoing recruitment efforts.

Over the years, nephrology fellowship programs are seeing a growing number of candidates interested in critical care. Questions to explore include what educational path these fellows took and what path they plan to take after completing their general nephrology training. Do they continue with further critical care fellowship training, or do they shift focus within nephrology or another subspecialty?

Pediatric nephrology fellows are rarely discussed on this platform, but the data shed light on their similar challenges. A total of 53 pediatric and adult/pediatric fellows participated, with the majority (73%) being USMGs. Similar to adult nephrology fellows, pediatric compensation remains a key concern—the annual median starting salary is reported at $190,000—especially as a majority of these fellows are USMGs with higher educational debt. Despite the challenges, 98% of those surveyed would recommend pediatric nephrology, as they value the opportunity to build long-term relationships with patients and enjoy the diversity of practice settings.

The 2024 ASN Nephrology Fellow Survey Report shows overall satisfaction in nephrology but highlights the known and ongoing challenges regarding compensation, work-life balance, and job availability, particularly among graduating IMGs. While 90% of fellows are satisfied with their career choice, the concerns of the remaining 10% are also important. Despite a modest increase in the median starting salary, several fellows perceive the gap between salary and the profession unfavorably. Private practice is such a dominant career path for nephrology fellows, possibly explained by its financial stability and independence. The growing interest in critical care and nephrohospitalist roles suggests a shift toward more structured, acute care-focused career paths, which likely reflects lifestyle preferences and changes in health care needs. These trends highlight the importance of addressing financial and lifestyle challenges while keeping the specialty appealing in the long run.

Although nephrology is viewed as a fulfilling field, the financial pressures, including higher educational loan debt, and work-life balance struggles can be a real source of stress for those just starting out in their careers.

Looking ahead, it is important that we expand our focus beyond recruitment to include supporting nephrology fellows in their careers after fellowship and continue the growth of our field. Their experiences will be the example for current residents looking at our specialty. ■

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The author reports no conflicts of interest.

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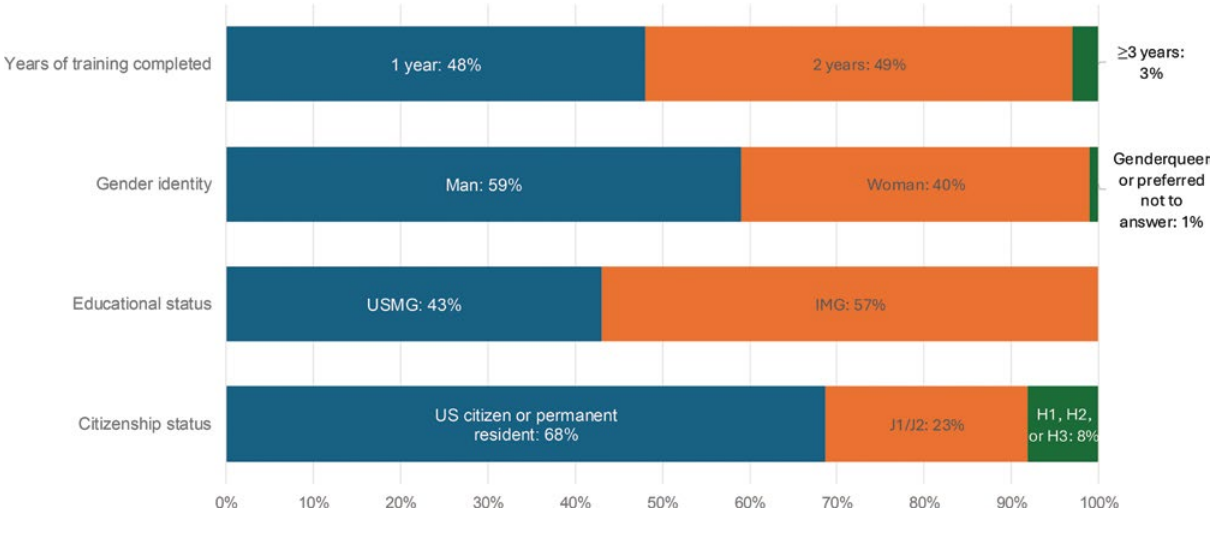
Figure. Adult fellowship participant demographics



Source: Pivert KA, et al.; American Society of Nephrology (1).

