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Kidney News

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First Living Patient Received Pig Kidney Transplant

By Bridget M. Kuehn

When 62-year-old Richard "Rick" Slayman of Weymouth, MA, left Massachusetts General Hospital in Boston on April 3, 2023, to recover at home after receiving the first pig kidney transplant into a living human patient, it marked a major milestone in the field of xenotransplantation. "It's the starting line in a revolution in the way we potentially find organs for our patients," said Leonardo Riella, MD, PhD, FASN, medical director of kidney transplantation at Massachusetts General Hospital, in an interview with *Kidney News*.

Riella credited 30 years of xenotransplant research for enabling the transplant. The US Food and Drug Administration (FDA) allowed the transplant under its expanded access protocol, also called a compassionate use exemption. These exemptions allow patients who are seriously ill and lacking other therapeutic options to access experimental therapies. Riella and his colleagues will now carefully follow Slayman and submit their data to FDA to lay the groundwork for human clinical trials. If larger clinical trials are successful, genetically engineered pig kidneys could provide a valuable alternative to human kidney allografts to the nearly 100,000 people currently on the waitlist for a deceased donor organ (1).

"I applaud the courage of the patient taking part in this latest milestone in xenotransplantation, which is marching closer to becoming an alternative source of organs for the many thousands suffering from kidney failure," said Robert Montgomery, MD, DPhil, the H. Leon Pachter, MD, Professor and chair of the Department of Surgery at New York University (NYU) Langone Health and director of the NYU Langone Transplant Institute, in an emailed statement. "He is truly a hero and will be an inspiration to many. The Massachusetts General Hospital and eGenesis teams should be acknowledged for their enormous contribution to this important work to save lives."

Rapid advancements

Slayman's transplant was the latest in a string of recent developments in the field of xenotransplantation. Building on decades of research studying the transplantation of genetically modified pig kidneys into nonhuman primates, scientists from eGenesis (a company that maintains it is committed to ending the global transplant shortage and transforming the treatment of organ failure), Massachusetts General, and several other US academic centers recently published results

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New KDIGO CKD Guideline Focuses on Patient-Centered, Life-Cyle-Based Approach

By Bridget M. Kuehn

Nephrologists often encounter people with chronic kidney disease (CKD) who may present with different circumstances, such as an octogenarian with a high pill burden or a young adult making the transition from pediatric to adult care.

"One size does not fit all," said Adeera Levin, MD, professor of medicine and head of the Division of Nephrology at The University of British Columbia, Vancouver, Canada. "You have to take the individual into consideration."

With that in mind, a new CKD guideline from the Kidney Disease: Improving Global Outcomes (KDIGO) consortium aims to help nephrologists leverage the latest evidence, diagnostic tools, and medications to help them better personalize patient care (1). Levin, who cochaired the work group that created the guideline, noted that although some of the recommendations apply to all people with CKD, others acknowledge that the best patient care may sometimes depend on patient characteristics, such as life stage, gender, or the underlying cause of their condition.

New medications, developments in genetics and diagnostics, and research on subsets of patients have facilitated these more patient-centric recommendations. For example, the guideline recommends sodium-glucose cotransporter-2 inhibitors (SGLT2is) even for people with CKD who do not have diabetes to prevent CKD progression. It concurs with

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Inside

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INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

ardelyx®

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

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

Most Common Adverse Reaction

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

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

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

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

7.2 Sodium Polystyrene Sulfonate

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Risk Summary

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

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

Juvenile Animal Toxicity Data

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

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

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

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

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

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

Administration and Handling Instructions

Instruct Patients:

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

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First Living Patient Received Pig Kidney Transplant

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showing that genetically altered pig kidneys could last years in nonhuman primates despite some of the challenges of working in this animal model (2).

"We take for granted small things that we do to manage our patients, but in nonhuman primates, the availability of tools, technology, and treatment is much more limited," Riella explained. "So just seeing these kidneys, working in nonhuman primates for 2 to 3 years, has given us the confidence that it was scientifically justifiable to move the needle and move to patients."

The eGenesis team used organs from a miniature breed of pigs to avoid having organs that might outgrow their human or nonhuman primate recipients. The investigators used CRISPR [clustered regularly interspaced short palindromic repeats]-Cas9 [CRISPR-associated protein 9] gene editing to make 69 changes in the pig's genome. Three genes encoding pig proteins that can trigger an immune reaction in humans were removed to prevent rejection, Riella explained. Scientists added seven human genes to the pig's DNA to make the organs more compatible with the human immune system or to reduce the risk of clotting. The other 59 alterations inactivated porcine endogenous viruses hiding in the pig genome. Concern about pig viruses spreading to humans has been one barrier to xenotransplants in humans.

In parallel to successful studies in nonhuman primates, transplant teams across the country have developed a human preclinical model for pig kidney xenotransplants in human recipients, declared dead based on neurologic function, who were maintained on mechanical support for up to 2 months (3–6).

The genetically modified pig organs used in these decedent studies had fewer genetic modifications. Montgomery and his colleagues used a single gene edit to remove the gene encoding the alpha-gal protein that can trigger hyperacute rejection and standard immunosuppression. Locke and her colleagues (4) used pig kidneys with 10 genetic modifications—three to knock out three pig antigens that triggered hyper-rejection in nonhuman primate studies, a fourth modification removed a gene encoding a pig growth hormone to prevent the organ from outgrowing its human recipient, and the six human genes were inserted into the pig's genome to modulate the human immune response to the kidney. Locke also deployed immunosuppressive drugs routinely used for human kidney allograft recipients.

"It's thrilling to see the progress unfolding," Montgomery said in the statement. "While each transplant center studying this takes different approaches with the number of gene edits and medications, another big step will be when the FDA authorizes clinical trials so we may better understand what will work best for patients on our waiting lists."

Paient selection

While both decedent and nonhuman primate models have proved valuable, Riella noted that both have limitations. He explained that studies in human recipients declared dead based on neurologic function can only be conducted for a short time, limiting researchers' ability to assess longer-term outcomes like rejection or the risk of the pig organ transmitting infections to human recipients. The only option to determine those outcomes would be studies in human patients. A team at the University of Maryland School of Medicine transplanted two pig heart allografts into living human recipients under compassionate use exemptions (7). The first patient lived for 2 months posttransplant and the second for 6 weeks (8).

About 2 years ago, Riella and his colleagues began searching for a potential human recipient who was an appropriate candidate for a pig allograft. They selected Slayman, who has type 2 diabetes and hypertension and previously had a successful human kidney allograft that lasted for 5 years, but he had to return to dialysis after the allograft failed. He was struggling on dialysis and required two procedures each month to keep his vascular access open and was running out of options for vascular access locations, Riella said. Slayman faced a long wait time ahead on the deceased donor transplant list.

"He was very uncomfortable, and it was affecting his quality of life," Riella noted. After several discussions about the known and unknown risks of a pig kidney xenotransplant with his clinicians, Slayman opted to take the risk to become the first living human to receive a pig kidney transplant.

Riella and his colleagues used a combination of thymoglobulin, rituximab, steroids, and an experimental complement inhibitor ravulizumab for induction immunotherapy. For maintenance therapy, Slayman was started on tacrolimus, mycophenolate, and prednisone, which are commonly used after transplant of a human allograft. He also received an infusion of the experimental immunosuppressant tegoprubart, an anti-CD154 antibody costimulation blockade therapy that is currently in human clinical trials, Riella said. He noted that the drug was part of the "secret sauce" that improved survival in nonhuman primate pig kidney xenotransplantation studies.

So far, the gamble has paid off for Slayman. Riella noted that Slayman reported enjoying small things that many people may take for granted, like being pain-free and being able to shower after having his vascular access removed. "For patients like him, a transplant can be life-changing," Riella remarked. "His energy is very good."

Riella shared that he and his colleagues are carefully monitoring Slayman's health. He will have blood draws three times each week and clinic visits twice each week. Eventually, they hope to space out visits and follow the same monitoring regimens used for human allograft recipients.

In his statement, Slayman, who has been a patient at Massachusetts General for 11 years, said he had the utmost trust in his clinicians, felt well-informed about the potential risks, and wanted to help others. "I saw it not only as a way to help me but also as a way to provide hope for the thousands of people who need a transplant to survive," he reflected.

If the transplant is successful and leads to a successful clinical trial, it could change the paradigm for kidney care away from dialysis toward transplant for most patients, Riella said. He noted that human kidney allografts would remain the gold standard, but individuals who do not have the luxury of waiting for a deceased donor organ would have an alternative. Some patients, he noted, may still require dialysis because they may not be good candidates for transplant.

Already, Riella and his colleagues have received an overwhelming response from patients with kidney failure. "The number of messages that we've received after doing the xenotransplant from patients sharing their hopes and also their struggles and how they

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were seeing a light at the end of the tunnel was even more impactful than we could ever imagine," he said.

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New KDIGO CKD Guideline

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recommendations from a previous KDIGO guideline recommending SGLT2is for people with CKD and diabetes.

"Everyone is very excited; we now have drugs that we can recommend to modify kidney disease progression that also have other benefits," Levin said. "This is the first time we've had strong evidence-based recommendations for the treatment of chronic kidney disease at all stages."

The breadth of new recommendations in the guideline is the result of major progress in the field, according to a statement from the cochairs of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), Sankar Navaneethan, MD, MS, MPH, FASN, Garabed Eknoyan, MD, Endowed Professor in Nephrology at Baylor College of Medicine in Houston, TX, and Jeffrey William, MD, assistant professor of medicine in nephrology at Harvard Medical School and internal medicine–nephrology physician at the Beth Israel Deaconess Medical Center in Boston, MA: "This is a testament to the broader effort by the nephrology scientific community and the funding agencies that have focused on improving early diagnosis, development of risk prediction tools, and generation of high-quality clinical trial evidence for various therapeutic options for CKD, a common, progressive, and expensive clinical condition."

Diagnostic tools

Levin noted that an accurate evaluation of kidney function using all of the diagnostic tools available is the first step to providing good CKD care. The guideline recommends estimating glomerular filtration rates (GFRs) using creatinine and, when available, adding cystatin C. The evidence of the advantages of this approach has been accumulating over the past 10 years, but in the last 2 to 3 years, there has been a groundswell of support for making the change.

"We all know that [the] eGFR [estimated GFR] is still not perfect, but in some instances, we need the most accurate approach that we can get," said workgroup member Rasheeda Hall, MD, MS, MBA, FASN, a nephrologist and associate professor of medicine at Duke University School of Medicine and staff physician at the Durham Veterans Affairs Health Care System in Durham, NC. "We felt like [the recommendation] was the best way to move everyone forward."

The guideline also recommends using race-free equations to estimate GFR. Many countries already use race-free equations, but race-adjusted kidney function estimation has been common in the United States until recently. Based on evidence showing that race-corrected eGFRs disadvantaged Black individuals and delayed kidney care, the National Kidney Foundation-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases in 2021 recommended dropping race-based formulas and using creatinine or, ideally, creatinine plus cystatin C for kidney function (2). The task force recommendation has led to rapid uptake of the change at many hospitals and prompted many laboratories to add in-house cystatin C. Hall noted that the guideline recommendation may help support policy changes needed to get more hospitals and laboratories on board.

The guideline also emphasizes the importance of identifying the cause of CKD in an individual based on their clinical evaluation, medical and family history, social and environmental factors, medications, and genetic or pathologic testing. "More and more we have targeted therapies for specific conditions, so it behooves us to know what the cause of kidney disease is [in an individual person] so that we can target the right therapy and even use the right prediction equation," Levin said.

Reinforcing the guideline's benefits, another member of the workgroup, Lesley Inker, MD, director of the Kidney and Blood Pressure Center and the Kidney Function and Evaluation Center at Tufts Medical Center, Burlington, MA, explained that some kidney diseases, such as polycystic kidney disease or immunoglobulin A nephropathy, have specific therapies, and for other kidney diseases, there may be ongoing clinical trials in which patients may want to participate. Levin predicted that even more targeted therapies are on the horizon as nephrologists identify and learn more about the genetic causes of CKD.

LaVarne A. Burton, president and chief executive officer of the American Kidney Fund, in a statement in March applauded the new guideline's focus on both patient-centered care and its emphasis on finding undiagnosed causes for kidney diseases (3). She noted that 5% to 15% of people with kidney diseases do not know the cause of their condition. The American Kidney Fund launched its Unknown Causes of Kidney Disease Project in 2020 to research the impact of undiagnosed or misdiagnosed kidney diseases on patient care and outcomes.

Life-cycle approach

The CKD guideline also emphasizes a life-cycle-based approach that balances goal-directed therapy with the patient's needs, age, gender, use of gender-affirming therapies, and other circumstances. "People at different phases of life [experience] different kinds of kidney disease. Understanding the disease-specific and person-specific issues will help nephrologists make the best treatment plan for every individual," Inker said.

Inker noted that treatment plans and treatment goals also must evolve over time as people age or their condition changes. Given the large number of older adults with CKD, Hall said, it was important for the guideline to emphasize the complexity of care for this subpopulation. She noted that in addition to frailty and loss of muscle mass with advanced age, these individuals are likely to be on multiple medications and have multiple prescribers. They may also have cognitive impairments that make medication changes and other instructions difficult to remember or follow.

The guideline also highlights the need for frequent medication reviews, dose adjustments, and collaborative care with pharmacists and other specialists to manage patients taking multiple medications. Levin stated that it is essential to check for known or unexpected drug interactions regularly and to make sure the medications that patients are taking are evidence informed. "The totality of patients' medications needs to be looked at, again, in the context of the individual," she said.

The guideline also encourages nephrologists to deploy a full spectrum of interventions to preserve kidney function, including nutrition and exercise, and provides information on managing patients' symptoms. Additionally, it outlines steps for the management of co-occurring cardiovascular disease with medications such as statins in individuals with elevated cholesterol or SGLT2is in people with CKD and heart failure.

"Cardiac disease is the most common complication in chronic kidney disease," Inker said. She noted a growing convergence of treatments for CKD, cardiovascular disease, and metabolic diseases like diabetes and obesity, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs), which are also discussed in the guideline. Inker anticipates that convergence will grow.

Navaneethan and William noted that the medication recommendations reflect the results of recent large clinical trials. "Despite slow uptake, nephrologists are now getting more comfortable in using [SGLT2is], and we believe they should continue to focus on adapting their practice to incorporate goal-directed medical therapy, which includes the use of [renin-angiotensin-aldosterone system inhibitors] as well," they wrote. "As evidence for other drugs such as GLP-1RA and ns-MRA [nonsteroidal mineralocorticoid receptor antagonist] emerges, sequential or combination therapy, especially for those with diabetic kidney disease, is also being recommended."

They also highlight the guideline's emphasis on personalizing care, which they note is an increasing focus across medical specialties. "With several new therapeutic options becoming available (such as GLP-1RA and ns-MRA) and CKD being more common in the geriatric population, the KDIGO guideline provides a framework for adoption of these agents by considering various elements such as age, comorbid conditions, and access to medication."

Navaneethan and William also applauded the guideline's emphasis on multidisciplinary, team-based care to achieve care personalization, reduce barriers to adherence, and match care to patients' values.

"Nephrology is a team sport, and it's very hard to do all of these things and manage the complexity of the patient journey as a solo practitioner," Levin said. She hopes the KDIGO guideline will help more institutions and countries embrace team-based care models.

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Predicting Cisplatin-Induced Kidney Injury: A Milestone in Onconephrology

By Prakash Gudsoorkar

One of the central challenges in oncology is striking the right balance between effectively eradicating cancer cells and safeguarding patient well-being. Cisplatin, a linchpin in chemotherapy regimens, is well-documented for its efficacy but equally notorious for its nephrotoxic potential. This toxicity can drastically affect patient outcomes and quality of life. In a groundbreaking study published in *The BMJ*, Gupta and colleagues (1) developed and externally validated a risk-prediction model for severe cisplatin-associated acute kidney injury (CP-AKI). This research represents a pivotal advancement in personalized cancer care.

To develop their risk-prediction model, Gupta and colleagues (1) conducted an extensive multicenter cohort study across six major academic cancer centers in the United States, meticulously examining data from 24,717 individuals treated with intravenous cisplatin therapy from 2006 to 2022. The primary outcome was moderate-to-severe AKI, defined by a twofold or greater increase in serum creatinine or the initiation of kidney replacement therapy within 14 days after administration, aligning with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for stage 2 or 3 AKI, thus focusing on the most clinically significant form of AKI. As secondary outcomes, the authors also investigated broader and stricter definitions of CP-AKI, along with the composite outcome of major adverse kidney events within 90 days, which further deepens our comprehension of the renal implications of post-cisplatin administration.

The authors implemented rigorous inclusion and exclusion criteria and collected detailed data on demographics, comorbidities, baseline laboratory values, and concomitant nephrotoxic chemotherapies. The study identified independent predictors of CP-AKI through multivariable logistic regression within a derivation cohort and subsequent external validation. The analysis of continuous variables using restricted cubic splines, backward elimination for variable selection with a p value threshold of 0.1, and multiple imputation for missing data culminated in a primary model that achieved a c-statistic of 0.75, greatly outperforming previous risk models for CP-AKI, which had c-statistics ranging from 0.60 to 0.68. The increased accuracy in predicting CP-AKI could facilitate closer monitoring and early intervention strategies for those at the highest risk.

Consider two hypothetical patients with cancer, each of whom is about to receive cisplatin therapy, as shown in the Table.

Table. Hypothetical patients with cancer

	Patient 1	Patient 2
Age (years)	25	60
Cancer type	Testicular	Lung
Hypertension	No	Yes
Diabetes mellitus	No	Yes
Cisplatin dose (mg)	100	150
Serum creatinine (mg/dL)[a]	0.8	1.4
Serum magnesium (mg/dL)[a]	2.0	1.0
Serum albumin (g/dL)[a]	4.0	2.5
Hemoglobin (g/dL)[a]	14.0	11.2
White blood cell count (K/mm^3)[a]	10.0	14.0
Platelet count (K/mm^3)[a]	250	125

[a]Indicates laboratories drawn before cisplatin administration.

By entering their clinical characteristics into the online risk calculator (https://kidneycalc.org/cp-aki-calculator/), the greatly different risks of CP-AKI between these two patients can be appreciated, as shown in the Figure.

The authors also found a strong association between CP-AKI severity and 90-day mortality, highlighting the clinical importance of these findings.

Despite its strengths, the study had some limitations, including the potential for limited generalizability, as it used data only from major US-based academic centers. Nevertheless, the study's merits, such as its extensive sample size (considerably larger than all prior studies combined), stringent definition of CP-AKI (prior studies used much more liberal definitions for CP-AKI), and the practical applicability of its online risk-prediction model, are noteworthy. The model's reliance on readily accessible clinical variables for risk assessment broadens its utility across various clinical settings, empowering health care practitioners to proactively identify patients with high risk with tailored nephroprotective strategies.

In summary, the research by Gupta and colleagues (1) signifies a substantial leap toward personalized medicine in oncology, presenting an innovative and practical tool for predicting severe CP-AKI in cisplatin recipients. This model hopes to enhance patient outcomes, reduce health care costs, and elevate the overall standard of cancer care. Looking forward, the prospective validation of this predictive model in a wider range of clinical environments and its integration into clinical workflows are crucial steps. