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American Heart Association Advisory Emphasizes Multidisciplinary Care for Cardiovascular-Kidney-Metabolic Syndrome

By Bridget M. Kuehn

Heart disease has long been the leading cause of death among patients with chronic kidney disease (CKD), but clinicians often treat the conditions separately. A new presidential advisory from the American Heart Association (AHA), published in *Circulation*, calls for a new, multidisciplinary approach emphasizing interconnections among the heart, kidneys, and metabolic diseases (1).

Advisory lead author Chiadi Ndumele, MD, PhD, a fellow of the AHA and associate professor of medicine and director of obesity and cardiometabolic research in the Division of Cardiology at Johns Hopkins University in Baltimore, MD, noted that multiorgan dysfunction is associated with premature deaths from heart disease and that the rising prevalence of these interrelated conditions has stalled progress on reducing heart disease deaths.

The new advisory defines cardiovascular-kidney-metabolic (CKM) syndrome as a condition caused by interactions among metabolic disorders and kidney diseases in individuals with cardiovascular disease or who are at risk of cardiovascular disease because of metabolic or kidney diseases. It lays out a four-stage paradigm for assessing an individual's risk for CKM and facilitating early intervention, suggests risk assessment and treatment algorithms, and proposes multidisciplinary care models to address CKM. It also highlights the importance of addressing social determinants of health, often critical drivers of CKM syndrome, and integrating social determinants of health assessments and interventions into care.

"We increasingly appreciate that cardiovascular, kidney, and metabolic conditions all closely interact and often cluster together," Ndumele said. "The time is certainly right to start to understand and address this directly in how we practice and engage with the public."

The advisory and scientific statement summarizing the evidence supporting this approach, published

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Preparedness Is Key for Dialysis Clinics Amid Record-Breaking Weather and Climate Disasters

By Karen Blum

According to an unofficial motto, "Neither snow nor rain nor heat nor gloom of night" may keep postal workers from their routes, but weather events like these may cause patients with kidney diseases to miss their hemodialysis appointments, even several days after a weather event, according to a recent study in *CJASN* (1). With the nation facing a record-breaking number of weather and climate disasters in 2023 so far (2), it behooves dialysis center personnel to pay attention and prepare, the authors said.

Rain, snow, wind, and other weather disruptions contributed to a 2% to 55% higher risk of missed appointments, study authors found after analyzing health records of over 60,000 patients with kidney failure who received in-center hemodialysis at Fresenius Kidney Care clinics across the northeastern United States from 2001 to 2019. The investigators also reviewed county-level meteorological data on rainfall, hurricane and tropical storm events, snowfall, snow depth, and wind speed and used statistical modeling to estimate the effect of inclement weather on missed appointments.

Looking at missed appointments by weather type,

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Inside

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

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INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

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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simultaneously in early October, were drafted by a multidisciplinary team that included nephrologists (2). Among them was Katherine Tuttle, MD, executive director for research at Providence Inland Northwest Health Services, and a professor in the Division of Nephrology at the University of Washington in Seattle.

"It's fantastic to see that people who have different backgrounds and complementary skills [come] together to solve common problems," Tuttle said. "We have some of the most powerful tools ever that really work across the spectrum now."

Early identification

Recognizing that progression toward CKM often begins early in life, the staging model starts with recommending interventions to promote healthy diets and activity in individuals with no metabolic or heart risk factors (stage 0), including children. The model outlines four more stages and suggests prevention approaches at each. The working group designed the model to allow "de-staging" individuals who reduce risk factors.

"We hope that through this staging construct, we can start to have people be aware of risk earlier and address risk earlier, primarily through healthy lifestyle," Ndumele explained. "We hope that this supports people getting the right therapies when needed and that we have a life-course approach to thinking about prevention from youth onward."

People with excess weight, larger waist circumferences, impaired glucose tolerance, or prediabetes fall into stage 1. Stage 2 includes individuals with hyperglycemia, hyperlipidemia, metabolic syndrome, diabetes, or moderate- to high-risk kidney diseases. The staging tool categorizes individuals with subclinical cardiovascular disease who have excess weight, metabolic risk factors, or CKD as stage 3. Stage 4 comprises individuals with heart disease, metabolic risk factors, and kidney diseases with or without kidney failure.

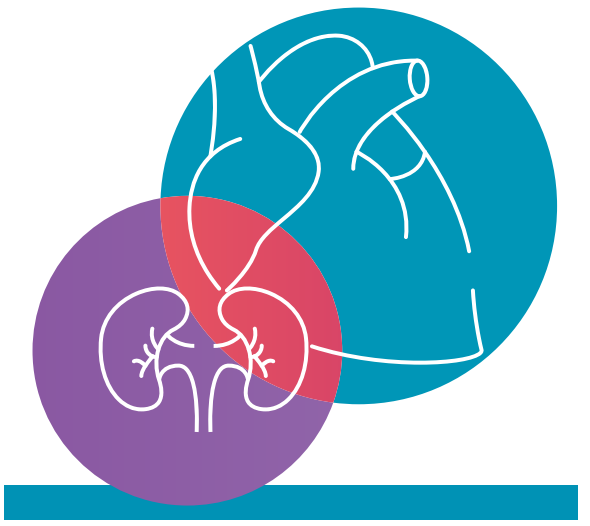
Ndumele said 90% of individuals in the United States will classify as stage 1 or higher and that primary care physicians will be the first point of contact for most. By applying the staging construct to identify risk and reduce it, Ndumele and his coauthors hope that primary care practitioners can reduce the number of individuals who progress to later stages of CKM. "We want to reduce the number of individuals who get to the point [in which] they need to see subspecialists because we are addressing risk earlier," he noted.

Advisory coauthor Janani Rangaswami, MD, section chief of nephrology at the Washington, DC, Veterans Affairs Medical Center and professor of medicine at George Washington University School of Medicine and Health Sciences, said that the document solidifies the role of the nephrologist in helping to identify cardiovascular risk as they follow patients across their disease progression.

"We now practice in an era [in which] we have multiple tools in our toolbox that not only improve kidney health and reduce the progression of CKD to kidney failure and prevent bad kidney outcomes, but we also can make a significant dent in the cardiovascular disease risk," said Rangaswami, who is also chair of the AHA's Council on the Kidney in Cardiovascular Disease and co-chair of AHA's CKM health initiative.

For example, Rangaswami noted that identifying patients who fall into stage 3 and do not yet have cardiovascular disease but are at high risk of it creates "a window of opportunity" for nephrologists to intervene with preventive approaches. "Ultimately, we want our patients with kidney diseases to live longer and better," she said. "Importantly, the biggest competing risk of death in our patients is largely cardiovascular disease at every stage of their lifespan."

Rangaswami noted that stage 4 highlights the unique considerations for patients with and without kidney failure, which are well known to nephrologists but may be less familiar to other specialties. "We want the whole CKM care community to be familiar with this," she added.



"There is so much crosstalk between these organ systems; that's how the disease process evolves.... The way we approach it has to mirror the disease."

Shared "playbook"

The advisory also outlines ways to streamline and standardize care for patients with CKM, including suggesting multidisciplinary care models and shared algorithms for using proven CKM interventions. "One of the biggest challenges that patients face in this circumstance is care fragmentation as a consequence of having to see multiple [practitioners] again, who may not always be using the same playbook and maybe giving slightly differing recommendations," Ndumele offered.

Rangaswami noted that primary care clinicians identify many patients with CKM syndrome and refer them to specialists who may be working in silos and not communicating effectively. She explained that a nephrologist may de-escalate therapies started by a cardiologist. But, as the scientific statement shows, the conditions are interrelated, she said. "There is so much crosstalk between these organ systems; that's how the disease process evolves," she explained. "The way we approach it has to mirror the disease."

Adam Whaley-Connell, DO, associate chief of staff for research at the Harry S. Truman Memorial Veterans' Hospital in Columbia, MO, and professor of medicine at the University of Missouri School of Medicine, said that it was gratifying to see research on the underlying connections translated into action after decades of research on these interrelated conditions. Whaley-Connell was not involved in drafting the advisory or review. "I was extremely excited to see that AHA put this working group together and [is] giving this priority," noted Whaley-Connell, who helped develop the *Journal of the CardioMetabolic Syndrome* (3) and the journal *Cardiorenal Medicine* (4). "We have evolved in our understanding that adipose tissue is a distinct endocrine organ that influences vascular and kidney health."

The advisory suggests that patients with two or more overlapping CKM conditions receive care from an interdisciplinary care team, including primary care, cardiology, nephrology, endocrinology, pharmacy, nursing, social workers, and community health workers. A CKM care coordinator, who organizes patient care and facilitates communication among care team members, would play a central role in the model. "We want to all be reading from a similar playbook, which makes things easier for patients," Ndumele said. When subspecialists are needed, the CKM care coordinator can help patients navigate across practitioners and ensure that they are receiving holistic care, he said.

The multidisciplinary model outlined in the advisory reinforces and expands on the multidisciplinary diabetic kidney disease care models recommended by Kidney Disease: Improving Global Outcomes (KDIGO) (5), the American Diabetes Association (6), and ASN (7), Tuttle said. She noted that this involves multiple specialties, including cardiology, endocrinology, and nephrology, as well as nurses, pharmacists, advanced practitioners, and social workers. "[CKM syndrome] is such an enormous problem," Tuttle explained. "There are so many people affected. If we can align on the guiding principles and overall care approaches, together we will have a much larger impact."

The advisory also provides broad guidance on how and when to use newer drugs that may benefit the patient's heart, kidneys, and metabolic health along with mainstay medications, noted Rangaswami. She expects this guidance to be updated regularly as new data emerge. In November at the organization's Scientific Sessions 2023, AHA unveiled a new cardiovascular risk calculator that considers CKM risk to help further guide patient assessment (8). "We are just really at a place where there is this embarrassment of riches with so many high-quality trials showing overwhelming benefit [for new classes of drugs]," she said. "It's up to us now to close this loop [and] implement these therapies, not just in a meaningful way, but in an equitable way."

Social determinants of health

The advisory also emphasizes the role that social determinants of health play in contributing to CKM and the need to identify and address them to care for patients successfully. "At every level, social determinants of health play a role in both the development and the impact of CKM syndrome," Ndumele noted.

Rangaswami explained that, for example, an individual with metabolic syndrome may be experiencing homelessness, food insecurity, racism, or other social determinants that can impact their outcomes. "If we don't screen and acknowledge that social determinants of health matter, then we won't have the ability to intervene and make that better," she said. "The advisory puts that up front."

It recommends systematically screening patients for social determinants of health and incorporating them into risk assessment. It suggests building social determinants of health into electronic health records, clinical workflows, and the make-up of patient care teams. For example, it recommends having team members who can address patients' social determinants of health and help them overcome barriers to care by leveraging community programs and resources. Rangaswami also emphasized the need to ensure equitable use of new therapies.

"Nephrologists are very familiar with the fact that patients who come from [populations that are disenfranchised] or are racial or ethnic minorities have a disproportionate burden of CKM syndrome, but they are also less likely to receive appropriate therapies," she said. Creating more systematic ways of identifying and treating CKM syndrome and addressing related social determinants will help reduce these disparities and allow patients to access

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preventive therapies earlier. "We hope patients will have optimal risk factor control and that a lot of them will be on RAAS [renin–angiotensin–aldosterone system] inhibitors or SGLT2s [sodium-glucose cotransporter-2s] before they even get to the nephrologist, who can then manage the additional risks patients have," Rangaswami continued.

Ndumele acknowledged that some practice models may only work in some settings. One of the next steps for him and his colleagues will be to develop implementation plans that help address the needs of specific practice settings. For example, rural settings with limited access to local specialists may leverage telehealth to connect patients with specialist care.

"Our intent is to make this as flexible as possible so that no matter where a person is in the world, that the guiding principles could help provide a framework [to] deliver care," Tuttle said. She noted that health systems can tailor how they implement the advisory to their contexts and hopefully share successful strategies. She also said that there is a need for implementation and cost-effectiveness studies.

Whaley-Connell agreed that more work is needed to develop multidisciplinary systems for caring for these complex patient populations and address some root causes, for example, crafting policies and guidance to address refined sugar, salt, and fat content and improving access in areas of food deserts. "The workgroup has provided an important conversation for the nephrology community to think about how we stage and address cardiometabolic health for patients with kidney diseases," Whaley-Connell said. "We can use the advisory with existing tools for diagnosis and management of kidney diseases."

Tuttle added that there will also be a role for professional organizations in advocating for policies that support the multidisciplinary care models that the advisory recommends. Having multiple professional organizations working across specialties and disciplines on advocacy will also likely have a greater impact on helping to enact the needed policy changes. "Health policy changes are critical," she said.

Tuttle also expressed gratitude for the AHA issuing the advisory and review and the scientific statement and bringing its expertise and experience targeting the early origins of disease to tackling CKM syndrome. "It's the right thing to do, and [AHA has] the influence to make substantial change," she said. ■

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Preparedness Is Key for Dialysis Clinics

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investigators found the average percentage of missed hemodialysis appointments was 2.5% for rain, 7.8% for hurricane or tropical storm events, and 4.9% for snow. A 10-mm higher rainfall was associated with a 2.6% higher risk of missed appointments on the same day. Wind advisory and sustained wind speed were associated with a 5.3% to 9.6% higher risk of missed appointments, respectively. Generally, rainfall-related risk of missed appointments dissipated after 1 day, whereas risk associated with snowfall, snow depth, and wind advisories persisted for several days. Hurricanes and tropical storms led to a 55% higher risk of missed appointments, sustained wind advisories led to a 29% higher risk of missed appointments, and wind gusts showed a 34% higher risk of missed appointments for the 7 days following an event.

"These inclement weather events lead to missed appointments for a [patient on hemodialysis], which can be quite detrimental in terms of the risk of hospitalization and other adverse health outcomes," said senior study author of the *CJASN* study (1), Amir Sapkota, PhD, professor and chair of epidemiology and biostatistics at the University of Maryland School of Public Health in College Park. "This is really significant from that regard."

Investigators analyzed records from 60,135 patients with kidney failure from 99 dialysis clinics within 27 counties in the northeast corridor from Washington, DC, to Maine. The patients were 19 years and older. The majority (57%) were male and were non-Hispanic Black (40%) or non-Hispanic White (40%). Overall, there were 454,932 missed appointments during the study period. Nearly one-half (47%) of patients reported missing at least one hemodialysis session, and 29% reported missing three or more sessions due to weather events.

Although the study assessed just one region of the United States, the reported trends should be generalizable to other areas of the country, as it pertains to weather disruptions and missed clinic appointments, Sapkota said. "What climate scientists have been telling us for some time now is that extreme weather events are increasing in frequency, as well as their duration and intensity," he said. "Even if we are extremely successful in our mitigation efforts, because of the changes that have already taken place, we will continue to see this trend into the foreseeable future."

The study results are unsurprising when one considers the characteristics of patients with kidney diseases, said Jeffrey Kopp, MD, section chief of the Kidney Diseases Branch of the National Institute of Diabetes and Digestive and Kidney Diseases. Kopp coauthored a recent commentary on disaster preparedness for patients with kidney diseases (3). "Some of our patients have frailty," he said, and worry about falls. "They may have lost muscle mass. They may have electrolyte disorders that are hard to control…. They don't want to put themselves at risk or put at risk the people who are driving them around."

Most severe weather events, such as hurricanes, blizzards, or periods of extreme heat, can be predicted days in advance, Kopp said. This means that nephrologists and dialysis center staff have time to be proactive. For example, if a storm is forecasted for a Sunday, and a patient receives dialysis on a Monday, Wednesday, and Friday schedule, clinicians could try to schedule the patient for Saturday or early Sunday before the storm for an extra dialysis session, so the patient could potentially sustain 3 or 4 days before needing another treatment. Nephrologists and other staff also could reach out to patients to remind them to get any needed medication refills before a storm hits.

The ongoing process of global warming can cause other issues, Kopp explained. Heat can cause an issue for people with chronic illness, as they may be unable to regulate body temperature as effectively as healthy individuals. Their ability to sweat and to regulate plasma chemistries and peripheral circulation may be impaired.

In preparation for these events, dialysis centers could host periodic seminars, either in person or online, to help patients plan ahead. What would patients do in case of a wildfire, a flood, or other event? Patients should be encouraged to prepare an evacuation bag with clothing, personal care items, and a list of personal contacts and medical care practitioners. Medications should be added immediately before the need to depart. Patients should review their plan at least twice a year, Kopp continued. "The upside about preparing [patients on dialysis] is that they're in the center three times a week, so you have an audience that's usually very willing to hear these messages," he said.

Sapkota also coauthored a commentary with tips for patients with chronic kidney disease and for dialysis clinics to handle extreme weather events (4). In case of power outages, dialysis clinics should be equipped with backup generators if possible and should anticipate staff having difficulties getting to the clinic or potentially needing help themselves, he said. Health care facilities should have contingency plans to ensure operations with staff shortages or to extend hours to accommodate patients from affected areas.

Dialysis centers also could provide patients with identification cards listing their medications, medical and dialysis treatment prescriptions, comorbidities and insurance, and emergency contacts, plus details for backup health care and dialysis facilities, added Sapkota.

"We must be proactive, to try to anticipate these [weather] threats ahead of time, prepare for them, and respond to them, instead of always reacting," Sapkota suggested. "With the ongoing climate change, we're going to see more and more of these threats, and [patients with end stage kidney disease] undergoing dialysis are among the most vulnerable." ■

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High-Impact Clinical Trials

Sparsentan for IgA Nephropathy and FSGS, SGLT2 Inhibitor Add-On Therapies, Transplant Immunotherapy Alternative Show Promise

By Bridget M. Kuehn

Sparsentan showed promise for treating immunoglobulin A (IgA) nephropathy and focal segmental glomerulosclerosis (FSGS), two kidney diseases with limited treatment options, according to results presented during the High-Impact Clinical Trials session at Kidney Week 2023. Additionally, two phase 2 trials demonstrated the potential benefits of adding a selective aldosterone synthase inhibitor or a selective endothelin receptor agonist to sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with chronic kidney disease (CKD). Other studies presented during the session highlighted a potential alternative to long-term immunotherapy for patients with kidney transplants and showed that multipronged intervention did not increase transplant uptake.

Sparsentan

A dual endothelin angiotensin receptor antagonist, called sparsentan, received accelerated U.S. Food and Drug Administration (FDA) approval (1) in February for use in adults with primary IgA nephropathy at risk of rapid disease progression, based on a 36-week interim analysis of results from A Study of the Effect and Safety of Sparsentan in the Treatment of Patients with IgA Nephropathy (PROTECT) trial demonstrating a reduction in proteinuria compared with irbesartan (2). During the Kidney Week High-Impact Clinical Trials session, Brad Rovin, MD, FASN, director of the Division of Nephrology and vice chair of research at The Ohio State University Wexner Medical Center in Columbus, presented pivotal results of the trial, which followed patients for approximately 2 years.

The PROTECT trial randomized 404 adult patients with IgA nephropathy at risk of progression, who were already receiving maximized angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB) therapy, to receive sparsentan or irbesartan and followed them for 110 weeks (3). By 36 weeks, patients in the sparsentan group had achieved a 41% reduction in proteinuria that was maintained throughout 110 weeks, Rovin said during the press briefing. Additionally, 31% of patients receiving sparsentan achieved a complete renal response, compared with 11% in the irbesartan group. The sparsentan group also had superior estimated glomerular filtration rates (eGFRs) to the irbesartan group, with a 1.1-mm/minute per 1.73 m^2 advantage in the chronic eGFR slope. There were no unexpected safety signals.

"We can consider sparsentan as a foundational therapy for [IgA] nephropathy upon which we can add immunosuppressive therapy guided by patient characteristics or kidney biopsy," Rovin said. He suggested that upcoming guideline updates may want to recommend achieving even lower rates of proteinuria using newer IgA nephropathy drugs.

"The PROTECT trial provides further proof that there are now a lot of possible therapies for patients with IgA nephropathy," said session co-moderator Tamara Isakova, MD, MMSc, the Margaret Gray Morton Professor of Medicine at Northwestern University's Feinberg School of Medicine, Chicago, IL. "Excitingly, this trial shows that for some patients with IgA nephropathy treatments that we consider to be hemodynamic, and not immunosuppressive, [the treatments] appear to have benefit. The key questions for patients and doctors are how best to know which of the many treatments to choose for which patient and which patients will still need immunosuppressive medications."

Sparsentan also showed promise as a treatment for FSGS, for which there are currently no FDA-approved therapies. "FSGS is a disease that has a very high risk of progression to end stage kidney disease," explained Michelle Rheault, MD, director of the Division of Pediatric Nephrology at the University of Minnesota Medical School in Minneapolis, during the press briefing. "Over 50% of patients will progress to end stage kidney disease within 5 to 10 years of diagnosis. There is a high unmet need for therapies that reduce proteinuria and help to slow the progression of kidney disease[s]."

Rheault presented the results of the phase 3 Study of Sparsentan in Patients with Primary Focal Segmental Glomerulosclerosis (FSGS) (DUPLEX) trial, the largest trial investigating FSGS to date, during the High-Impact Clinical Trials session (4). The trial randomized 371 patients between the ages of 8 and 75 years, with primary and genetic forms of FSGS, to receive sparsentan or irbesartan. At 36 weeks, patients receiving sparsentan were 55% more likely to achieve partial remission, with those results persisting at 108 weeks. At 108 weeks, patients in the sparsentan group showed a 50% reduction in the urine protein-to-creatinine ratio compared with a 32% reduction in the irbesartan group, Rheault also indicated during the press briefing. By the end of the study, 18.5% of the sparsentan group achieved total remission compared with 7.5% of the irbesartan group. There was no difference in the drugs' safety profiles. "This is the first time that we are seeing an immunosuppressive or non-immunosuppressive drug for patients with FSGS that can make a difference long term," she stated.

The trial, however, did not show a statistically significant difference in the eGFR slope between the two groups. "The study is promising with regard to a proteinuria endpoint, but it is disappointing [that] the necessary eGFR endpoint was not met," Isakova said. "It is still a big step forward to have a trial for FSGS completed, and it is especially important to note that children were included in this trial."

Rheault noted that the non-statistically significant improvement of approximately 1 mm/minute per year may still be clinically meaningful, particularly for pediatric patients with FSGS, by helping to delay kidney failure by 1 or 2 years. "Just getting them through high school or the first 2 years of college can make a big difference," she said.

SGLT2 inhibitor add-ons

Several blockbuster trials have demonstrated the heart, kidney, and metabolic benefits of SGLT2 inhibitors in patients with kidney diseases, and the latest results show benefits for potential add-on therapies. "People with CKD remain at high risk of progression despite treatment with ACE inhibitors, ARBs, and SGLT2 inhibitors," said Katherine Tuttle, MD,

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High-Impact Clinical Trials

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FASN, executive director at Providence Health Care and clinical professor of medicine at the University of Washington in Seattle, during the High-Impact Clinical Trials session at Kidney Week.

Excess aldosterone may accelerate progression. ACE inhibitors and ARBs do not fully block this effect and may contribute to hyperkalemia, Tuttle noted. However, adding SGLT2 inhibitors may add benefits while potentially helping to mitigate hyperkalemia. Aldosterone synthase inhibitors may add further benefit by reducing aldosterone production.

A phase 2 trial (5), conducted by Tuttle and her colleagues, showed that a selective aldosterone synthase inhibitor, called BI 690517, reduced albuminuria by up to 40% compared with placebo. The trial randomized 714 patients with CKD, taking a renin-angiotensin system inhibitor, to empagliflozin or placebo and then randomized 586 of the patients a second time to receive BI 690517 or placebo and measured the drugs' effects at 14 weeks. Approximately 50% of patients taking the BI 690517 with placebo and 70% of patients taking the drug with the SGLT2 inhibitor empagliflozin achieved an albuminuria reduction greater than 30%, suggesting an additive benefit. Hyperkalemia occurred more in patients taking BI 690517 with or without empagliflozin. However, most cases did not require treatment, and there were no fatal hyperkalemia events, Tuttle said during a press briefing about the trial. "Aldosterone synthase inhibition is a promising new therapy that may add benefit to SGLT2 inhibitors in patients with CKD with and without diabetes," she stated during the briefing. During the session, Tuttle announced the launch of a phase 3 trial, the EASi-Kidney trial, that will recruit 11,000 patients with CKD.

Similarly, the phase 2b Zibotentan and Dapagliflozin for the Treatment of CKD (ZENITH-CKD) trial (6) showed that a low, 0.25 dose of the selective endothelial receptor antagonist zibotentan given with the SGLT2 inhibitor dapagliflozin reduced albuminuria more than did dapagliflozin alone. Hiddo Jan L. Heerspink, PhD, PharmD, professor and clinical pharmacologist at the University Medical Center Groningen, the Netherlands, noted in the press briefing that previous studies showed that endothelial receptor antagonists alone can reduce albuminuria and poor kidney disease outcomes but increase the risk of fluid retention and heart failure. However, combining an SGLT2 inhibitor, which has diuretic effects, may prevent fluid retention and related adverse events.

The ZENITH-CKD trial initially enrolled patients into six groups. The Data Safety Monitoring Committee stopped the 5-mg zibotentan monotherapy group—a 5-mg zibotentan plus 10-mg dapagliflozin group—and a placebo group due to excess fluid retention, Heerspink said. With a total of 447 patients, 0.25 zibotentan/10 mg dapagliflozin, 1.5 mg zibotentan/10 mg dapagliflozin, and placebo/10 mg dapagliflozin groups continued. Both zibotentan/dapagliflozin groups reduced the urinary albumin-to-creatinine ratio more than the dapagliflozin-alone group. However, there were modest increases in body weight and fluid retention in the 1.5-mg-dose group and two cases of heart failure. There were no changes in body weight or fluid retention in the 0.25-zibotentan group, but there was one case of heart failure. "The fluid retention profile for a low-dose combination zibotentan, 0.25 mg, with dapagliflozin supports further clinical trials," Heerspink noted. He announced the launch of a phase 3 trial with 1500 patients during the session.

Isakova said the trials are part of the next phase in understanding how to best use SGLT2 inhibitors and said that she expects many more trials will investigate combining SGLT2 inhibitors with new medications. For example, upcoming company trials will also examine combining SGLT2 inhibitors and sparsentan to prevent CKD, she added. Isakova said it will be important for the phase 3 trials evaluating zibotentan and BI 690517 to use well-accepted, hard endpoints for kidney and cardiovascular disease. "Safety will also need to be evaluated further," she noted.

Transplant trials

Updated results from the phase 3 Cellular Immunotherapy in Recipients of HLA-Matched, Living Donor Kidney Transplants (MDR-101-MLK) trial (7) showed ongoing immunotolerance among kidney transplant recipients treated with an immunomodulating cellular therapy created from their donors' cells. "Kidney transplantation requires lifelong immunosuppression," explained Daniel Brennan, MD, consulting chief medical officer of Medeor Therapeutics, which produces the therapy, and medical director of the Comprehensive Transplant Center and professor of medicine at Johns Hopkins Medicine, Baltimore, MD, during the press briefing. "[Immunosuppression] is associated with side effects, toxicities, infection, malignancy, and is expensive."

To reduce the need for immunosuppression, Brennan and colleagues developed a cellular therapy that uses transplanted immune stem cells from the donor to induce immune tolerance in the recipient. Healthy donors received stem cell production-stimulating therapies, and immune stem cells were then collected from the donors and stored for transplantation. After transplant, recipients underwent total lymphoid irradiation; they began receiving their donors' cells from 11 to 39 days after transplant. On day 40, patients started on tacrolimus therapy. Investigators monitored patients for "mixed chimerism," or a mix of their own and donor immune cells at 6 months. If the donor cells remained, the patients tapered off tacrolimus over 6 months and were monitored for another 2 years.

Of the 22 patient-donor pairs screened for participation, Brennan said 20 completed the transplant, and 19 achieved mixed chimerism. Fourteen patients have completed the 2-year study, and 12 have remained free of immunosuppressive drugs. Four more patients have not yet completed the study. There were two rejections in the treatment group compared with one in a control group, and no deaths, graft loss, or graft-host disease were reported. Recipients who had eliminated immunosuppressive drugs also reported improved quality of life and a reduced burden on their families. "This study shows that some kidney transplant recipients can achieve 'functional tolerance' and be free of immunosuppressive drugs normally required to prevent rejection and failure of the kidney transplant," said Brennan in a statement.

Isakova noted that many additional steps will be necessary to ensure that this approach is safe and efficacious, including longer and larger studies. But she called the results a step forward. "Innovation in how we manage transplant recipients is long overdue," Isakova said. "Many immunosuppressive medications have adverse effects that affect the quality of life of patients and over time for some patients, result in death with functioning allograft. The approaches presented in this study are a step forward in figuring a new way to avoid immunosuppression."

The Enhance Access to Kidney Transplant and Living Kidney Donation (EnAKT LKD) trial compared the effects of a multipronged intervention to increase the number of patients completing four steps toward receiving a kidney transplant with the effects of usual care practices across Ontario, Canada (8). "We know that patients with advanced chronic kidney disease have their best chance of a longer and healthier life if they receive a kidney transplant," said Amit Garg, MD, PhD, associate dean of clinical research at the Schulich School of Medicine and Dentistry, Western University; medical director for the Living Kidney Donor Program, London Health Sciences Centre; and site director for the Institute for Clinical Evaluative Sciences (ICES) in Ontario. "From a health care system perspective, every hundred kidney transplants save the health care system $20 million over 5 years predominantly from averted dialysis costs because dialysis is a very expensive therapy. But the reality is, in many developed countries, many eligible patients today will never receive a transplant."

The EnAKT LKD trial included 26 CKD programs serving more than 20,000 patients who were potentially transplant-eligible over approximately 4 years. Investigators randomized half of the programs to the intervention, which included administrative support for quality-improvement programs, transplant education resources, transplant donors and recipients sharing lived experiences, and program-level performance reviews, and half to usual care. The results were presented at Kidney Week and published simultaneously in *JAMA Internal Medicine* (8).

The four steps to transplant included 1) referring to a center for evaluation, 2) having a potential living donor contact a center for evaluation, 3) being added to the deceased donor waitlist, and 4) receiving a transplant. There was no increase in the number of patients who completed these steps in the intervention group compared with the usual care group. Garg said the COVID-19 pandemic, which occurred in the middle of the trial, dramatically impacted it, with patient and donor educators having to switch from in-person to virtual education and many clinicians choosing to retire.

"Although the results are disappointing, it is important to acknowledge that the investigators were attempting to do something really hard in a very pragmatic approach during a very challenging time," Isakova said. She noted that additional studies are underway, including through many recently funded initiatives supported by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases, that emphasize community-level interventions to eliminate racial and ethnic disparities in kidney health in the United States.

Garg and his team are currently revamping the intervention to improve implementation and results. "We are not giving up because this is a critically important problem," Garg said. "We are deeply committed to fixing it because we know patients would benefit."

Other trials presented during the High-Impact Clinical Trials session featured:

- Bardoxolone methyl (BARD), a Keap1-Nrf2 pathway activator, slowed kidney function decline without reducing kidney failure rates in patients with diabetic kidney disease without heart failure risk factors (9). The phase 3 trial enrolled 1013 patients and found no differences in heart events compared with placebo. A previous phase 3 trial of the drug found elevated rates of heart failure in the BARD group (10).
- The Aldosterone Antagonist Chronic Hemodialysis Interventional Survival Trial (ALCHEMIST) enrolled 644 patients on hemodialysis with a cardiovascular co-morbidity or risk factor and found treatment with spironolactone did not reduce a composite endpoint of cardiovascular events compared with placebo. It did, however, lower heart failure hospitalization compared with placebo (11). ■

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ASN President's Update

End of the Year Thoughts: Looking Backward and Forward

By Michelle A. Josephson

December is a month of numbers: 12 days of Christmas, 8 days of Chanukah, and seven principles of Kwanzaa. December is also the 12th month of the year and the final month of my ASN presidency.

There is so much I would like to share about the past 12 months, such as participating in the federal government's Kidney Interagency Coordinating Committee, which met in October; describing the many projects that we are pursuing with other societies; and emphasizing how much I have learned from writing these editorials for *Kidney News*. I could highlight 365 activities but will limit it to 12 due to space constraints.

1 **Transitioning governance structure.** Under the new structure, I am the first person to serve on the ASN Council's 4-year executive track. Before I started in 2021, councilors spent 7 years on the council, with the sixth year as their president's year. The ongoing joke was that the councilors were told to simply observe for their first year. Now there are three distinct 4-year tracks: an at-large councilor, an executive councilor, and a treasurer track. Executive councilors now spend the first year as secretary, the second as president-elect, the third as president, and the fourth as past president. On this accelerated track, councilors jump into the action quickly and can no longer just observe for their first year. My time on the council has been a whirlwind but always fulfilling, meaningful, and a lot of fun.

2 **Reconfiguring our publications' organizational structure.** We have implemented a more integrated publication oversight structure. In the past, the three ASN journals (*JASN*, *CJASN*, and *Kidney360*) worked independently. In the new structure, *JASN* will serve as the flagship with the editors-in-chief (EICs) of *CJASN* and *Kidney360* being in close contact with the *JASN* EIC. This approach enables more opportunities for manuscripts that may not be appropriate for one journal to find a home in another journal in ASN's portfolio.

3 **Ending the COVID-19 pandemic.** On May 5th, the U.S. public health emergency ended. I started on the council in January 2021, mid-pandemic, only weeks before vaccines became available. This timing was brought home for me very literally, as I had my first bout of COVID-19 in December 2020. During my first year, many of the council meetings were conducted virtually as was Kidney Week 2021. These virtual meetings are very helpful, but they are not as fulfilling as in-person meetings. With the return of in-person Early Programs and more than 12,000 people attending Kidney Week 2023, it feels like the pandemic is finally over.

4 **Hosting Kidney Week 2023.** What a great meeting! On a personal note, having the meeting in Philadelphia, PA, was particularly meaningful. In some ways, like coming home, because I attended medical school at the University of Pennsylvania, it was returning to the city in which I started my medical journey. A big shout out of appreciation and gratitude to the co-chairs of the ASN Kidney Week Education Committee: Dianne McKay, MD, and Mark Perazella, MD, FASN. Their leadership was extraordinary. The incredible program for Kidney Week 2023 reflects the efforts of the talented and dedicated individuals who served on the ASN Kidney Week Education Committee. The meeting's success was also due to the amazing ASN team. The plenary sessions, oral presentations, and posters were such high quality because of the hard work of all of these individuals, as well as you, the kidney community, who submitted abstracts, participated, and provided expertise. It takes a village….

5 **Taking a village.** The ASN staff (https://www.asn-online.org/about/staff.aspx) is an amazing group of individuals. They are dedicated, smart, professional, effective, creative, and simply a pleasure to work with. Having the opportunity to interact with and be involved in several projects with the staff made this year particularly enjoyable. The ASN staff is highly effective. I cannot say enough good things about them.

6 **Celebrating milestones.** We marked the 10-year anniversaries of KidneyCure (https://www.kidneycure.org/); the Kidney Health Initiative (KHI) (https://khi.asn-online.org/); and our commitment to diversity, equity, and inclusion. If you attended Kidney Week 2023, you saw some videos about each of these landmarks. KidneyCure is a separately incorporated, not-for-profit organization that focuses on curing kidney diseases through research and innovation. A partnership between ASN and the U.S. Food and Drug Administration (FDA), KHI includes more than 75 member organizations, such as patient groups, other health professional societies, dialysis organizations, and pharmaceutical companies. ASN's commitment to diversity, equity, and inclusion has resulted in transformative efforts, such as awarding travel grant support for 19 ASN members to attend the 2023 Network of Minority Health Research Investigators Annual Workshop (bringing the 10-year total to more than 100 participants); the ASN Loan Mitigation Pilot Program; and multiple targeted activities at Kidney Week.

7 **Supporting research, discovery, and innovation.** Each year, ASN's sponsorship of KidneyCure spends more than $2.5 million to fund nearly 50 investigators. This is the largest outlay of grant support from any kidney organization. The awards include the ASN-Harold Amos Medical Faculty Development Program (in partnership with the Robert Wood Johnson Foundation), the ASN Pre-Doctoral Fellowship Program, the Ben J. Lipps Research Fellowship Program, Transition to Independence grant recipients, and the William and Sandra Bennett Clinical Scholars Program. Developed to cultivate collaboration to improve patient safety and develop novel therapies, KHI hosted its Annual Stakeholders meeting in September. FDA Commissioner Robert Califf, MD, was the Keynote Speaker and later posted the following on social media: "I was delighted to speak yesterday at the Kidney Health Initiative's annual meeting. This is an area of medicine & science of great interest to me, both because of the enormous scientific & clinical challenges posed as well as the enormous opportunities tied to medical advances." Finally, the Kidney Innovation Accelerator (KidneyX) (www.kidneyx.org) also enjoyed an impactful year, hosting webinars, holding an in-person summit, and announcing eight new prize winners of the Artificial Kidney Prize, Phase 2 competition.

8 **Engaging ASN members.** Over the course of the year, several members expressed interest in becoming more engaged in ASN but were unsure how to do so. With this in mind, and as a first step, ASN has added the following sentences to the website, providing a mechanism for members to express interest in becoming more involved: "If you are interested in learning more about ASN's committees, workgroups, task forces, and other panels (or in serving the society), please email operations@asn-online.org." During the next year, I plan to work with the council and staff to implement additional plans to engage our members. One activity that always needs volunteers is Kidney Week abstract review. Please contact kidneyweek@asn-online.org to express your interest in abstract review and indicate your area of expertise.

9 **Transforming transplant.** As a transplant nephrologist, I am proud that the second pillar of the "We're United 4 Kidney Health" campaign (https://4kidneyhealth.org/) commits ASN to transplant, and I am excited that considerable federal interest exists in this arena. We saw years of advocacy efforts pay off with the Securing the U.S. Organ Procurement and Transplantation Network Act becoming law (SUS OPTN). Making possible changes that we will see in years to come with the Health Resources and Services Administration Modernization Initiative, SUS OPTN is not the end of ASN's transplant journey, just one big milestone to make the most of and to celebrate along the way as we continue forward. I am also excited about the newly appointed ASN–American Society of Transplantation (AST) Task Force (Table 1), charged with making the case for the Accreditation Council for Graduate Medical Education (ACGME) to accredit transplant nephrology fellowships.

10 **Strengthening training.** In this year's ASN survey, 92% of nephrology fellows stated that they would recommend nephrology to medical students and residents. With the publication of the final report from the ASN Task Force on the Future of Nephrology, it is clear that we have begun to reinvigorate training. Working with the entities responsible for regulating training (ACGME) and certification (American Board of Internal Medicine), ASN is implementing the ASN Task Force on the Future of Nephrology's 10 recommendations. In 2024, for example, you will see more of an emphasis of training in-home modalities such as peritoneal dialysis. ASN also partnered with the Home Dialysis University this year to help at least 30 fellows participate in this excellent program. One-half of U.S. nephrologists and nearly two-thirds of our future workforce completed medical school outside of this country, which is why ASN—in concert with our colleagues at the American Nephrologists of Indian Origin—is engaged in efforts to help international medical graduates seeking to train and work in the United States. ASN is also working to reintroduce the Healthcare Workforce Resilience Act, important legislation that seeks to recapture unused visas and provide them to physicians and nurses at the system level. This month, we met with leadership from the American Nephrology Nurses Association to discuss how we can work together to best support the kidney care team.

11 **Pursuing sustainability.** ASN took steps to address climate change and nephrology's relationship with the environment by joining The Medical Society Consortium on Climate and Health and the International Society of Nephrology's (ISN's) GREEN-K (Global Environmental Evolution in Nephrology and Kidney Care) Initiative. With alterations in weather patterns related to climate change, we are seeing more intensified natural disasters like hurricanes and wildfires. These catastrophic events can pose insurmountable barriers for patients to receive lifesaving dialysis treatments. Through its Emergency Partnership Initiative, ASN works closely with the Kidney Community Emergency Response Coalition, Direct Relief, the European Renal Association (ERA), ISN, and other stakeholders to ensure that kidney patients have access to the care they need and to ensure that kidney health professionals can provide that care. We also collaborated with ERA and ISN to begin to develop a plan for which organization will take primary responsibility for geographic regions of the world and how we will notify membership of the response to emergencies. Together, we tried to help throughout the world.

12 **Prioritizing patients.** Determining what is best for patients always guides ASN. It is no surprise, therefore, that ASN's commitment to excellence in patient care made substantial progress this year. With Alan S. Kliger, MD, at the helm, ASN's activities in this arena are extensive. Last month, for example, ASN conducted a community-wide, after-action meeting with the Centers for Disease Control and Prevention to assess what worked, what did not work, and what we can learn for the future based on our experience during the COVID-19 pandemic.

When the calendar flips from 2023 to 2024, ASN will mark several transitions. Josephine P. Briggs, MD, will step down as EIC of *JASN*, a position she has held since 2018. The high-quality and excellent science that is a trademark of *JASN* is testament to Josie's efforts. I cannot thank her enough. Stepping down as *CJASN* EIC, Rajnish Mehrotra, MD, MS, FASN, will succeed Josie as *JASN* EIC. Connie M. Rhee, MD, MSc, will succeed Raj as *CJASN* EIC.

As I reflect on this year, I feel a tremendous amount of gratitude for having had the opportunity to work with such a wonderful group of people. My fellow councilors: Jeffrey S. Berns, MD, FASN; Deidra C. Crews, MD, MS, FASN; Linda F. Fried, MD, MPH, FASN; Crystal A. Gadegbeku, MD, FASN; Keisha L. Gibson, MD, MPH, FASN; Patrick H. Nachman, MD, FASN; Susan E. Quaggin, MD, FASN; and Prabir Roy-Chaudhury, MD, PhD, FASN, were always engaged, thoughtful, and helpful. And before this year, I served on the council with Anupam Agarwal, MD, FASN, and David H. Ellison, MD, FASN. All of these individuals provided me with honest and useful discussions, direction, and friendship.

Several ASN councilors will also end their terms. Since January 2020, Crystal Gadegbeku and Keisha Gibson have served as ASN councilor-at-large and treasurer, respectively. They have brought thoughtful and impactful engagement. They have both guided the organization during the difficult years of COVID-19. Crystal was instrumental in the work done to remove race from the calculation of estimated glomerular filtration rate, and Keisha made difficult decisions to keep ASN financially solvent during the pandemic. I thank Crystal and Keisha for their years of exemplary service.

After 8 years, Sue Quaggin will also rotate off the council. We all owe her an extra debt of gratitude for staying on council to serve as president for an additional year after Barbara T. Murphy, MB BAO BCh, FRCPI, passed away. Sue led ASN with vision, strength, and grace. She did so in the face of the pandemic and the tragic passing of Barbara, a dear friend to Sue, and to all of us. On a personal note, I cannot thank Sue enough for the guidance she provided me, the generosity with which she gave of her time (even when she did not have any), and for our Chicago dinners.

Looking forward to 2024, Deidra Crews will become ASN president on January 1, 2024. Deidra is a clinical researcher whose focus is on health equity. She gave us a preview of her plans at Kidney Week, and she will share more details of her vision for 2024 with us in future editorials. We also welcome three new councilors: Jeffrey H. Miner, PhD, FASN, will become treasurer; Samir M. Parikh, MD, FASN, will become secretary; and Daniel E. Weiner, MD, MS, FASN, will become a councilor-at-large in January. ASN is in good hands.

In 2024, as past president, I look forward to chairing the Awards Committee and the Council Nominations Committee. With that in mind, please nominate your deserving colleagues for the society's awards and to the society's leadership.

In the meantime, wishing you and your loved ones a happy and healthy holiday season and New Year. It has been my honor, privilege, and pleasure to serve as your president this year. See you in San Diego, CA, in October for Kidney Week 2024… if not before! ■

Table 1. ASN–AST Task Force on ACGME Accreditation for Transplant Nephrology

Members
Deborah B. Adey, MD, FAST
Roy D. Bloom, MBChB, MD, Chair
Beatrice P. Concepcion, MD, MS, FASN, FAST
Gaurav Gupta, MD
Michelle A. Josephson, MD, FASN, FAST*
Vineeta Kumar, MD, FASN, FAST
Mark G. Parker, MD, FASN
Deirdre Sawinski, MD, FAST*
Neeraj Singh, MD, MBA, FASN, FAST, Vice Chair
Staff
Rachel N. Meyer, ASN Strategic Policy Advisor to the ASN Executive Vice President
Molly Rubin, ASN Leadership Development Manager
Chad Waller, AST Associate Executive Director

*Nonvoting Ex Officio

10 Years of ASN's Annual Nephrology Fellow Survey—Lessons Learned and Questions Unanswered

By Suzanne M. Boyle and Kurtis A. Pivert on behalf of the ASN Data Subcommittee

This year marked the 10th anniversary of ASN's Annual Nephrology Fellow Survey. With a robust response rate of 47% in 2023 (range, 43%–50% on recent iterations), it provides a snapshot of current U.S. nephrology fellows' trajectories from medical school through fellowship graduation (1).

After 10 years, what have we learned? Nephrology fellows are largely internationally educated, and nearly one-third require work visas (J-1 waiver or H-1B sponsorship). Just under 40% are women, and 10% identify as Black or African American. Approximately 7% of fellows have not completed residency training in the United States and to become board-eligible must either: 1) perform a U.S. residency after fellowship, or 2) be accepted to the American Board of Internal Medicine's Pathway A, an option for exceptional fellows who are hired as U.S. or Canadian faculty members for 3 years (2). Fellows decide to become nephrologists mostly between their second and third year of residency, but nearly one-fifth of international graduates pursue nephrology after practicing internal medicine post-residency.

After graduation, most fellows are private practice-bound and expect to work in both outpatient and inpatient settings. Despite anecdotes about nephro-hospitalists and nephrologist-to-hospitalist conversions, only five respondents were entering hospital medicine in 2023. Approximately 10% of graduates pursue advanced fellowship training, most commonly transplant (44%; n = 18) or critical care (34%; n = 15).

Quality of life is the chief metric by which new graduates evaluate potential job opportunities. Weekend or weeknight call frequency and a desirable location consistently top the list of most-valued job characteristics (outstripping compensation). However, inadequate compensation is the most common reason cited by new graduates for an inability to find a satisfactory position.

So, how do we contextualize these cross-sectional data and use them to promote a sustainable workforce that benefits both nephrologists and patients? This is particularly important in light of the increasing burden of kidney diseases worldwide coupled with the looming retirement of a significant proportion of the physician workforce (3).

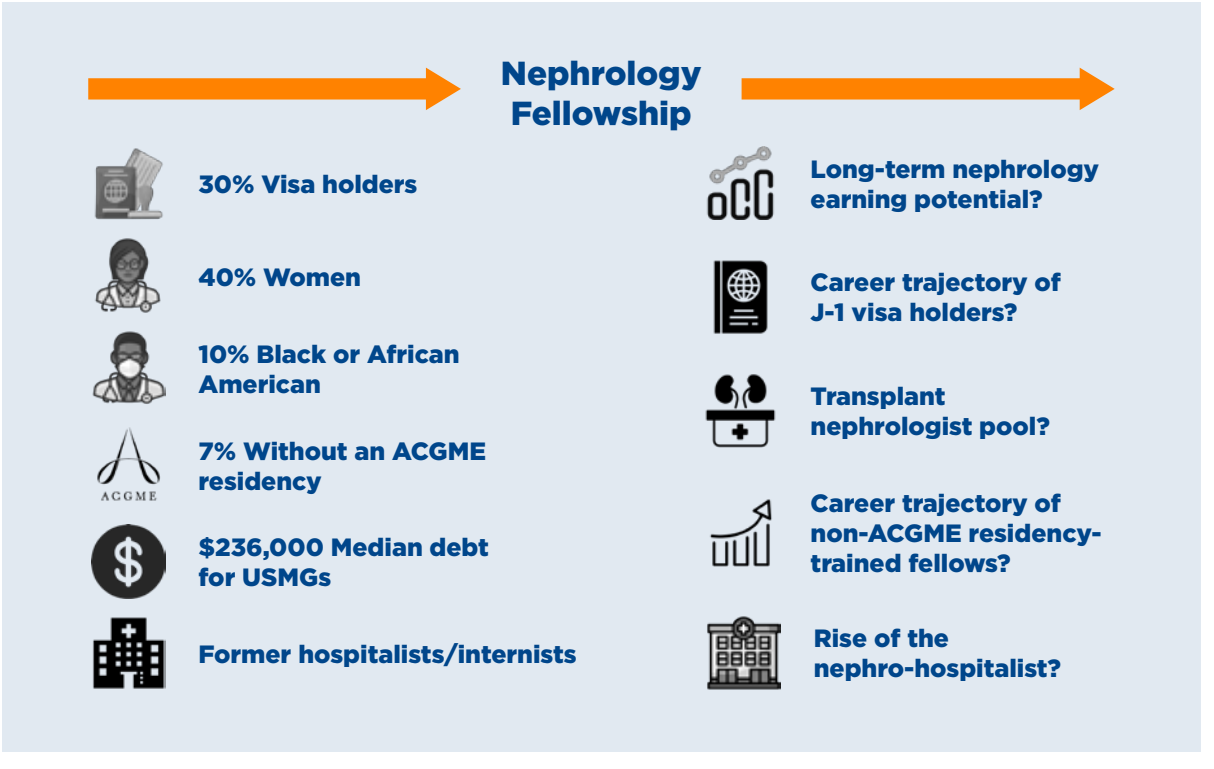
The data give us a great snapshot of the new graduate workforce, but they leave us wondering about the fate of future personnel (Figure 1). For example, what is the career trajectory of J-1 visa holders? Do they continue to live and work in the underserved communities where they complete their waivers? Or do they return to more densely populated metropolitan areas or pursue advanced fellowship training in subspecialties such as transplant, which their original visa requirements may have precluded?

What about the hospitalist movement that has likely diverted talent from the nephrology training entry pipeline? Does it continue to siphon off talent in the years beyond training with the allure of higher salaries and more predictable work hours? The median base salary reported for all of the 2023 nephrology graduates (including academic, private practice, and hospital employers) was $231,000. For comparison, the Association of American Medical Colleges reported that the median assistant professor-level salary for academic hospitalists in 2021–2022 was $250,049 versus $221,264 for nephrologists at the same rank (4). Although the income disparity favoring hospitalists persists at the associate level (median $2,017 more than associate professor nephrologists), at the professor level, median nephrology salaries overtook hospitalists ($314,406 versus $303,703), arguing that academic nephrology's earning potential over the long run was higher than in hospital medicine. But to brand-new internal medicine (IM) residency graduates, who are often saddled with significant educational debt (U.S. nephrology fellows reported a median $236,000 of debt in 2023 [1]), pursuing the short-term gain of immediate higher salaries is more attractive than considering the long-term potential of a nephrology career. The question remains whether future or early-career nephrologists are aware of their own long-term earning potential (including revenue from opportunities like joint ventures) and if this is actualized over time.

There are still more questions. What happens to fellows who pursue nephrology fellowship before IM residency training? Do they reenter nephrology after being away from the practice for 3 years, or do they practice general IM? What are the challenges to reentry? What about training kidney transplant specialists so that the United States can realize the bold goals set by the Advancing American Kidney Health Executive Order (5)? There are 62 accredited transplant fellowships in the United States, yet only 18 fellow graduates reported pursuing transplant fellowship in 2023. Will we have enough transplant specialists to care for our patients, and, if not, how can we change this?

To begin to answer these questions, the kidney community will need to both design and participate in longitudinal studies. These studies will need to use creative methods to sample representative cross-sections of kidney health professionals, including J-1 visa holders, nephrology subspecialists, underrepresented minorities, women, and those who completed residency after fellowship. In addition to longitudinal surveys, focus groups and semi-structured interviews are needed to explore the depth of these questions. We need to leverage existing partnerships, like ASN's collaboration with Phairify, to obtain accurate statistics about the current nephrology practice and forge other connections with professional organizations and government entities that will help us quantify the demand for nephrology care. Together, we must take collective responsibility for answering these questions to sustain a healthy and productive workforce. ■

Figure 1. ASN Annual Nephrology Fellow Survey pipeline: Who is in it, and what happens when they exit?



The ASN Annual Nephrology Fellow Survey provides valuable data about who is entering and exiting the nephrology training pipeline, but the data raise important questions about what happens beyond the pipeline. Longitudinal studies are needed to understand the career trajectory of nephrologists over time so that we can sustain the workforce. ACGME, Accreditation Council for Graduate Medical Education; USMGs, U.S. medical graduates.

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

The authors report no conflicts of interest.

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A Different Type of Practice

Workforce Trends and Mentorship Opportunities Highlighted at Kidney Week

By Karen Blum

There continues to be a limited supply of nephrologists available to manage an increasing number of patients with kidney diseases in the United States, Eleanor Lederer, MD, FASN, said during Kidney Week 2023. As care is being delivered more in a team-based fashion, and technology options are increasing, nephrologists will need to keep pivoting toward a different type of practice.

During a session on the nephrology workforce for the 21st century, Lederer, the John S. Fordtran, M.D., Professor in Calcium Research at The University of Texas Southwestern Medical Center's Charles and Jane Pak Center for Mineral Metabolism and Clinical Research in Dallas, explained that there are currently an estimated 11,000 nephrologists in the United States, but approximately 37 million individuals with chronic kidney disease (CKD) and 800,000 with end stage disease.

A 2016 report from ASN and The George Washington University estimated that the number of nephrologists would increase from 8533 in 2016 to 17,256 by 2030 (1), said Lederer, a past president of ASN and assistant chief of medical services for research and co-director of the Network of Dedicated Enrollment Sites (NODES) program at the U.S. Department of Veterans Affairs North Texas Health Sciences Center. While the workforce has increased, it is not quite keeping up with projections, she said. This has occurred in the face of a declining number of applicants to the field.

The year 2023 saw an encouraging increase to 458 nephrology match applicants, but for the appointment year 2024, the number declined to 379, Lederer noted. However, the overall percentage of fellows going into nephrology has remained relatively stable since 1991, at approximately 7% to 8%, she continued (2). According to Lederer, several trends will challenge the nephrology workforce going forward:

- **Democratization of health care delivery.** As much as health care is being consolidated into larger health systems, patients tend to identify with these systems more than individual practitioners. There also has been much more emphasis on a team approach to care. "It has really switched around the relationship between the patient and the physician," Lederer said. "The physician is certainly no longer at the top of the pyramid." Instead of the doctor giving instructions to the patient or other caregivers, multiple practitioners are interacting with the patient, who is no longer in a subservient position. Additionally, there has been a steady increase in the number of physicians employed by an entity and a progressive decrease in the number of independent practitioners.
- **Shift to task-oriented focus.** Health care is seeing both an increase in the division of responsibilities among health care practitioners as well as an accumulation of ancillary requirements, Lederer said. Physicians were once considered to be diagnosticians and knowledge and treatment experts. Today, they are also expected to know about documentation, data entry, coding, insurance, and value-based medicine. "It doesn't take a genius to see that once all these other responsibilities are added to every time I see a patient…it's going to be a distraction from my primary focus, which may be helping this person cope with their CKD," she said. "There's a marked decrease in thinking time." Work is trending toward decision making based on immediate data, without necessarily taking the time to conduct full medical histories, she said.
- **Sub-sub-subspecialization.** Niche practices have been developing requiring advanced skills, such as onconephrology, Lederer said, which raises the question of who is going to care for "garden-variety" CKD.
- **Patient autonomy in health care decisions.** Multiple sources of health care information—from the internet to direct-to-consumer advertising to virtual medical care—also have disrupted the traditional physician-patient relationship and have given greater power to patients to weigh in on treatment decisions, demand for therapies, and referral patterns. Patients will continue to assume more responsibility for their care as time goes forward, Lederer predicted.
- **Artificial intelligence (AI) and other technological advances.** "I think we all realize that we're living with AI right now," Lederer said. Big health systems are using AI to assess practice patterns, outcomes, costs, and patient satisfaction, she continued. But it also can be used to improve health care delivery and transitions of care. Potential applications could help with accumulation of data, identification of patterns within each patient, classifications of diseases, and differential diagnoses. Generative applications could be "an amazing timesaver," allowing for creation of notes and letters and chatbots for patient interactions, she said. However, she cautioned, "physicians need to understand the limitations of this resource."

Going forward, Lederer said she expects that nephrologists will be team members with advanced practice providers (APPs) and others, developers of diagnostic and therapeutic algorithms, secondary resources and diagnosticians for "outliers," and overseers of population health trends. "We actually may not need as many nephrologists as we think we do," she said. Yet, there will be a need for APPs, support personnel, and computer scientists and information technology specialists.

Stimulating interest through mentorship

Mentoring potential future nephrologists is important to increase interest in the field, said Samira Farouk, MD, MSCR, FASN, an associate professor of medicine and medical education and associate program director of the nephrology fellowship program at the Icahn School of Medicine at Mount Sinai in New York City.

Nephrology is ranked 11th in the percentage of programs filled and 12th in the percentage of positions filled, according to 2022 statistics from the National Resident Matching Program, Farouk said (3). In one study that surveyed internal medicine subspecialty fellows about why they did not choose nephrology, common responses included that there were no role models or mentors to guide them toward the field, the subject matter was too difficult, and it was not taught well (4). Access to mentors also was cited as important in selection of a subspecialty, according to a more recent survey (5).

There has been "an explosion" of free open access medical education tools that nephrology mentorship programs are using to make the field less complicated and to attract trainees, Farouk said. ASN has supported a number of mentorship efforts, including Kidney TREKS (Tutored Research and Education for Kidney Scholars), which offers a 1-week course for medical students and connects them with a nephrology mentor, and Kidney STARS (Students and Residents), which provides support to attend Kidney Week, plus group and peer mentoring.

In 2021, Farouk and colleagues started NephSIM Nephrons, a 6-month virtual mentoring program that places trainees and mentors in small groups called tubules. Trainees also receive 1:1 mentor sessions and are encouraged to connect with others in a chat group. The program hosts one to two events each month designed to give a 360° view of nephrology and what careers look like. "Our goals are to increase and diversify the pipeline of nephrology trainees by giving them tailored learning experiences, showing them the diverse potential careers they can have, to stimulate interest among medical students and residents," in addition to mentoring, Farouk said.

In participant surveys from 2021 and 2022, the majority (94%–96%) agreed that the program had a positive impact on their views toward a career in nephrology. Approximately 66 participants in the 2022 program said they were either a current nephrology fellow or likely to pursue nephrology fellowship.

Open comments focused on similar themes, Farouk said. "They want more mentorship, they want more lectures, and they want more time with their tubule…. It's reassuring that they do want more because it seems like they like what we're trying to provide for them." ■

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Fellows First

Kidney Week 2023: Trainees' Experiences and Insights

By Paul Hanna and Rasha Raslan

Last month marked ASN's annual Kidney Week conference, the premier gathering for ASN, bringing together approximately 12,000 health care professionals, including a substantial representation of trainees who embody the future of nephrology. The opening plenary speech by ASN President Michelle A. Josephson, MD, FASN, emphasized "workforce training" as one of ASN's three future priorities.

Ahead of Kidney Week, trainees participated in a series of polls posted on X (formerly known as Twitter) run by *Kidney News*' editorial fellows to discuss their expectations for the conference. In the initial survey, which received 84 votes, 47.6% of trainees said that networking would be their main expectation, followed by new research (23.8%) and skill development (21.4%). Of the respondents, 7.1% said that their main expectation was to collaborate.

As *Kidney News*' editorial fellows, we reached out to trainees from different levels to gauge their experiences of Kidney Week 2023.

Joseph Wahba

Joseph Wahba is an undergraduate student at the University of Pennsylvania who gave an oral presentation on exploring unconscious bias in peer-to-peer interactions at medical conferences. According to Wahba, "As a pre-med student, it felt wonderful to share my research with those in the medical field in such a prestigious setting. It was great to contribute and be part of an event [in which] like-minded individuals and firms come together to learn and share fascinating discoveries within our field. [At ASN Kidney Week], I got a glimpse [of an] exciting future that was potentially in store for me and is certainly a motivator for me to continue pursuing my professional goals."

Christopher Gitter, BS

Christopher Gitter, BS in Pharmacology and Toxicology, a third-year medical student at the Medical College of Wisconsin, participated in the ASN Kidney Students and Residents (STARS) program, which is designed to stimulate nephrology interest among medical students, residents, and graduate students. Gitter shared, "ASN Kidney Week allowed me to connect key care dilemmas and novel treatments in the hospital to leading research in nephrology across the country. ASN's Kidney STARS program gives structure to a vast conference from the medical student perspective and excels at facilitating networking opportunities for trainees. Specifically, [its] recommended 'Trainee Track' helped guide my choice of sessions to attend throughout the week and glean meaningful clinical pearls."

Christina Tamargo, MD

We asked Christina Tamargo, MD, PGY-3, at Johns Hopkins University and current applicant to the Nephrology Match, about her Kidney Week experiences. Per Tamargo, "The conference was very useful in preparing me for the upcoming match and a career in nephrology. First, it allowed me opportunities to connect with people in the field, particularly people working on research and clinical care in areas that interest me and at institutions I am considering for fellowship. Second, I learned infinite clinical pearls and left the conference feeling much better informed about the state of nephrology and the latest research. Finally, it got me even more excited about nephrology—it was inspiring being around so many people so passionate about the kidney! I would recommend Kidney Week to anyone strongly considering a career in nephrology."

Ritu Seethapathy, MD

Ritu Seethapathy, MD, a second-year resident at New York Medical College/Landmark Medical Center and ASN Kidney STARS program participant at Kidney Week, noted that "Kidney Week can be overwhelming to any novice," but the STARS program "provided a structure to the madness, in addition to the opportunity to meet mentors and fellow kidney enthusiasts." Witnessing passionate debates among top nephrologists was a unique experience at Kidney Week 2023, in addition to the unveiling of groundbreaking advances in nephrology. Seethapathy also noted how the farewell STARS luncheon, featuring patient perspectives, grounded attendees in the reality of their work. According to Seethapathy, amidst the challenging task of choosing sessions, the conference's real value lies in the connections forged. The welcoming atmosphere and mentorship, exemplified by Kidney STARS mentors, make it a pivotal event for those considering a career in nephrology. The career guidance panel, she noted, was a boon for aspiring nephrologists. "ASN Kidney Week helped tremendously in cementing my interest in the field."

Omar Osman, MD

Current nephrology fellows in programs around the country also found the conference useful in navigating potential job opportunities. Omar Osman, MD, is chief fellow at the Cleveland Clinic, and he reported, "Didactics are always great to catch up on cutting-edge data and visions for the future, but for fellows in their first or second year, I think having a physical space to meet with future employers or recruiters is of great value and expedites the process of planning your career once training is done. It's also a great place to catch up with friends and always fun to see a new city every Kidney Week!"

Luis Perez, PhD, RD

"Since my second year of graduate training in 2016, attending ASN's annual Kidney Week has been pivotal in shaping my career in nutrition, research, and kidney-focused work," reflected Luis Perez, PhD, RD, with Veterans Affairs. Describing the significance of Kidney Week, Perez noted, "For my first attendance year, fortunately, Kidney Week was close to my training school at the University of Illinois." The second year Perez was supported by university travel funds and awards, and in 2018, Perez earned his first Kidney STARS travel support and program participation. Expressing gratitude, Perez emphasized, "It is without a doubt an exceptional

program that has helped me every step along my journey and career." As Perez progressed, ASN pipeline training programs continued to provide invaluable support, culminating in being chosen to speak at a Kidney Week STARS graduate student career panel. He shared, "My participation was particularly significant because I once stood in the same position as the attendees, having been a STARS attendee and trainee myself." Perez underscored the impact of mentorship at Kidney Week, as well as the relevance of poster and oral abstract sessions as a highlight of attendance. Lastly, he expressed a desire for more mentoring sessions and workshop opportunities at Kidney Week, emphasizing the value of one-on-one conversations and personalized advice for trainees.

ASN Kidney Week 2023 stands out as a pivotal event that not only provides a platform for academic exchange but also nurtures enthusiasm, fosters connections, and shapes the future of nephrology. The diverse experiences shared by attendees underscore the conference's multidimensional impact, making it imperative for ASN to continue expanding exposure opportunities for trainees. As the conference solidifies interests and fosters connections, it remains a vital force in advancing the field of nephrology through education, collaboration, and inspiration. Looking forward, the emphasis on mentorship and personalized advice, as expressed by Perez, suggests a potential avenue for further enhancement of the conference's impact on the careers of aspiring nephrologists. ■

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The authors report no conflicts of interest.

LETTER TO THE EDITOR

By Terrence Jay O'Neil

What a marvelous time to be a nephrologist as we stand at a crossroads in end stage kidney disease care. The old technology—dialysis—a life-saving application of a ridiculously simple principle of physics, can be further refined into implantable devices that provide some but not all of the benefits of functioning kidneys. Complex machines incapable of healing from damage, they only become affordable at an enormous scale. As discussed in the October/November issue of *Kidney News* (1) and other recently published articles (2–5), a new biological technology, using pig tissue genetically engineered to evade human immune trip-wires, is real kidney tissue, theoretically able to perform all of the functions of a human kidney. It is also initially hugely expensive but self-replicating and likely scaling to affordability quite rapidly. Yes, there are risks of endogenous retroviruses, and the melange of hormones and other effectors it makes is not human, with inherent riska of dysregulation of the multiple metabolic pathways in which human kidneys participate.

Must we choose one over the other? Not necessarily. We will likely need both approaches because for various reasons, not every patient will find one or the other optimal. But now there are dawning alternatives to a lifetime of hemodialysis or peritoneal dialysis and the chronic shortage of human homografts. I say again, what a marvelous time to be a nephrologist! ■

Terrence Jay O'Neil, MD, FACP, FASN, Col USAF MC (Ret), is president of HD Clean LLC, specializing in development of dialysis safety devices and education for patients at-risk for progressive chronic kidney disease. He serves as a member of the ASN Quality Committee.

Disclaimer: The views and opinions expressed in Letters to the Editor are those of the individuals and do not necessarily reflect the views or positions of the entities they represent.

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Bringing Nephrology Clinical Trials to Patients: The Role of Community Practices

By Suneel Udani, Peale Chuang, and Nancy Cipparrone

The nephrology field has witnessed significant advancements in treating both common and rare kidney diseases in recent years. These breakthroughs have energized the medical community and pharmaceutical industry to develop innovative therapies further. However, transitioning from development to clinical use, including executing phase 2 and phase 3 trials, remains challenging. One of the focal points in these trials is achieving recruitment goals and ensuring a diverse representation of clinical trial participants, including traditionally underrepresented groups.

Conducting research in community practices provides potential advantages in achieving this broad range of goals, as it integrates trials with patient care, enhancing trust and recruitment. The inclusion of varied patient scenarios enhances the applicability of findings to real-world medical settings, thereby forming a valuable link between research and clinical practice that stands to benefit a more diverse range of patients. "As a community, we work collaboratively to ensure the success of clinical trials through our partnership with FDA [U.S. Food and Drug Administration] via the Kidney Health Initiative and forums [in which] people with kidney diseases, trialists, industry sponsors, and clinicians can discuss and exchange ideas," said Melissa West, ASN Senior Director for Strategic Relations and Patient Engagement. "ASN's efforts to accelerate innovation and expand patient choice require 'building research readiness, inclusiveness, and translation in kidney medicine, which requires championing clinical trials.' Adding the perspective of community practices, where people with kidney diseases receive their care would greatly enhance our discussions and potential for success" (1).

Community-based nephrology practices have yet to traditionally have the ability and capacity to build and sustain a clinical research program. We propose a framework based on our experiences as a potential guide to build more widespread community, nephrology-based clinical research programs (Figure 1).

Part 1. Establishing value of a clinical research program

Community practices, typically physician-operated and financed, require upfront investments in staff, equipment, and research space. Demonstrating the clinical research program's value is vital for securing financial support. These practices often collaborate with dialysis organizations to establish dialysis clinics, and a clinical research program's investment can be presented similarly.

The initial investment can be categorized as financial support for research staff and physical space. While some research space can be integrated into clinical care areas, separate space is essential for storing clinical trial documents and study equipment, such as phlebotomy tables, centrifuges, and electrocardiography machines. The required amount varies based on the number of research sites and staff hired.

Similar to any joint venture, the initial years of operation should be seen as an investment in the program, without immediate financial returns. Nonetheless, there are non-financial benefits that can be highlighted to support the initial required investment. Participation in clinical trials provides access to the latest research findings and collaboration opportunities with experts and reinforces the practice's reputation as a nephrology research leader, attracting new patients. Clinicians also appreciate clinical trials as alternatives to off-label treatments for progressive kidney diseases, benefiting patients and advancing nephrology.

To ensure sustainability, the practice and research team must devise a financial plan, outlining annual progress and transitioning from initial investments in staff and facilities to generating revenue distributed among participating members.

Part 2. Building and supporting the team

Effective leadership is vital, encompassing logistical management and clinical expertise. Hiring an experienced research director skilled in research operations, including budget management, timelines, and regulatory compliance, is essential. This role is often assumed by someone with research coordinator experience, expanding responsibilities to evaluate and hire research coordinators, assess study protocol feasibility, negotiate research study budgets and contracts, and complement the clinical director. The clinical director, ideally, comes from within the practice and is an individual with trusted clinical credibility, research trial experience, and sufficient availability to direct time.

Once leadership is established, the next step is assembling a team of principal investigators with similar qualities to the clinical director and research coordinators who are dependable and have demonstrated the ability to pay careful attention to detail.

To ensure program success, uniform expectations and requirements for the entire team, including standardized training in Good Clinical Practice and trial execution, must be established. Finally, to ensure sustainability, financial support for investigators to offset clinical time loss should be a goal.

Part 3. Trial selection

Choosing clinical trials for a community practice-based research site involves evaluating multiple factors to optimize decision-making; factors to consider can depend on the capacity and interests of the program and are outlined in Table 1.

Part 4. Trial execution

After securing institutional support and assembling the research team, execution follows. Community-based research programs can operate efficiently in streamlining study approval by using a central institutional review board (IRB) and integrating clinical trial space with clinical facilities. The use of a central IRB and the ability of a capable research director to singularly negotiate contracts and budget can shorten start-up time.

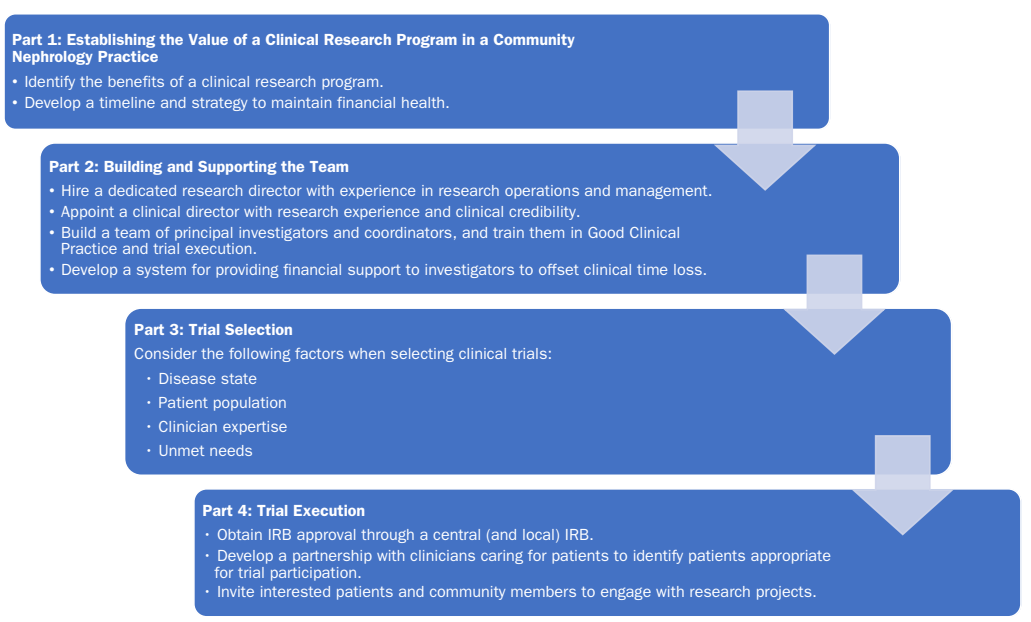
Once active, recruitment efforts begin, and although challenges persist, efforts should focus on understanding patient and clinician motivations for trial participation while building trust as a care partner. Outreach can be directed to patients and treating clinicians using the following two approaches.

1. Publicize clinical trial activity on the practice website, in waiting rooms, and on social media. Encourage interested individuals to contact the research team, even if no suitable trial is available immediately, and invite them to be a part of a database of individuals to be contacted if future studies that are appropriate to their condition become available.
2. Search the medical record database to identify individuals who may qualify for clinical trials based on their medical history. However, to reinforce the research team's position as a care partner, the team should respect the patient-physician relationship by consulting a patient's primary nephrologist before contacting a patient to discuss their care and whether trial participation would be appropriate. This is done to ensure that the patient's nephrologist is involved in the decision-making process and that the patient is fully informed about all of their options.

Ultimately, for both patients and referring clinicians, trust in the research process and program is fundamental. Accordingly, the study team must ensure that the study design aligns with best practices, including the principle of equipoise for randomized clinical trials. Success for a research program cannot be measured by enrollment numbers but by how successfully the program is considered a partner in patient care.

Although this process can require time to develop, building a sustainable and successful program requires patience, persistence, and partnership so that trusting patient-clinician and clinician-investigator relationships, which are crucial for successful recruitment and retention, can develop.

Figure 1. Building a community practice-based nephrology clinical trial program



Recent breakthroughs have revitalized the field of nephrology, spurring innovative therapies and clinical trials. The exciting advancements and increased investment are vital to counteract recent trends of a declining nephrology workforce. Transitioning from development to commercial use remains challenging, with participant diversity and representation being important considerations for clinical trial execution. Community-based research programs can play an important role in this endeavor.

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Table 1. Factors to consider in selecting clinical research studies

Disease-state factors	Non-therapeutic interventions	Therapeutic interventions	External factors	Diversified study portfolio
Patient representation	Clinician expertise	Unmet needs	Trial support duration	Complementary therapies
Observational study appeal	Diagnostic test invasiveness	Therapy delivery	Sponsor funding	Study design comparison
Disease-state need	"Standard of care" alignment	Equipoise	Site capability	Method of drug delivery
Feasibility of completion	Proximity of similar trials			Adverse effects comparison

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Understanding Reporting of Transplant-Related Outcomes in the United States

By Jillian S. Caldwell and Xingxing S. Cheng

Tracking waitlist and kidney transplant outcomes is no easy feat. Patients who undergo transplant are cared for by many practitioners in nephrology clinics, dialysis centers, and transplant programs throughout the transplant process, creating transition points at which delays may occur or patients may be lost to follow-up. Three main data sources track pre- and post-transplant outcomes: the United Network for Organ Sharing (UNOS), which has held the contract for the Organ Procurement & Transplantation Network (OPTN), the main regulatory body for transplantation in the United States; the Scientific Registry of Transplant Recipients (SRTR), which provides statistical and analytic support to the public and regulatory agencies through maintenance of its own data registry; and the United States Renal Data System (USRDS), which supplements data from UNOS with social security death data from the Centers for Medicare & Medicaid Services (CMS) to monitor all individuals with kidney diseases (Figure 1).

In a recent issue of *JASN*, Yu et al. (1) examined the outcomes of over 300,000 transplant recipients between 2000 and 2019 from these three datasets (UNOS, SRTR, and USRDS) to measure their concordance. The authors found wide variability in number of deaths by data set. The greatest number of post-transplant deaths was reported by the USRDS. By 20 years, mortality was more than 10% higher when reported by SRTR or USRDS than when reported by UNOS. Conversely, when tracking pretransplant outcomes, UNOS captured more waitlisted patients, but USRDS still reported the greatest numbers of deaths.

Differences in data inputs explain some of these discrepancies. For example, the UNOS registry no longer has access to the complete Social Security Death Master File (2), so it likely underestimates the death rate. CMS is notified of all patients initiating chronic dialysis and could identify kidney graft failures independent of transplant programs, but these data are not systematically cross-referenced by UNOS, again resulting in discrepancies (3).

Based on these findings, the data-sharing and cross-referencing processes currently in place appear to be inadequate. Policymakers should mandate data sharing and transparency among federally funded registries and have a validated, unified definition of ascertainment of key outcomes, including death and dialysis initiation, to ensure consistency and accuracy of kidney transplant data. Researchers may consider USRDS to report the greatest number of post-transplant deaths, whereas UNOS is more accurate for waitlisted patients, and should be careful to use the appropriate data source when analyzing corresponding transplant outcomes.

Jillian S. Caldwell, DO, is a nephrology fellow and Xingxing S. Cheng, MD, MS, is an assistant professor both in the Division of Nephrology at Stanford University in Palo Alto, CA.

The authors report no conflicts of interest.

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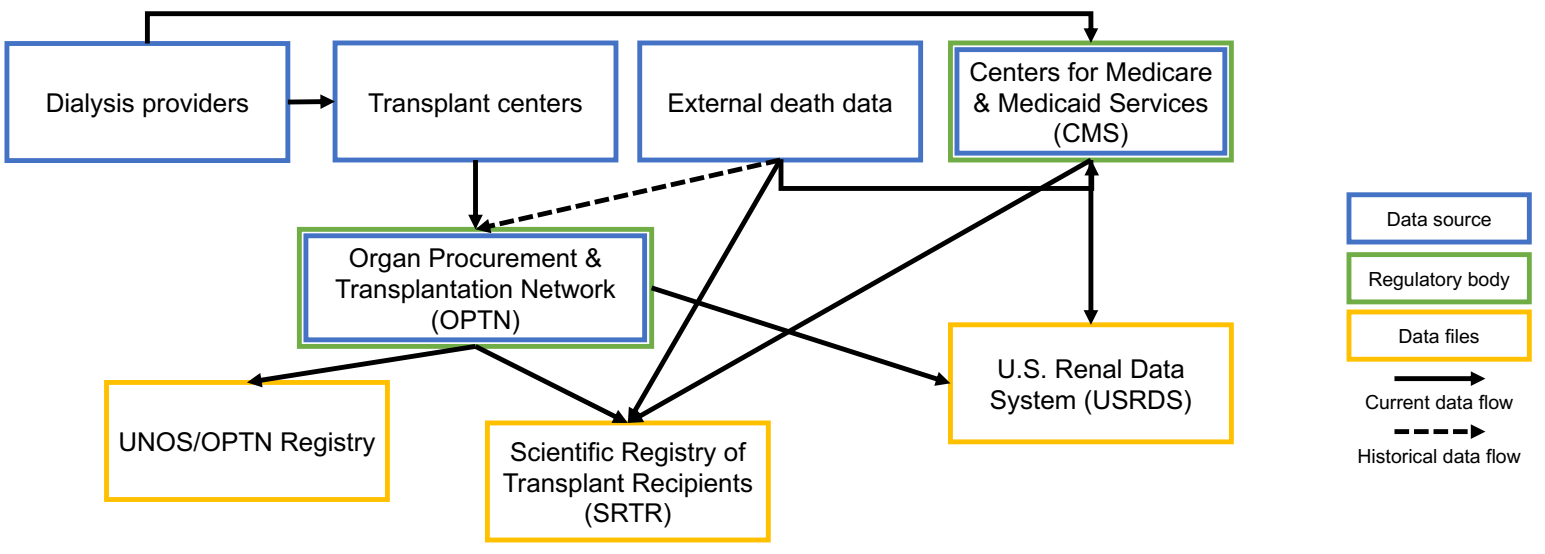
Figure 1. Main kidney transplant databases



Adapted from Yu et al. (1).

No Kidney Left Behind: Interventions Needed to Improve Use of Donor Kidneys

By Karen Blum

Undergoing a transplant in the United States is a complex, multistep process and one historically focused almost exclusively on outcomes, speakers said during a Kidney Week 2023 session on optimizing use of deceased and living donor kidneys. A more transparent process and open communication with patients could lead to better shared decision making and potentially, use of more extended criteria organs and better health outcomes.

Patients with end stage kidney disease need to be educated about dialysis and referred to a transplant center for a comprehensive evaluation, said Sumit Mohan, MD, MPH, FASN, associate professor of medicine and epidemiology at Columbia University in New York City and director of quality and outcomes research for the transplant initiative at New-York-Presbyterian Hospital. Then, there is somewhat of a "black box" of being selected to get on a waitlist, he said, which no doubt leads to attrition at each step.

"What's frequently not discussed is that there is a lot of variation in terms of what happens between the waitlist and transplantation," Mohan said. "The common refrain is, 'If we need to increase transplantation rates, we need more donors.' I would argue perhaps a better first step would be improving deceased organ utilization rates, which are abysmal in the U.S."

Approximately 7500 kidneys procured for transplant were discarded in 2022, he said, and we are on pace to discard 8000 kidneys this year. Common reasons cited for passing up organs include physicians thinking an organ is of poor quality, taking too long to find a recipient, or not locating a recipient, he said. However, studies have shown that kidneys from donors who are diabetic, for example, do well (1). Approximately half of the kidneys ranked at 60% or higher using the Kidney Donor Profile Index are being discarded, Mohan said, equivalent to a kidney from a 55-year-old donor with hypertension (2). "I think the vast majority of us in this room, if we needed a kidney transplant, would say yes to that," he said.

Kidneys often are turned away because of subconscious bias or preferences on the part of physicians, he added, or because medical centers set up filters for certain characteristics, which results in organs not being offered to their patients. Additionally, kidneys procured over the weekend are 20% more likely to be unused (2). "That's not a quality problem; that's a transplant center challenge," Mohan continued. Whether a patient gets a transplant also can rely on geographic region, with areas more likely to accept organs more likely to be transplanted. The process often is opaque to patients, he said.

From 2008 to 2015, 14 million deceased donor kidney offers were made, Mohan stated (3). Of those, 84% were declined at least once, and 76% of patients on the waitlist received at least one offer for a kidney. However, only 2.6% of offers were declined for a recipient-related reason.

To improve access to transplantation and lower discards, Mohan posits that transplant centers need to begin with transparency with patients and incorporate patient preferences to inform organ-offer choice. However, he noted, they should not wait until they have an organ in hand to decide. Instead, they should begin communications early and periodically update people on the waitlist about organs offered for them that the center declined, providing reasons. The process would allow for increased engagement with both patients and nephrologists and "eliminate this idea of paternalism that exists in traditional medicine, where we think these decisions are too complex for our patients," he said.

Enhancing live donor kidney transplants among the Black community

Another discussion in the session examined expanding live donor kidney transplantation for Black or African American individuals by engaging their friends and family members to become living donors. Black individuals are less likely to receive live donor kidney transplants in the United States, and data indicate that the trend is worsening, said L. Ebony Boulware, MD, MPH, dean of Wake Forest University School of Medicine and chief science officer and vice chief academic officer of Advocate Health in Winston-Salem, NC. Black individuals were 55% less likely than White individuals to receive a live donor kidney transplant from 1995 to 1999 and 73% less likely from 2010 to 2014 (4).

Black individuals with kidney diseases face multiple obstacles to live donor transplant, from worries about donor and recipient safety and finances to recipient guilt, hesitation to discuss live donor transplants with potential donors, social determinants of health, and more. Boulware said, "One little intervention is not going to solve this issue. This is a complex, multidimensional problem, and we need to think about how we can address several barriers simultaneously."

In some cases, physicians discussed live donor transplantation less often with people with advanced chronic kidney disease (CKD) who were Black, as well as with females, people with a low educational level, and those living in poverty, Boulware said, suggesting that variability in patient-practitioner interactions also affects people's knowledge and understanding of live donor kidney transplantation as a treatment option (5).

Boulware discussed several initiatives in which she has been involved to try to increase live kidney donation among the Black community. One decade ago, her group developed a social worker intervention called TALK (Talking About Live Kidney Donation) to increase discussion about live kidney donation and transplantation (6). Participants with CKD were randomized to receive usual care (routine care with their nephrologist); an educational video and booklet that explained the donor and recipient process to live kidney transplantation; or the video and booklet plus outreach by a social worker to discuss any barriers. Those who received the video and booklet were more likely to have discussions about live transplantation with family and friends and their physicians; that was amplified with the addition of the social worker intervention.

An update to that work among newly registered Black adults on the kidney waiting list randomly assigned individuals to receive the TALK intervention with or without the offer of financial assistance to cover items such as travel, lost wages, and childcare (7). Surprisingly, neither intervention improved donor activation. Many on the waitlist said they already had discussed donation with family and friends, and others did not use the financial help. "I'm still thinking about why this study didn't work," Boulware said.

Boulware is now engaged in a National Institutes of Health-funded study, called STEPS (System Interventions to Achieve Early and Equitable Transplants), looking at ways to address several roadblocks accessing live donor kidney transplants. The study, which has recruited nearly 1200 of a projected 1500 patients, aims to identify patients who may need a transplant early and encourage them to discuss transplantation with physicians and family members; provide quick referral to kidney transplant centers; and get patients to complete a pre-transplant evaluation. The host sites are Geisinger Health System in Pennsylvania, Duke University Medical Center in North Carolina, and The University of Mississippi Medical Center in Jackson.

The study has several components, Boulware said, including assigning some participants to receive social worker outreach and education and screening for and addressing social determinants of health, including housing instability and food insecurity.

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Dahl et al., Journal of the American Society of Nephrology[1]

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Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron It's been a while, Mac. What do you have for me?

Mac I have a 68-year-old with a kidney transplant and now with chronic diarrhea.

Nephron (*excited*) Whoa! Stop right there—that is a GI consult. I am sorry, but I am a nephrologist.

Mac Trust me, you are going to love this one! You are like a king when it comes to figuring out non-nephrology stuff. Aren't transplant nephrologists the kings and queens of all internists?

Nephron Well, in that case, we may have to put on my transplant hat or call a friend over for some NY-style coffee. I think I shall invite my friend, Dr. Graft Guardian. He is just a phone call away.

Mac Hmm…oh well. I can totally relate to that one.

Pause as Dr. Graft Guardian enters.

Guardian Dear Nephron and Mac, please continue to discuss the case. The "Transplant Guru" has arrived.

Mac This is a 68-year-old male with a history of deceased donor kidney transplant in 2008 for end stage kidney disease secondary to hypertension (or as some believe). He had a history of bilateral, native kidney nephrectomies for renal cell carcinoma and was on maintenance immunosuppression therapy with mycophenolate sodium 360 mg p.o. b.i.d. [by mouth, two times a day], tacrolimus 1 mg b.i.d. (with a goal level of 4–6 ng/mL), and prednisone 5 mg p.o. daily. His baseline creatinine was 1.7 mg/dL.

Nephron Stop…nice! What an amazing topic. Nephrologists love and hate hypertension. Didn't we have an editorial in the September issue of *Kidney News* on who should own hypertension?

Mac (*laughing out loud*) Can we move on? The focus is diarrhea.

Guardian (*angry*) Oh, come on! Please continue.

Mac (*angry*) He presented to the clinic with complaints of fatigue, decreased appetite, chronic diarrhea (two to three loose, watery stools daily), and significant weight loss of approximately 20 kg over the last 1½ years. He denied any fever, sweating, cough, hematemesis, or melena. His blood pressure was low (90/55 mmHg). Laboratory work showed non-anion gap metabolic acidosis (HCO_3 13 mEq/L) and AKI with a serum creatinine of 3.5 mg/dL. The tacrolimus level was elevated above goal, at 14 ng/mL, and this was attributed to ongoing, severe diarrhea. The kidney transplant ultrasound showed patent flow in the transplant renal artery and vein without any significant obstruction.

We need to focus on something that all the patients would have been exposed to since they all had the same signs and symptoms.

Nephron (*bored, rolling his eyes*) Oh, yes, you just nailed point number 1: This is a boring transplant case.

Guardian Interesting. Diarrheal illness in transplant patients is a tough one. Medications and infections usually top the list. Malignancy may be a distant third. I assume mycophenolate acid was not the suspect here these many years out, and he was also on the enteric-coated mycophenolate. Enteric-coated MMF [mycophenolate mofetil] has the potential to reduce the incidence of diarrhea by delaying release of MPA [mycophenolic acid] into the small intestine instead of the stomach. In a recent review of the U.S. Renal Data System database of 41,442 renal transplant recipients in the United States, the 3-year cumulative incidence of diarrhea was 22%, with 18% classified as non-infectious. While infections can cause death, non-infectious diarrhea episodes can also lead to graft loss and death. The most common causative agent of diarrhea in solid organ transplant patients is MMF. In some studies of liver-transplant recipients taking 3 gm of MMF daily, the incidence of diarrhea is as high as 51%. Often, non-immunosuppressive agents can be implicated in causing diarrhea, as solid organ transplant patients often receive many medicines, such as other antibiotics. Other, less common causes of diarrhea in transplant recipients include post-transplant lymphoproliferative disorder (PTLD), inflammatory bowel disease, colon cancer, and bacterial overgrowth syndromes.

Nephron (*winking*) Dr. Guardian, are we done with your medicine lecture yet?

Mac Let me tell you more to explain the situation. He was admitted to the hospital for supportive care, and an extensive workup for his symptoms was undertaken. Hydration resolved his AKI. Stool *Clostridium difficile* toxins A and B were negative. Stool culture was negative for growth of any routine enteric pathogens and *Vibrio cholerae*, and a qualitative fecal fat test to rule out malabsorption was negative. Serum cytomegalovirus (CMV) polymerase chain reaction (PCR), Epstein Barr virus PCR, and cryptococcal antigen were negative. HIV and tuberculosis T-SPOT testing were negative as well. A cancer antigen 19-9 level was obtained, which was normal. His last colonoscopy done 6 months ago did not detect any concerning lesions. There were no masses on a chest x-ray and on ultrasound imaging, and his nephrectomy beds were negative for any recurrent or remnant disease. Echocardiography showed normal ejection fraction and no valvular vegetation. Now what?

Nephron (*laughing*) Pre-renal AKI resolved. Great…done. We can sign off!

Guardian I am sorry, but I cannot sign off on a transplant patient's case. This is my forte, regardless of what part of medicine it is. This is the best part of being a transplant nephrologist. I think we know more IDs [infectious diseases] than ID docs, more heme-onc [hematology-oncology] than hematologists, and more immunology than immunologists.

Nephron Talk about modesty! Hmm….

Mac (*trying to remember*) As part of the malignancy workup, an esophagogastroduodenoscopy was done, which was unremarkable except for peptic duodenitis. A stool PCR test for Shiga toxin 1 and 2, *Cryptosporidium*, *Giardia*, *Cyclospora*, *Campylobacter*, *Yersinia enterocolitica*, adenovirus, and rotavirus was negative as well.

Guardian (*jumping in*) I think what you have done is a very good workup. Stool cultures and ova and parasites (O+P) evaluations are important. Conventional stool cultures are also useful, especially in bacterial causes. The yield is low, with acute, watery diarrhea. With bloody stools, the laboratory should be requested to look for Shiga toxin-producing *Escherichia coli*. With seafood ingestion, the laboratory should be requested to look for *Vibrio*. A stool can be tested for *C. difficile* toxin A and B by EIA [enzyme immunoassay] or cytotoxin assay, although some hospitals are moving toward PCR testing. Recent antibiotic use and hospitalization are traditional risk factors, but they are increasingly being seen in outpatients, so there should be a low threshold for diagnostics with diarrhea and leukocytosis. Send stool for O+P exam *Giardia* antigen testing, especially with chronic diarrhea. You need to request a modified, acid-fast stain for *Cryptosporidia*, *Cyclospora*, and *Isospora* and a trichrome stain for microsporidia. A CMV PCR should be obtained in patients where CMV enterocolitis is considered, especially with other constitutional symptoms in individuals with moderate to high risk. However, they may have negative or low-level viremia and still have active GI disease. Finally, CT scans and endoscopic evaluations, as you did, are excellent next steps.

Silence

Mac Hmm…and then we have the culprit.

Nephron (*shocked*) Let me guess, it's SARS-CoV-2?

Mac (*smirking*) No, no, it's not COVID-19-induced this time around. Although, adding that to the title of any publication would probably lead to quicker acceptance of a paper on this case.

Guardian Go on with the real stuff of the harder part of the case, and let's leave SARS-CoV-2 out of this. In all seriousness, we lost many of our patients to the pandemic. Please respect the virus.

Silence

Mac (*decisively*) Norovirus (NoV) PCR is positive on the stool PCR. The repeat value confirmed this.

Guardian Hmm…fascinating. NoV infections are the most common cause of acute gastroenteritis worldwide. In the transplant population, NoV infections can result in chronic diarrhea, which has long-standing after-effects on nutrition, quality of life, elevated tacrolimus levels, and resultant toxicity and graft dysfunction. Even though the first cases were reported in 2009, awareness about this infection and approaches to its management leave room for improvement.

NoV binds to antigens on enterocytes, causing edema and severe enterocyte injury resulting in diarrhea. Clinical manifestations of NoV/sapovirus gastroenteritis in patients who are immunocompromised include non-bloody, watery diarrhea; nausea; vomiting; abdominal discomfort; bloating; weight loss; and wasting. Fever is unusual. It spreads mainly via the food-borne, fecal-oral routes but also through person-to-person contact or contaminated surfaces. Both T cell and B cell responses are required to clear NoV infection, and immunosuppressive therapy is a risk factor for prolonged infection. In kidney transplant recipients, because of iatrogenic immunosuppression, NoV symptoms can be prolonged and chronic, with periods of symptom exacerbation and remission. If not treated, kidney graft dysfunction can occur due to severe dehydration. The diarrhea can also disrupt the P-glycoprotein efflux pump, leading to supra-therapeutic tacrolimus levels, further worsening the AKI. Also, patients are at higher risk of rejection due to immunosuppression reduction that is done to allow the host immune response to eliminate the infection.

Nephron (*showing off*) Good point. A 2021 study by Gäckler et al. in *Transplantation* addressed the gaps in our understanding of the clinical characteristics of NoV infections post-kidney transplantation. The study enrolled 60 patients with kidney transplants diagnosed with NoV infection by a positive stool PCR test. It aimed to identify the characteristics of chronic NoV infections in kidney transplant recipients and their effect on allograft function. The study also evaluated the safety and efficacy of using intravenous immunoglobulin (IVIg) as a therapeutic measure in 18 patients with chronic diarrhea. NoV gastroenteritis occurred a median of 52 months after transplant, resulting in a cumulative median hospital length of stay of 8 days for patients admitted with acute gastroenteritis. Thirty-one of the 60 patients were found to have chronic infection. Compared with those with acute infection, patients with chronic infections stayed longer in the hospital (10 vs. 7 days), and they were hospitalized more frequently for their illness (17 patients vs. 1 patient). Multivariate analysis showed that both diabetes mellitus and the administration of lymphocyte-depleting induction therapy were independent prognostic factors for the development of chronic NoV infection among kidney transplant recipients.

Guardian (*jumping in*) Nephron, you just stole those lines from the March *Kidney News* issue, in which it was highlighted as an important topic.

Mac IVIg? Interesting…. Why not hold MMF and start nitazoxanide?

Guardian No therapy has shown to be consistently effective, and there are no specific therapies for treating NoV infection. Symptom relief should include intravenous hydration, anti-motility agents to relieve diarrhea, and reduced immunosuppression. Immunosuppression reduction may help reduce clinical symptoms and prevent chronic carriage and recurrent infection. Reduction of immunosuppression in organ transplant recipients should be done carefully due to the risk of precipitating a rejection. Limited case studies have shown nitazoxanide to be effective in treating NoV with a significant reduction in time to resolution of symptoms. Nitazoxanide is a thiolide antimicrobial agent that exerts its effect against parasitic worms, protozoa, bacteria, and viruses. The antiviral effects of nitazoxanide are two-fold, including activation of natural antiviral defenses and inhibition of cellular pathways that lead to viral replication. Nitazoxanide therapy for the treatment of NoV should be continued until stool RNA studies are negative. A systematic review of activity of nitazoxanide on viral gastroenteritis concluded that nitazoxanide may be useful in reducing the disease burden in transplant recipients who are immunocompromised. Now, with IVIg, as Detective Nephron pointed out, a recent study showed some good benefits. In that study, he mentioned that 18 kidney transplant recipients with chronic NoV infection were treated with IVIg based on severity perceived by treating clinicians. Thirteen of these patients had no further clinical signs of NoV infection and did not require further hospitalizations. However, 10 of the 13 patients demonstrated NoV in stool samples even following therapy, so it didn't completely clear the virus.

Mac (*nodding*) So, what do we do here?

Nephron (*puzzled*) Do all of the above: start nitazoxanide therapy, give a few doses of IVIg, and hold MMF. I doubt he will reject his kidney these many years out with an elevated tacrolimus level.

Mac You are so dramatic!

Guardian (*laughing out loud*) On a serious note, he may be correct. As I had mentioned, currently, there is no single, proven therapy to cure NoV in the kidney transplant population who are immunocompromised. Treatment with medications such as nitazoxanide and Ig has proven effective in limited cases. Reducing immunosuppression for the patient's immune system to clear the infection may lead to renal transplant rejection, so we must be careful.

Nephron Mac! What are you going to do? The ball is in your court.

Mac (*confidently*) We will hold MMF, give the nitazoxanide, and eventually monitor for renal function and graft rejection. IVIg may have a role in the next few weeks if clinically there is no improvement, and symptoms don't resolve.

Guardian Sometimes, you must make tough decisions in transplant nephrology. No evidence is going to help guide you; it will be your clinical acumen.

Nephron (*jumping in*) Yes, of course. Tell the team your plan.

A few days later

Mac (*surprised*) Well, we did as we planned. He did clear his virus, and kidney function remained stable at 1.8 mg/dL. We did do a protocol renal biopsy, and no rejection was noted.

Nephron Fantastic! I assume he stays off MMF?

Mac For now.

Guardian Preventive measures for NoV are important given the morbidity associated with the infection. Hand hygiene is of paramount importance.

Silence

Nephron You sound like a joint commission surveyor.

Mac (*winking*)

Nephron (*laughing*) There you go again! Fascinating diagnosis and treatment, Mac, and special thanks to our transplant nephrologist in helping us with this tough case. I must say, transplant nephrologists are truly the best internists on the planet. Now, let's have some NY-style coffee.

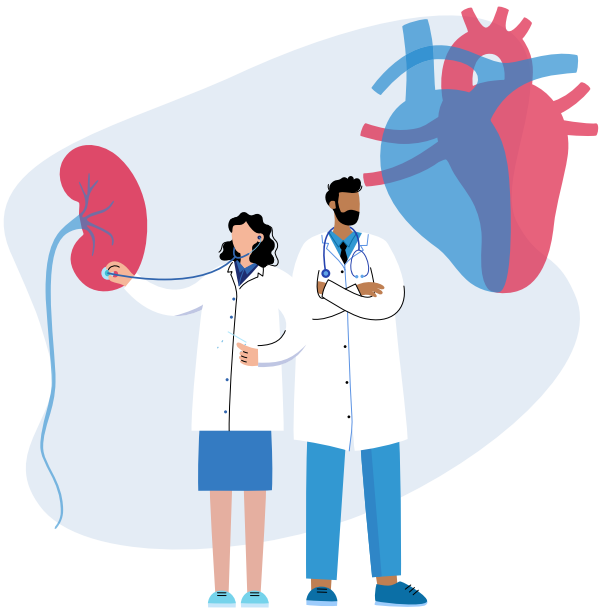
Dr. Graft Guardian takes a bow and winks. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, FASN, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. Special thanks are extended to Dr. Rimda Wanchoo, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Dr. Sam Kant, assistant professor of medicine at Johns Hopkins University; and Dr. Prakash Gudsoorkar, assistant professor of medicine at the University of Cincinnati, for their editorial assistance. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.

Bridging the Heart-Kidney Divide

Nephrocardiology Services and Clinics Aim to Bring Cardiologists and Nephrologists Together to Treat Complex Conditions

By Bridget M. Kuehn



The relationship between heart and kidney health—and sometimes between cardiologists and nephrologists—can be fraught. "The struggle is that there's very complicated pathophysiology happening and it's a little bit like a marriage or a relationship, where if one person's unhappy, the other person tends to be unhappy as well," explained Jacob Stevens, MD, FASN, an assistant professor of nephrology at Columbia University Irving Medical Center in New York City. However, Stevens and other clinicians across the United States are working to improve the care of patients with heart and kidney diseases and close the gap between specialties by building cardiorenal services or clinics. During the "Nephrocardiology Care Models: From Idea to Implementation" session at Kidney Week 2023, Stevens and three other presenters shared how several institutions provide nephrocardiology (also known as cardiorenal or cardionephrology) care.

The session occurred amidst growing recognition of the need for multidisciplinary care for patients with cardio-renal-metabolic diseases, including a recent presidential advisory from the American Heart Association (AHA) (1), which was co-authored by Janani Rangaswami, MD, section chief of nephrology at the Washington, DC, Veterans Affairs Medical Center and professor of medicine at The George Washington University School of Medicine and Health Sciences, who co-moderated the session at Kidney Week. Session presenter Nisha Bansal, MD, FASN, professor of medicine in nephrology at the University of Washington (UW) in Seattle, noted that there has also been increasing calls from within the nephrology field over the past 5 to 10 years to increase kidney-cardio care specialization.

"Interdisciplinary care models were highlighted [in the AHA advisory] as a critical need to actually achieve the goals of managing cardio-kidney-metabolic disease," Bansal said. "Given the call from nephrology, as well as now cardiology, I do think the time is now to think about how to move nephrocardiology care forward."

Patients with complex conditions

Growing incidence of congestive heart failure and improvements in care have led to more patients living longer with advanced heart failure, Stevens noted. Use of mechanical circulatory support, such as extracorporeal membrane oxygenation or intraballoon pumps in intensive care units (ICUs), can provide a bridge to transplant or to receiving a durable mechanical support device like a left ventricular assist device, he explained. More patients are also receiving heart transplants and surviving after the procedures, he said.

"Not only is the volume of patients that we are seeing increasing, but they are increasingly complex," Stevens said. "They are living longer and have a lot higher rate of comorbid illnesses, which is good because it means cardiologists are doing a good job of keeping them alive."

Heart transplant recipients often have pre-existing comorbid conditions that may have contributed to the development of heart failure, and they may also experience acute kidney injury (AKI) during transplant or other procedures and ongoing kidney stress from immunosuppressants and other medications, Stevens said. These factors may contribute to persistent kidney injury in patients who have limited kidney reserve, which leads to AKI transforming into chronic kidney disease (CKD) or end stage kidney disease (ESKD) at much higher rates in this population. One year post-heart transplant, 15% of patients have a 50% reduction in their estimated glomerular filtration rate (eGFR), and by 10 years post-transplant, 15% have ESKD and are either treated with dialysis or have received a kidney transplant (2). Additionally, nearly one-quarter of patients with advanced heart failure have CKD (3).

Patients undergoing other types of heart surgery also have increased AKI risk (4), with many progressing to CKD, Stevens noted. He also noted that there are special considerations for patients with ESKD or CKD who are undergoing cardiac procedures and for patients who need dialysis after heart surgery. "Caring for these patients requires a special knowledge set," Stevens said.

Yet, despite the need for integrated heart and kidney care, Bansal noted that traditional care pathways can create barriers to appropriate care for patients with concurrent heart and kidney diseases. Prior to launching a nephrocardiology service at UW, Bansal noted that care protocols were not standardized and often varied depending on who was attending. Transitioning patients from inpatient to outpatient settings was also complicated by numerous subspecialists and limited communication among them. "These patients were in the hospital with multiple consultants, multiple revolving attendings, and we found that communication was often disjointed, and there wasn't a high level of trust between subspecialists."

Nephrocardiology service?

Stevens proposed a checklist of questions for hospitals considering whether to create a nephrocardiology program to meet these growing needs. Chief among them was whether an institution had enough patient volume to support the service. At Columbia University, which has over 7000 ICU admissions each year and more than 2200 heart procedures performed each year, Stevens and his colleagues, who perform the nephrocardiology services, have an average patient census of 18 to 22 patients. Twelve of Columbia's 33 nephrologists attend the service, and there is a fellow and sometimes medical students, residents, or anesthesia or critical care fellows participating.

"It's really important to work with the electronic health records team at your institution to start pulling some numbers," Stevens said. He suggested looking at the numbers of nephrology consults requested by cardiology and cardiothoracic surgery or the number of consults for patients admitted or discharged with kidney diseases and a heart condition.

Bansal noted that UW underwent this process and decided it did have the volume of patients with medically complex conditions to support it. She explained that UW serves a five-state region, including Alaska, Idaho, Montana, Washington, and Wyoming. The analysis revealed that 65% of patients admitted for heart failure also had AKI, and 40% of patients who had mechanical circulatory support during hospitalization needed dialysis (5). Patients with heart failure and AKI had longer lengths of stay, higher inpatient death rates, and higher readmission rates.

"We saw a clear need and an opportunity to improve outcomes," she said. The consultation service was launched in August 2020 amidst the COVID-19 pandemic. Initially staffed by herself and two other nephrologists, they take turns rotating and seeing patients of the cardiology or cardiothoracic surgery team. Their average patient census is approximately 15 but can range as high as 27 patients, she said.

Liam Plant, MBChB, clinical professor in renal medicine at Cork University Hospital, Ireland, offered an international perspective from a national health care system. In his presentation, he noted that in some countries or provinces, there may be fewer nephrologists than are included in the nephrocardiology teams at Columbia University or UW, and they may be serving a much smaller number of patients. In such cases, the volume may not justify a dedicated service, and patients may be better served by improving care in existing care pathways. "We probably need to broaden and deepen the integration of our current care pathways and perhaps also add a new subspecialty, which we might call cardiorenal," Plant said. "We need to be careful that in addressing complexity, we don't invent a complex solution that leaves us with the rest of things undone."

Plant suggested leveraging primary care clinicians to help identify patients with chronic diseases, like kidney diseases, which Ireland's health system pays primary care clinicians to do. He suggested that, in addition to finding patients with comorbid heart and kidney diseases, primary care clinicians may be able to execute more structured treatment regimens and provide CKD education. He noted that the rollout of a growing number of cardio-renal-metabolic medications has contributed to enhance education among clinicians about treating this subset of patients.

At Cork University Hospital, nephrologists and cardiologists already closely collaborate. He said that the nephrologists perform approximately 2100 consults each year with approximately 42% involving patients with heart disease, and they typically have approximately 12 patients with cardiorenal dysfunction in the hospital at a time. "We don't have a separate [dedicated] cardionephrology team," Plant explained. "It is implicit and it's embedded."

Stevens said it is important to assess the interest of other departments in using a nephrocardiology service. He noted comments from colleagues at Columbia—which has had a nephrocardiology service for 16 years—highlighting the ability to improve processes and working toward shared care goals across disciplines. "It can really benefit not only patients but also clinicians in the hospital," Stevens said. "It allows for differentiation and professional development of your faculty. It's been a win for everybody."

Bansal agreed that the need for unique expertise and multidisciplinary training is creating new opportunities for the field of nephrology. Bansal said that UW's service was built with goals of improving care, training the next generation of clinicians, and bolstering research in this subspecialty, including quality improvement studies. "I truly believe it's a way to innovate our field and move forward," she said.

All three of these speakers emphasized the need to update nephrology training curricula to include nephrocardiology care.

Improved outcomes

Since the Kidney Heart Service at UW launched, Bansal and her colleagues have seen 550 patients with unique conditions. They have observed approximately a 2.3-day reduction in length of stay for patients with co-occurring heart and kidney diseases compared with before the service launched, as well as a 5% reduction in readmissions, a small reduction in patients requiring dialysis, and a trend toward reduced inpatient deaths (5). They have also seen some intangible benefits, Bansal said. She noted that she and her colleagues on the service join cardiology colleagues on rounds and discuss mutual patients. "We've developed more streamlined communication," she said. "We've developed a high level of trust."

That trust has allowed them to work together with their cardiology colleagues to develop standardized approaches to care. They also share resources and new information either through informal bedside discussions or formal joint conferences. "What I've really enjoyed being on this service is the bidirectional learning," she said. She and her colleagues have developed expertise on mechanical circulatory support; trained in point-of-care ultrasound; and developed new protocols for diuretics and when to add adjunctive therapies, like sodium-glucose cotransporter-2 (SGLT2) inhibitors or spironolactone, with the cardiology team. Both cardiology and nephrology fellows have joined the service, and internal medicine residents and some medical students are also participating.

Bansal and her colleagues are also using their experience to identify research questions and build multidisciplinary research teams. So far, they have received two National Institutes of Health grants to study patients with kidney-cardio conditions. One grant is to investigate kidney injury biomarkers that can guide inpatient and outpatient diuretic and heart failure; another is to study bioethical issues in the care of patients with kidney-cardio conditions and patient preferences. "We continue to think about what's next for our group," she said. The team also recently welcomed a fourth nephrologist and is analyzing ways to incorporate nutritionists, social workers, and other health professionals.

Outpatient options

Conrad Macon, MD, an advanced heart failure and transplant cardiologist at the Oregon Health and Science University in Portland, co-directs the outpatient Cardiorenal Clinic at the institution. The clinic was launched to help improve the use of medications in patients with cardiorenal disease. "We know that people who have renal dysfunction plus heart failure do worse, yet the people that need medications and therapies most are least given it," he said during his presentation.

For example, he cited data that showed only 45% of patients with an eGFR from 30 to 45 mL/min/1.73 m^2 were getting renin-angiotensin system (RAS) inhibitors, and only 24% of those with eGFRs below 30 mL/min/1.73 m^2 were getting them (6). Only 15% of patients were receiving triple therapy with a RAS inhibitor, β-blocker, and mineralocorticoid receptor antagonist (MRA). Macon also cited data showing that quadruple therapy may reduce patient mortality from 35% to 9.5% with a number needed to treat of approximately 4 (7). Macon explained that most clinicians are comfortable prescribing β-blockers for patients with renal dysfunction, which can reduce patient mortality from 35% to 23%, but patients are missing out on additional benefits from added therapies. "We're missing a potential 41% reduction in mortality in this population," he said. "It's pretty remarkable."

Macon blamed difficulties treating patients with medications after discharge and medication myths for driving undertreatment. For example, he said that many physicians believe medications that have shown to be beneficial in heart failure, like angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or SGLT2 inhibitors, are nephrotoxic. However, he said that clinical trials for the drugs demonstrate benefits. "We know these things improve outcomes in heart failure," he said. "They improve outcomes in renal dysfunction." He explained that an initial dip in an eGFR on some medications or the "dreaded creatinine bump," which resolves over time, may contribute to the myths. "We've all experienced this moment of panic; did I do this?" Macon said. "This is something you should expect and treat through." But he noted that for other drugs, like MRAs, the data are more convoluted, suggesting that they improve mortality in patients with heart failure while their renal effects are more questionable.

Drug costs are another deterrent to their use, Macon said. He cited GoodRx data from Portland that show SGLT2 inhibitor prescriptions cost more than $500, while finerenone costs more than $650, and the potassium binder patiromer costs more than $1300 (8). They also can be time and labor intensive to titrate and require frequent visits. But that is what he and his colleagues' day-to-day work at the clinic entails. They also use remote hemodynamic monitoring, which helps with medication adjustments.

Having a multidisciplinary team at a clinic, including a nephrologist, a clinical pharmacist, and heart failure nurses, is effective. He explained that the clinical pharmacist helps patients obtain medications at an affordable cost, handles prior authorizations, and performs titration visits every 2 weeks. The heart failure nurses answer patients' frequent electronic medical record questions, follow up on lab results, and man-age the remote hemodynamic monitoring. "It really takes a village to [operate] a cardiorenal clinic," he said. ■

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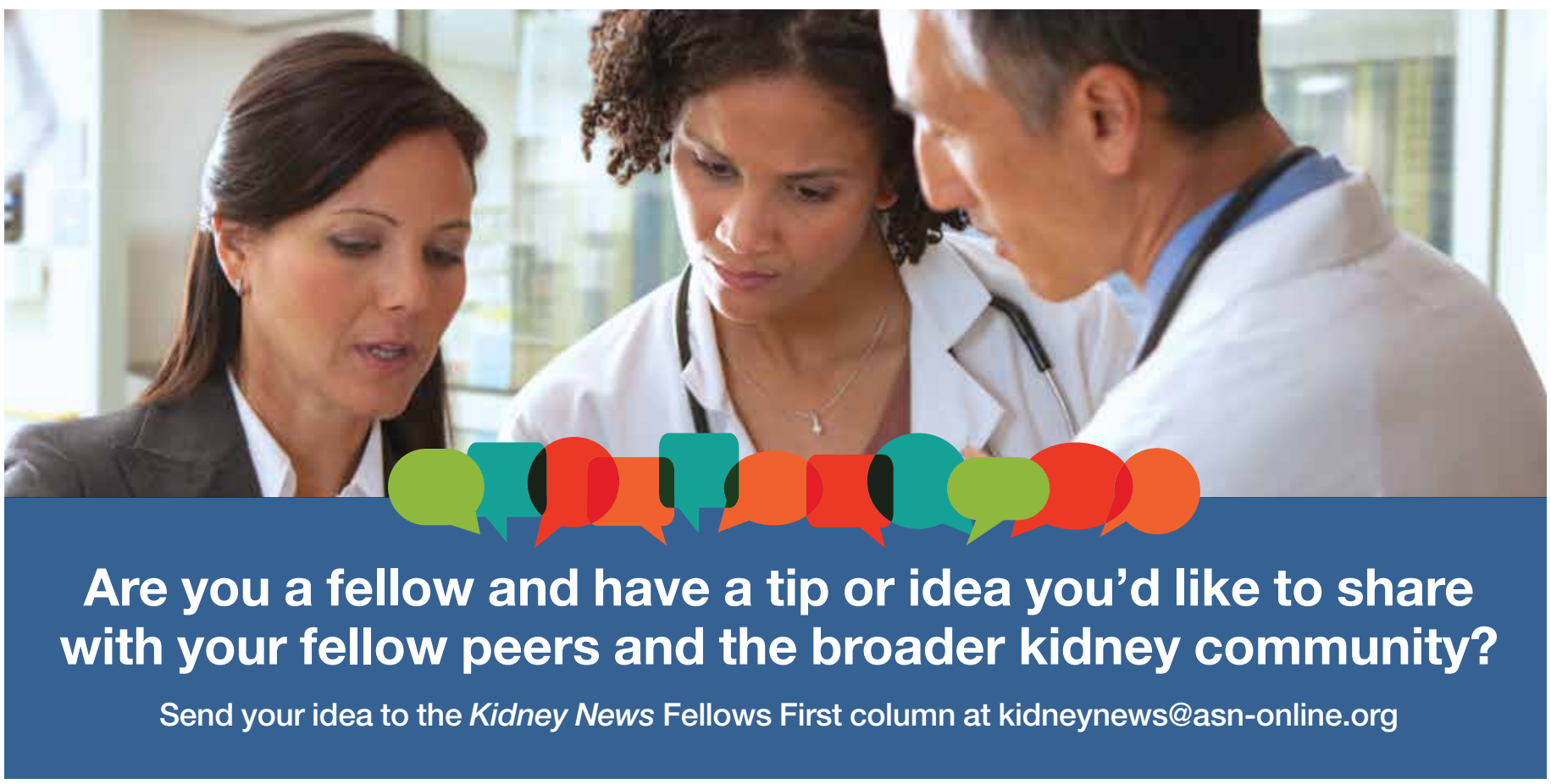

Disparities in the Care of Patients with CKD and ESKD: The Saga Continues

By Jay Wish

It is well known that disparities exist in chronic kidney disease (CKD) prevalence, progression, treatment, and outcomes based on demographic, socioeconomic, and geographic factors (1–3). Sex- and gender-based disparities exist in CKD care (4), particularly with regard to transplant access (5). Once patients are on dialysis, disparities in outcomes persist (6–11). Kimmel et al. (6) reported that among White patients on dialysis in the U.S., income inequality was associated with increased risk of mortality; among Black patients on dialysis, residence in highly segregated areas was associated with increased mortality. Hall et al. (7) found that a significantly greater proportion of dialysis facilities serving racial and ethnic minority patients had worse than expected survival compared with facilities serving predominately White patients. The death rate for White patients on dialysis (207.4 per 1000 patient-years) exceeds that for Black patients (135.8 per 1000 patient-years), but this may be due to survival bias—the ability of healthier racial and ethnic minority individuals to reach dialysis therapy (8). Studies accounting for kidney transplantation as a competing risk eliminated the survival benefit in younger Black patients (9). Garg et al. (10) reported an association of higher neighborhood income with decreased mortality and increased likelihood of placement on the kidney transplant wait list among 3000 patients on dialysis. A recent scoping review of health inequities in dialysis care noted disparities based on race and ethnicity, sex and gender, underserved rural populations, and income (11).

An association between a 3-day interdialytic interval and mortality among patients receiving three times weekly hemodialysis (HD) was first reported in 2011 by Foley et al. (12) using data from the U.S. Renal Data System. Increased hospitalization rates were reported when surgery was performed on the third interdialytic day (13). Irrespective of the timing of surgery, patients on dialysis experience a marked increase in perioperative mortality compared with patients with normal kidney function, ranging from an odds ratio of death of 4.0 following vascular surgery to 10.8 following orthopedic surgery (14). Given the vulnerability of patients undergoing HD by the third interdialytic day, elective surgery should be scheduled soon after the HD treatment. This could be later in the day of the dialysis procedure or on the following day to optimize the patient's biochemical and fluid status in the perioperative period. Accordingly, several authors, including Palevsky (15), recommend that patients undergoing major surgical procedures receive dialysis the day preceding surgery, which may require adjustment in the patient's dialysis schedule.

In 2022, Fielding-Singh et al. (16) performed a retrospective cohort study of 1,147,846 surgical procedures among 346,828 Medicare beneficiaries undergoing HD. The patients were stratified by 1-, 2-, or 3-day intervals between the most recent HD treatment and the surgical procedure and whether the patient underwent HD on the day of the surgical procedure. Longer intervals between the last HD session and surgery were associated with a higher, 90-day mortality risk in a dose-dependent manner. Undergoing HD on the same day as surgery was associated with a significantly lower risk of mortality vs. not doing so.

In a follow-up July 2023 publication, Fielding-Singh et al. (17) analyzed the same cohort for exposures by age, sex, race and ethnicity, and social deprivation index (SDI). The primary outcome was the proportion of procedures with a 2- or 3-day interval between the last HD session and the surgical procedure. Older age, female sex, non-Hispanic Black race, and each increasing decile of the SDI were significantly associated with longer intervals between HD and surgery and, by implication from their prior study, increased risk of 90-day mortality. The reasons for the disparities are unclear, and further research is clearly needed. Possible explanations include an inflexibility of the patient's home HD facility to reschedule dialysis closer to an elective surgical procedure, transportation issues for the patient to access dialysis treatment if modified from the usual schedule, and poor communication between the hospital in which the surgery is performed and the dialysis center. Given this opportunity to improve perioperative outcomes among patients who are highly vulnerable, practitioners should explore and overcome barriers to dialysis within 1 day of an elective surgical procedure. ■

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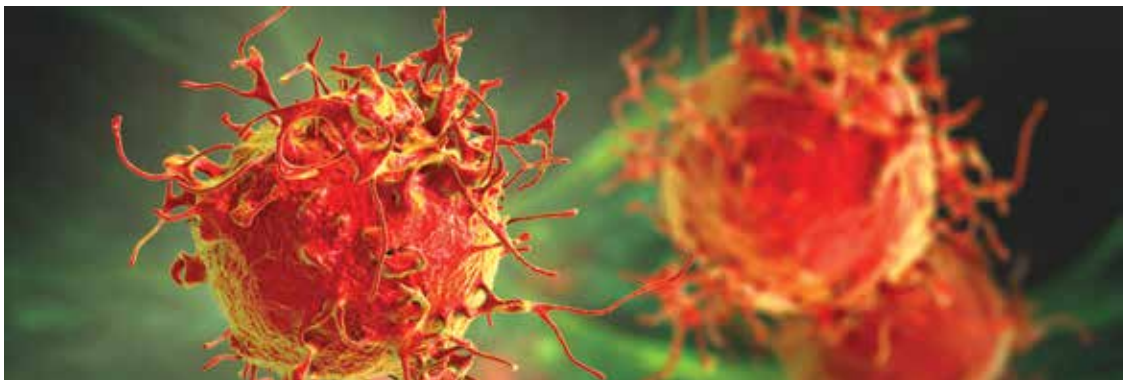
Myeloma-Related Renal Impairment Management Update



By Motoko Yanagita

Kidney impairment is a frequent and prognostically relevant complication in multiple myeloma (1). Up to 50% of patients with multiple myeloma present with kidney dysfunction at diagnosis, and 2%–4% require dialysis (2). In addition, kidney dysfunction is associated with shorter overall survival and increased risk of early mortality in patients with multiple myeloma. The average survival of patients with renal dysfunction is approximately 20 months. On the other hand, with current therapies, only a small percentage of patients experience a significant decline in renal function within the first 12 months. Because kidney dysfunction in patients with multiple myeloma is reversible (especially in the early stages), a multidisciplinary approach to diagnosis and management is required (3). In recent years, the introduction of novel agents for multiple myeloma has expanded its treatment options, and the International Myeloma Working Group (IMWG) has updated its clinical practice recommendations for managing renal dysfunction associated with multiple myeloma (4) (Table 1).

First, for the diagnosis of kidney dysfunction in multiple myeloma, it is recommended that measurements of serum creatinine, estimated glomerular filtration rate (eGFR), electrolytes, and free light chain (FLC), as well as 24-hour urine total protein, electrophoresis, and immunofixation, be performed. Kidney biopsy is not recommended if proteinuria is light chain-dominant, and serum FLC levels are elevated because these findings indicate the presence of cast nephropathy, the most common and important kidney pathology in patients with multiple myeloma. On the other hand, a kidney biopsy is justified if the patient shows nonselective proteinuria (primarily albuminuria) or serum FLC levels less than 500 mg/L when there is no known cause of worsening kidney function.

Next, the IMWG criteria were recommended to define the renal response concerning treating kidney dysfunction due to multiple myeloma. This criterion is superior because it has already been validated in several studies. As for treatment details, all patients require high-dose dexamethasone and supportive care (hydration, correction of hypercalcemia, and avoidance of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs). Bortezomib-based regimens are fundamental to managing patients with multiple myeloma and kidney dysfunction, but the potency and drug resistance of bortezomib have been therapeutic limitations, leading to the development of a new generation of agents. Studies have shown that prolonged persistence of light chains after diagnosis of myeloma worsens kidney prognosis and that rapid reduction of serum light chain levels increases the likelihood of kidney function recovery. Therefore, extracorporeal removal of FLC using high-cutoff dialysis or plasma exchange in addition to standard therapy may improve the rate of dialysis independence.

Furthermore, dialysis is indicated in acute kidney injury (AKI) with severe fluid overload and electrolyte abnormalities, regardless of myeloma status. The new four- and three-drug regimens, including proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies, have improved kidney function and survival outcomes in patients who are newly diagnosed and relapsed or refractory. The panel recommended intensified therapy with daratumumab, bortezomib, dexamethasone, weekly FLC response assessment, and a second cycle of immunomodulatory agents, particularly for patients who are newly diagnosed. Notably, the report mentioned kidney adverse effects with carfilzomib, including thrombotic microangiopathy, albuminuria, and grade 3 AKI. If kidney damage due to carfilzomib is suspected, a re-biopsy of the kidney may be considered. Additionally, the dose adjustment of renally excretable anti-myeloma drugs in patients with kidney dysfunction is discussed. Antibody-drug conjugates, chimeric antigen receptor T cells, and bispecific T cell engagers are well-tolerated and effective in patients with moderate kidney dysfunction. Although the level of evidence is low, kidney transplantation can be considered for patients with end stage kidney disease (ESKD) and persistent myeloma control (i.e., minimal residual disease-negative for 2 years) (5).

The shortcomings of prior research encompass varied and inconsistent methodologies for evaluating kidney dysfunction, the omission of patients with severe kidney impairment from clinical trials, and the application of chronic kidney disease equations for estimating kidney function in patients with AKI. A differential diagnosis of kidney dysfunction in patients with multiple myeloma needs to be implemented appropriately. The optimal treatment for myeloma in patients with impaired kidney function has yet to be established and requires further study. ■

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Table 1. Summary of IMWG recommendations

Diagnosis	• Serum creatinine, eGFR, electrolytes, FLC, 24-hour urine total protein, electrophoresis, and immunofixation • Kidney biopsy (optional)
Kidney response	• The IMWG criteria
Treatment	• High-dose dexamethasone and supportive care for all patients with kidney dysfunction due to multiple myeloma are suggested. • Bortezomib-based regimens are the cornerstone of management of patients with multiple myeloma and kidney dysfunction at diagnosis. • New four- and three-drug combinations, including proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies, have improved kidney and survival outcomes in patients who are newly diagnosed and relapsed or refractory. (The panel specifically recommended daratumumab-bortezomib-dexamethasone, weekly FLC response assessments, and intensified therapy with immunomodulatory agents for the second cycle in patients who are newly diagnosed.) • Dose adjustment should be considered for all anti-myeloma drugs excreted from the kidneys in patients with impaired kidney function. • Antibody-drug conjugates, chimeric antigen receptor T cells, and bispecific T cell engagers are well-tolerated and effective.
Kidney transplantation	• Kidney transplantation can be considered in patients with ESKD and sustained myeloma control.

NephCure Event Focuses on Kidney Disease Burden among Black Americans

By Melanie Padgett Powers

At age 17, Joshua Albright took pride in eating healthy and staying active. He loved playing basketball with his friends in their Atlanta suburb. But one day, at his uncle's house, he and his cousins were experimenting with a blood pressure monitor. And to everyone's surprise, Albright's blood pressure was high, approximately 160/90. No one was quite sure what to do.

The results weighed on his mother's mind, so the next day, she called Joshua and said: "Your dad's taking you to the doctor. You need to go right now." In the children's emergency department, after clinicians checked his blood pressure, Albright remembers two doctors looking really shocked at how high it was. The teenager was soon diagnosed with focal segmental glomerulosclerosis (FSGS), a rare, protein-spilling kidney disease.

Looking back, Albright had experienced frequent headaches. But it was in 2020, during a pandemic and at-home schooling, so he chalked it up to stress. A few months after his diagnosis, Albright was eligible for a clinical trial for an oral medication for patients with FSGS who were found to have the genetic variant of the apolipoprotein L1 (*APOL1*) gene from genetic testing. Patients of western or central African ancestry who have the high-risk genetic variant are at increased risk of kidney diseases. The gene mutation evolved in Africa to protect against a parasite that causes African sleeping sickness.

In the United States, it is believed that one out of every five people of African ancestry with the high-risk *APOL1* genetic variant will develop protein-spilling kidney disease, said nephrologist Barbara Gillespie, MD, MMS, FASN, vice president and therapeutic head of nephrology at Fortrea (a company that provides clinical development and patient-access tools to the life sciences industry) and adjunct professor in the Division of Nephrology and Hypertension at the University of North Carolina School of Medicine, Chapel Hill.

Albright, now 20 years old, shared his story during the NephCure conference, "Addressing the Unequal Burden of Kidney Disease on Black Americans," on September 19th in Washington, DC (1). "I share my story because I know I can be an advocate for a lot of people with rare diseases," Albright said. "I've seen the impact that my story can have on others, and I tell my story to help other people and give an insight [into] what we go through." NephCure funds research and provides support and education to people affected by kidney diseases.

The full-day summit brought together patients, physicians, and researchers. This conference was particularly unique because of the other stakeholders in attendance: leaders from the church, community, historically Black colleges and universities, and the entertainment industry. The event included Grammy-nominated rapper Freeway and a video message from National Basketball Association Hall-of-Famer Alonzo Mourning, who both shared their story about having kidney diseases. Georgia Senator Raphael Warnock sent a video message of hope and support. A highlight of the summit was a 2-hour audience discussion focused on demystifying genetic testing and articulating calls to actions.

"This was one of the most unique conferences I've ever attended," said Sreedhar Mandayam, MD, MPH, MBA, FASN, nephrology professor and principal investigator at The University of Texas MD Anderson Cancer Center in Houston. "Patients—the people that actually deal with the problem—came up and spoke about their experiences … interspersed with physician scientists talking about how they discovered what they discovered and about new treatments coming up. It was very uplifting and very unique in that it was completely patient-focused, and the physician scientists played a supporting role."

Raising awareness about APOL1

When Black Americans share their journey with kidney diseases, it can have a significant impact. Gillespie pointed out that 13% of the U.S. population is Black or African American, yet Black patients make up about 35% of patients in dialysis units. This gap must be addressed and include efforts to ensure that Black Americans are appropriately represented in dialysis trials, she said. In 2020, Black or African Americans comprised only 8% of study participants in clinical trials for drugs approved that year, according to the U.S. Food and Drug Administration (2, 3). "It is likely that APOL1 kidney disease may be contributing to the progression of kidney disease and the need for dialysis in a fair amount of African Americans," Gillespie said. "If we can identify such patients with genetic testing and ultimately develop targeted therapies for APOL1 kidney disease, hopefully we can delay, and perhaps even decrease, the need for dialysis."

The good news is that there are ongoing clinical trials for patients with APOL1 kidney disease. However, both a lack of awareness of clinical studies (including registries, observational studies, qualitative research, and interventional trials) and an understandable historical mistrust of the medical community mean that many patients might be missing out on genetic testing and clinical study opportunities, Gillespie explained.

That is why including Black leaders in the NephCure summit was so important. An event last spring illustrates the importance of these partnerships. NephCure had reached out to the Enon Tabernacle Baptist Church, a 12,000-member church in Philadelphia, PA, predominantly attended by Black congregants. Coincidentally, it was just a few weeks before the church was hosting "Know Your Numbers," its 13th annual men's health event for the surrounding community. After talking with NephCure representatives, the organizers added a kidney disease screening to the event, said Reverend Leroy Miles, a community health consultant and associate pastor of care and counseling at Enon Tabernacle, who also attended the DC NephCure event.

The church transformed a woman's bathroom into a urinalysis testing site. Medical student volunteers from the Perelman School of Medicine, University of Pennsylvania, conducted urine protein dipstick tests and gathered participant information. A team of nephrologists were in the next room to talk with men with abnormal results. If the physicians recommended follow-up screening, the church referred the men for a blood test with Labcorp, one of the event's sponsors.

The outreach is personal for Miles: "I am a Black man who is, at this point, beyond middle age at age 57." The life expectancy of a Black man in Philadelphia is aged 69 years, he pointed out (4). Beyond his personal values, his church also believes strongly in this mission. "The church historically is about saving souls," he said. "But what about life while you're on Earth, and what about health and wellness? Health is wealth. Movement is medicine." After Miles attended the NephCure event, he planned to work with his church to add an opportunity for the surrounding Black community to get *APOL1* genetic testing.

Prioritizing genetic screening

One challenge in the medical community is that not many nephrologists are aware of how to screen for the *APOL1* mutation, Mandayam said. "Every patient [who] comes to my hospital with a diagnosis of any kind of cancer gets their genetics done," he said. Unfortunately, that is not yet the case in nephrology. "Nephrologists are aware that this disease exists, and there is a gene that people are looking at, but most don't seem to know enough about how to order the test, what to do, [and] how to incorporate it into their workflows."

The *APOL1* genetic screening test is not included in standard electronic medical record systems, which means physicians have to order the test separately. Mandayam orders the test for any patient of African descent with an unexplained kidney disease. He explains, "There has been a lot of hesitancy in the nephrology world doing things like this because historically there has been no treatment: Why use it and give you a name for your problem if I don't know how to treat it? But if we don't start somewhere, then we'll never develop treatments for the named problems."

It is also incumbent on nephrologists to encourage patient participation in clinical trials, said Mandayam, who is a principal investigator for the AMPLITUDE study (5). The trial is studying the effectiveness of the oral drug inaxaplin in patients with FSGS and the *APOL1* mutation. The study is currently in phase 3. In preclinical studies, inaxaplin selectively blocked APOL1 channel function and reduced proteinuria. In Mandayam's phase 2a study, by week 13, the mean from the baseline urinary protein-to-creatinine ratio decreased 48% for participants treated with inaxaplin.

Improving health equity

At a NephCure reception the night before the summit, songwriter and music producer Brian Kennedy shared his story while playing the piano. Kennedy had a kidney transplant in 2017, after being diagnosed in 2010 with FSGS (without the *APOL1* variant). "My brother Kevin gave me his kidney.… It was life-changing. I feel better now at 40 than I did in my 20s."

Kennedy and his wife, Angelique Cinelu, a songwriter and creative director who also attended the NephCure event, co-founded Hits to Healing in 2020 (6). The nonprofit organization uses music to promote health equity and foster communication between health care entities and patients from marginalized communities. "Music is universal," Cinelu said. "We're both in music, and we thought that we could really use our creative tools to help break down some of these communication barriers."

The couple, who are both Black, has each experienced medical situations in which health care professionals were not listening to them. The same year that Kennedy had his transplant, Cinelu gave birth to their first child. "I had a pretty traumatic birthing experience,…and I started to see that I was not the only person who looked like me who had these experiences in hospitals while giving birth." She and Kennedy started to talk more about their medical care experiences.

"The common denominator was what we look like," Cinelu added. "He and I come from very different backgrounds,…and we found that there was a similar treatment. And we also found, as we spoke about our experiences to a broader community, that people had the same experience. So we felt really passionate about trying to find a way to improve the communication between diverse communities and the medical world."

It is critical that the health care community works on building better trust among patients, particularly with those from marginalized groups, Kennedy said. Collaborations like the ones NephCure is fostering can help make that happen. The couple want to use their experiences and connections in the music and entertainment industries to

create accessible messaging for both sides. "What I find that is missing is not so much the connection to access the health, but the trust," Kennedy said. "We're trying to build a bridge of trust." ■

Acknowledgments on behalf of Dr. Gillespie: Dr. Gillespie was honored to serve on the Steering Committee of the NephCure conference, alongside Reverend Leroy Miles (Enon Tabernacle Baptist Church); Kevin Mott, AAMS, CRPC (Edward Jones and NephCure board member); and two esteemed co-chairs: Keisha Gibson, MD, MPH, FASN (University of North Carolina School of Medicine), and Opeyemi Olabisi, MD, PhD (Duke University). This unique conference would not have occurred without the vision and leadership of NephCure, including Joshua Tarnoff (chief executive officer), Lauren Eva (executive vice president), Maurice Madden (director of stakeholder engagement), and Sarah Prince (manager of industry relations).

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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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