Model-Based Clustering: A Solution for ANCA-Associated Vasculitis Classification?

By Nicole Wyatt, Brian Monk, and Koyal Jain

https://doi.org/10.62716/kn.000082024

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is part of a group of small vessel vasculitides affecting multiple organ systems. There are currently no standardized classification criteria for AAV; however, common practice for AAV diagnosis is driven by clinicopathologic phenotypes (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) and serotype classifications (proteinase 3 [PR3]-ANCA and myeloperoxidase [MPO]-ANCA) (1–3). Although most cases of GPA are associated with PR3-ANCA, and most cases of MPA are associated with MPO-ANCA, there can be variability in disease incidence, particularly with geography and race and ethnicity (4), likely reflecting human leukocyte antigen influence (5, 6). Additionally, studies suggest that an ANCA serotype is a more accurate predictor of a clinical outcome and a treatment response than a phenotypic diagnosis alone (7, 8). Given the heterogeneity of AAV that is not represented well in the binary nature of current classification systems, there is interest in using machine learning to classify AAV in an unbiased, data-driven nature.

Gisslander et al. (9) performed model-based clustering on data from the FAIRVASC (Findable, Accessible, Interoperable, Reusable, Vasculitis) project, which included six European registries. The authors analyzed 3868 patients with newly diagnosed GPA and MPA and identified five clusters based on 17 mixed-type clinical variables (e.g., demography, symptom, serum creatinine, C-reactive protein [CRP], and ANCA status) and specific outcomes (e.g., kidney failure and death). These five phenotypic clusters included three groups with high frequency of kidney involvement and two groups with lower kidney involvement (Table). Each cluster had distinct outcomes for death and kidney failure.

Unsupervised machine learning requires the use of large populations for accuracy. This was a strength in this study, which included, to our knowledge, one of the largest cohorts of AAV patients to date. Additionally, the use of real-world patient data allowed inclusion of populations not typically included in many clinical trials. By removing the concept of distinct disease subtypes, the authors were able to truly represent the nonbinary nature of AAV. Current classification methods have issues including overlapping classifications, undervaluing or overvaluing criteria items, and unclassifiable cases; however, this data-driven subclassification limited subjectivity and provided an unbiased view of AAV phenotypes. In contrast to studies supporting serotype-based classification, this study revealed that ANCA status had limited influence on cluster designation. Instead, the main driver of clustering was kidney involvement. The results interestingly showed a higher predictive power for overall patient and kidney survival than current practices, which re-emphasizes the significance of kidney involvement on clinical outcome irrespective of extrarenal manifestations.

There are several weaknesses with this study, including the model being very complex, difficult to interpret, and potentially difficult to incorporate into patient care. Although serum creatinine was included as a modifier for kidney involvement, it is not clear how organ involvement was measured outside of "symptoms," and without a weighted disease activity inclusion, this leans toward a kidney-centered clustering, which may confound the severity and outcomes of the clusters. This study is limited in geography, race, and ethnicity, which hinders generalizability given the influence these characteristics have on AAV. This study relied on variables like creatinine and CRP for grouping; however, a portion of patients had missing data for CRP (n = 1059) and creatinine (n = 347), which could impact the outcomes of these clusters, given that model-based clustering inherently requires available variables to group diverse patient populations into clusters. To this end, a small-scale simulation study was performed to evaluate the potential impact of multiple imputation methodology and showed accuracy was 86%.

This study presents a compelling case for a data-driven, cluster-based subclassification of AAV. However, there are aspects of current classification criteria, including the American College of Rheumatology/European Alliance of Associations for Rheumatology and the Chapel Hill Consensus Conference, that we believe would be important to evaluate prior to using this as a prediction tool. Key factors affecting clinical outcome and prognosis were missing, including histology, weighted organ involvement, and radiography. We question how these clusters may change if a kidney pathology or a disease activity score was added into such model-based clustering. It is important to note that this model did not explore treatment effect or relapse rates, which have important influence on patient outcomes. Further investigations are necessary, including the above, as well as inclusion of biomarkers of disease activity and validation against other cohorts, before implementing this subclassification within the AAV population. ■

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The authors report no conflicts of interest.

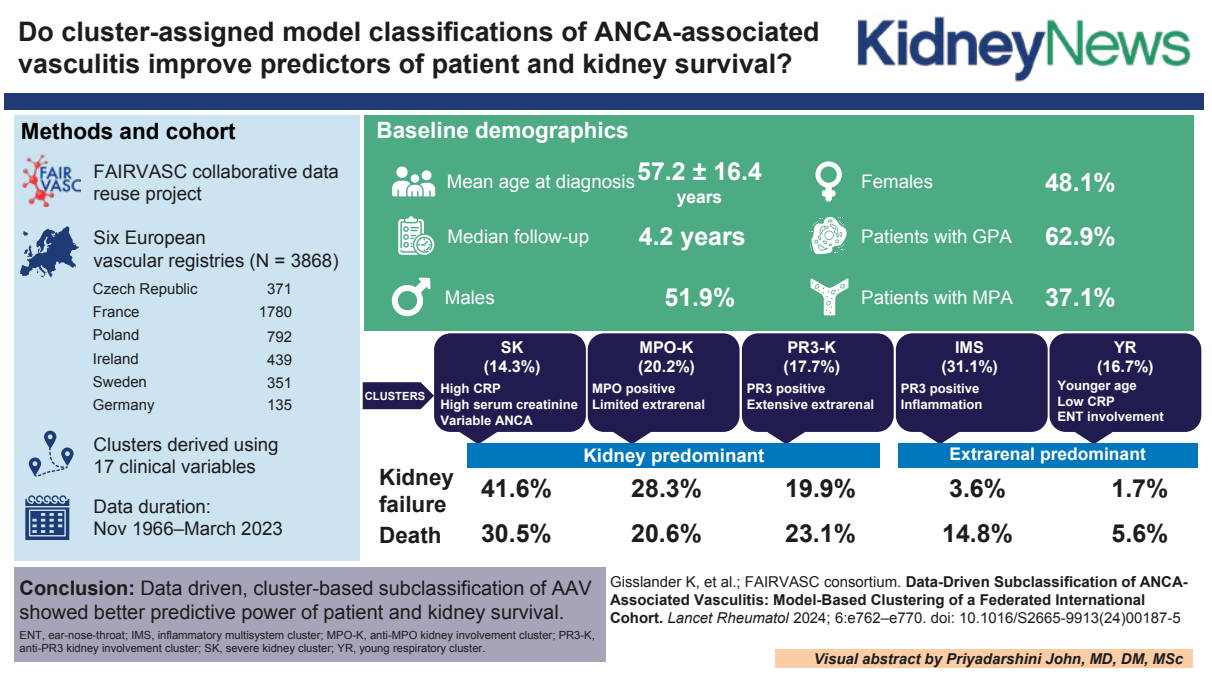

Table. Clusters with diagnosis, ANCA serotype, main organ systems affected, and outcomes

Cluster	SK	MPO-K	PR3-K	YR	IMS
Patient total (N = 3868), No.	555	782	683	646	1202
Diagnosis, %	38.0 GPA 62.0 MPA	23.7 GPA 76.3 MPA	83.5 GPA 16.5 MPA	82.0 GPA 18.0 MPA	78.0 GPA 22.0 MPA
ANCA, %	37.3 PR3 57.7 MPO 5.1 negative	17.3 PR3 74.8 MPO 7.9 negative	82.3 PR3 12.8 MPO 5.0 negative	60.0 PR3 22.2 MPO 17.8 negative	67.6 PR3 23.8 MPO 8.6 negative
Main systems affected, %	Kidney, 99.8 Constitutional, 61.4 Lung, 51.7 MSK, 44.1	Kidney, 98.5 Constitutional, 34.3 Lung, 35.2 MSK, 30.8	Kidney, 99.0 Constitutional, 88.8 ENT, 69.9 Lung, 66.8 MSK, 80.0	Constitutional, 39.4 ENT, 69.7 Lung, 42.0 MSK, 42.7	Constitutional, 72.2 ENT, 60.0 Lung, 57.3 MSK, 65.0
Outcome, %	Death, 30.5 Kidney failure, 41.6	Death, 20.6 Kidney failure, 28.3	Death, 23.1 Kidney failure, 19.9	Death, 5.6 Kidney failure, 1.7	Death, 14.8 Kidney failure, 3.6

ENT, ear-nose-throat; IMS, inflammatory multisystem cluster; MPO-K, anti-MPO kidney involvement cluster; MSK, musculoskeletal; PR3-K, anti-PR3 kidney involvement cluster; SK, severe kidney cluster; YR, young respiratory cluster.

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Calculators Help Estimate GFR for Adolescents Transitioning to Adult Nephrology Care

By Karen Blum

https://doi.org/10.62716/kn.000392024

The transition from adolescence to adulthood is a critical time in development, and estimating the glomerular filtration rate (GFR) at this juncture can help nephrologists best determine care for their patients. Fortunately, there are several calculators available to help.

Historically, physicians have used separate formulas to estimate GFR, developed in two different populations: those younger than 18 years and those aged 18 or older. These measures included the Chronic Kidney Disease in Children (CKiD) formula and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, said Susan Furth, MD, PhD, chief scientific officer, executive vice president, and an attending physician at the Children's Hospital of Philadelphia, PA, in a presentation at Kidney Week 2024.

Of the two formulas, Furth offered, "But it's important in our work to look at longitudinal changes in GFR, to look at effects on GFR decline." She explained, "For clinical decision-making, the period around late teens to early adulthood is a really vulnerable period for individuals with CKD. Being able to accurately assess GFR for finding when one should accelerate treatments to try to slow progression, or make plans for transplantation, is a really important criteria."

The CKiD study, authored by Furth and colleagues, has evaluated over 1100 participants with mild to moderate CKD, assessing risk for kidney function progression—as well as cardiovascular disease risk factors—and CKD effects on growth and neurocognitive development. They are now recruiting for the fourth cohort, targeting adolescents ages 14–17 years to follow them through transitions to adult care.

Through the study, investigators have conducted direct measurement of GFR annually for the first 2 years and every-other year after, using plasma clearance of iohexol. To date, they have calculated nearly 2700 GFR measurements.

Furth said that nephrologists who care for patients in this age group have recognized for a long time that there were "big gaps" when going from a pediatric to an adult equation. Her team previously used the revised Bedside Schwartz formula from 2009 and then compared results with the CKD-EPI equation, including age, sex, and race, and the CKiD serum creatinine and cystatin C equation in 2012. However, she said, using those measures when a child turned 18 years old could return big variances in estimated GFR (eGFR).

In a 2018 study (1), Furth's team reviewed all visits (N = 548) from 219 CKiD study participants with a median age of 19 years, of which 279 person-visits had measured iohexol GFR from 187 individuals. The CKiD serum creatinine and cystatin C equation demonstrated agreement with iohexol GFR, but both the serum creatinine CKiD equation and the CKD-EPI equation showed substantial biases in opposite directions, she said. "A simple fix was to take an average of the CKD-EPI and CKiD serum creatinine equations. This resulted in an overall valid estimate of GFR," Furth said.

As she and her colleagues continued to collect data from CKiD formulas, and some of this population moved into young adulthood, Furth and her team wanted to revisit the equations. "We knew that we needed valid, accurate estimates of GFR," she said, noting that although GFR direct measurement is more exact, it is not generally available in clinical care. "We wanted to have the best estimates possible, particularly during this transition to adult care…. We knew there were challenges in the 18-to-25-year age group, with pediatric equations underestimating GFR and adult equations overestimating GFR. We were hoping to develop equations that would be applicable across the life course for pediatric to young adult [populations with CKD]."

The team developed the CKiD U25 equation (U25) (2), which can be used to monitor kidney function and disease progression over time, for patients ages 1 to 25 years with mild to moderate kidney diseases. The equation estimates GFR using either serum creatinine or cystatin C alone or the average of both factors. U25 eGFR with sex- and age-dependent κ values can be used without bias across the pediatric age spectrum into adulthood, Furth said.

The equation can be accessed online through QxMD (qxmd.com or via the free mobile application). It factors in patient age, sex, serum creatinine, height, and cystatin C to provide serum creatinine eGFR, cystatin eGFR, and the average of both. Although it is just an estimate, it is a useful tool to have at the bedside, Furth said.

The code and software are available online for download at the CKiD study site (ckidstudy.org), under the Investigator Resources tab. Several children's hospitals have incorporated this into their electronic health records, Furth noted.

A recent study (3) compared U25 with CKD-EPI among 1491 participants from 21 studies. The mean age was 31.7 years and mean measured GFR was 92.7 mL/min/1.73 m^2. At higher GFR levels, U25 did not perform as well as CKD-EPI, she said, indicating that when working with young adults in their 20s and 30s, there is a substantial underestimation of GFR using U25.

Another available marker is the European Kidney Function Consortium (EKFC) eGFR calculator, designed to overcome the limitations of equations like U25 and CKD-EPI regarding age and race modeling. Its key element is the Q-value, the median normal value of serum creatinine in a given population. The calculator is available online through EKFC (ekfccalculator.pages.dev/) and MDApp (mdapp.co).

A recent study published in *The New England Journal of Medicine* (4) showed the performance of different equations to estimate GFR with respect to bias and P30 (the conventional measure of precision) according to age. For children known to have had CKD in childhood, who are now in their later teenage years with only mild or modest decreases in GFR, the EKFC equation or the CKD-EPI equation may perform better than U25, Furth said.

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Greener Nephrology Essential in the Face of Climate Change

By Bridget M. Kuehn

https://doi.org/10.62716/kn.000382024

With a growing proportion of the world facing water shortages, energy costs on the rise, and more frequent violent weather events disrupting access to the resources needed for dialysis, there is a pressing need for more sustainable approaches to care, said Suzanne Watnick, MD, FASN, professor of medicine at the University of Washington; a practicing nephrologist with the Veterans Affairs Puget Sound Health Care System, WA; and ASN Health Policy Scholar in Residence.

Watnick joined a panel of speakers during the Kidney Week 2024 Green Nephrology: Innovations That Address the Carbon Footprint Conundrum in Dialysis session on October 24, 2024. The group addressed potential ways to make kidney care more sustainable. She noted a bidirectional relationship between kidney care and the environment. Extreme heat events can contribute to acute kidney injury, kidney stones, and increased hospitalizations. Hurricanes and other extreme weather events can cut off access to dialysis and other forms of care and lead to shortages of supplies.

Often, climate change disproportionately affects patients who are already at greater risk of kidney diseases because of social determinants of health in the United States and globally, noted speaker Mukta Baweja, MD, an assistant clinical professor at the Icahn School of Medicine at Mount Sinai in New York, NY, and a former medical officer with the United Nations. She noted that middle- and lower-income countries that produce the lowest greenhouse gas emissions often face the worst effects of climate change and have the least resources for health care and resilience measures. "Climate change is an environmental and social justice issue," Baweja said. "Climate change, or the involuntary exposure of climate change, exacerbates existing inequities and creates new ones."

Watnick and other speakers at the session highlighted promising approaches to curbing unnecessary waste and increasing the sustainability of kidney care to help reduce contributions to climate change and its harmful effects. Many of those approaches start with simple steps by frontline and behind-the-scenes staff at dialysis facilities.

Carbon footprint

Overall, health care contributes about 10% of US greenhouse gas emissions, Watnick noted. She explained that the average dialysis facility produces greenhouse gas emissions comparable to 93 homes, and a single hemodialysis session produces an equivalent amount of emissions to a 149-mile drive in a gas-powered vehicle.

"The sustainability of our practice and our ability to take care of patients and provide these life-saving treatments depend on our understanding of the carbon footprint and minimizing the carbon footprint where we can," said Anne Huml, MD, MS, a transplant nephrologist in the Department of Kidney Medicine at the Cleveland Clinic, OH. With about 3.3 million patients receiving dialysis 3 times per week globally, the impact of dialysis-related carbon emissions is substantial, noted Huml.

In 2022, Huml and her colleagues analyzed the carbon footprint of dialysis in collaboration with a small dialysis organization in Ohio that runs 15 dialysis centers (1). They analyzed the use of electricity; waste production and recycling; and transportation of staff, patients, and supplies. They found that each treatment for a patient at a dialysis facility had an estimated carbon footprint of 58.9 kg of carbon dioxide (CO_2). The main contributors to that carbon footprint were staff and patient transportation, electricity, and natural gas use. Varying distances that staff and patients had to travel for care contributed to differences in the carbon footprint across facilities, Huml noted.

Annually, Huml noted that global carbon emissions for each patient undergoing in-center hemodialysis vary widely from country to country, from about 3000 CO_2 equivalents per year to about 10,000 CO_2 equivalents per year. Peritoneal dialysis also has a smaller but substantial carbon footprint ranging from about 1200 to 1900 CO_2 equivalents per year (2). "Transporting the peritoneal solutions from where they are produced to the endpoint where the patient uses them has a significant emission footprint," she explained.

Huml explained that the carbon footprint of kidney transplantation has not been analyzed. However, an analysis of the carbon footprint of liver transplants suggests that the carbon footprint of chartered flights to transplant organs is substantial, resulting in an estimated 815 million tons of carbon emissions at one center over the course of a year (3). She noted that the amount of recycling or reforestation necessary to offset that is prohibitively large. "It is not necessarily a problem that we can recycle our way out of," Huml said. "It is not a problem that we can reforest our way out of."

Water hungry

In addition to requiring large amounts of energy, hemodialysis and peritoneal dialysis both use large amounts of water. Watnick noted that a single hemodialysis session could use an entire bathtub's worth of water. However, variation in use by facility or machine suggests room for improvement. She stated that more efficient water treatment systems at dialysis facilities discard about half of the water used, compared with 70% waste in less efficient systems. "Still, inordinate amounts of water are being wasted," Watnick said. She suggested first working with facility staff to identify and rectify faults in the system or purchase more efficient systems.

Rejected reverse osmosis system water, which is highly purified and filtered, may also be reused for steam generation, landscaping, janitorial purposes, cleaning, or potentially as water for animals. Amy Yau, MD, FASN, clinical assistant professor of medicine at The Ohio State University, highlighted a study conducted in Malaysia that used nitrogen- and phosphorus-rich spent effluent in an aquaponics system to grow fish and produce for staff and patients. The system generated 50–150 tilapia every 6 months and 3–8 kilos of produce each month (4). She said the system provided a return on investment for the facility within 2 years.

Changes in nephrology practice may also help reduce water use, Watnick said, such as starting dialysis later in a patient's kidney disease development and starting dialysis incrementally. She also noted studies demonstrating success with reduced flow rates for dialysis and that some machines can facilitate slower flow rates. Yau agreed, noting recent studies support lower flow rates.

"There are a lot of things that we do that haven't been updated in decades," Watnick said. "A lot of the dialysis software [developers] for hemodialysis machines haven't thought about how you can match blood flows and dialysate flows to make things more efficient and more effective."

Developing more water-efficient peritoneal dialysis would also benefit patients. Watnick noted, for example, that point-of-care dialysate production could help prevent the need to transport large amounts of dialysis across long distances to patients in rural areas. KidneyX (Kidney Innovation Accelerator), a public-private partnership between ASN and the US Department of Health and Human Services, will award $7.25 million early this year for its Sustainability Prize to support projects to reduce water or power usage in dialysis care. "Kidney care solutions that reduce the water and power used during dialysis can improve resiliency during disasters and make ongoing care more sustainable," said Admiral Rachel Levine, MD, assistant secretary of the US Department of Health and Human Services, in a video shared during the session. "New solutions may also promote more equitable access to kidney care."

Solid waste

In addition to emissions and water use, kidney care generates enormous amounts of solid waste. Yau noted that each hemodialysis session generates 2.5 kg of solid waste, and peritoneal dialysis generates about 1.7 kg of plastic waste daily.

Yau said that several approaches to reducing solid waste and emissions from the transportation of dialysis supplies had been successfully implemented in other countries. She described a UK study, which found that having dialysis acid delivered in bulk instead of individual containers would reduce 4.2 tons of plastic waste, eliminate 16 tons of carbon emissions annually, and provide a return on investment in 5 years (5).

She also highlighted a nurse-led initiative in Canada that reduced solid waste by increasing the recycling of recyclable materials (6). The initiative focused on education for clinicians and use of separate bags to help with sorting. It also saved their unit $2000 per year in biohazard waste costs by ensuring that biohazard wastes were sorted more carefully from other forms of waste. "If we can better identify what our waste is, we can better recycle it," Yau said.

Prevention is key

Many speakers emphasized that the most potent approaches to reducing the environmental impact of kidney diseases may be focusing on prevention and curative therapies, like transplants. Watnick said nephrologists should concentrate on catching kidney diseases early, slowing progression, and reducing the demand for dialysis. She noted that this is consistent with the Advancing American Kidney Health initiative, which aims to reduce the number of patients progressing to dialysis by one-quarter.

Yau agreed, adding that currently, only 50% of patients with chronic kidney disease (CKD) are treated with renin-angiotensin-aldosterone system inhibitors as indicated, and only 10% of patients with diabetes and CKD are treated with sodium-glucose cotransporter-2 inhibitors as guidelines recommend. She noted that there are challenges that prevent more patients from receiving appropriate preventive therapies, including delayed diagnosis and the need for referral to a nephrologist from primary care. However, she suggested more collaboration with primary care to address these issues. She also emphasized the need to increase transplants and reduce discarded kidneys.

Baweja expressed that prevention and preparation are also key when trying to mitigate the impact of extreme weather like flooding or hurricanes on patients with kidney diseases. She said that such events can cut off vulnerable patients' access to medical care and medications and make it difficult for patients to reach dialysis centers. Patients on home dialysis may also experience electrical outages, lack of water, or delayed supply deliveries. "There's a demonstrated increase in mortality from kidney failure even 30 days after a climate event like hurricanes," she said. "It can also have a direct impact by increasing the risk of CKD death and disability."

Baweja noted that providing early dialysis sessions prior to extreme weather events has been shown to reduce emergency department visits, hospitalizations, and mortality for patients on dialysis. Additionally, the Centers for Medicare & Medicaid Services has issued a preparedness rule requiring dialysis facilities to have preparedness plans for emergencies. "We should also prepare the emergency room for increased visits, including for acute kidney injury, especially during hot weather," she said. Baweja also recommended steps to prevent intravenous fluid shortages and the spread of vector-borne diseases, particularly in lower-income countries.

Working toward solutions

Political leaders and professional organizations are already banding together on solutions. Watnick noted that the past three presidential administrations have worked bipartisanly and bicamerally to improve and modernize kidney care. Yau highlighted that ASN released a statement on climate change calling for steps to reduce the impact on patients and the environmental impact of kidney care (7). Similarly, the International Society of Nephrology has a GREEN-K initiative (Global Environmental Evolution in Nephrology and Kidney Care) to promote environmentally sustainable kidney care (8).

There are also many steps that dialysis centers can take to become more sustainable. Watnick suggested that dialysis facilities form collaboratives to identify and share successful sustainability initiatives. Building more eco-friendly dialysis centers or retrofitting existing ones may also help, Yau suggested. She recommended using motion-sensor lights, installing solar or high-efficiency bulbs, increasing natural light, or adding more heating and cooling efficiency measures. Upgrading to newer dialysis machines that are 70% to 85% water efficient may also help. She noted that these upgrades can reduce costs in addition to reducing carbon emissions and electricity use.

Watnick emphasized the importance of identifying local sustainability champions to lead efforts to reduce local contributions to climate change and help educate other staff. "Think about the frontline people who might have great ideas to decrease the impact on the environment," Watnick urged. "Not just nurses, physicians, and dialysis techs, but the people managing the facility practices, hospitals, patients, [and] the people in the chairs receiving dialysis or doing it themselves at home sometimes are the people that have the best ideas." ■

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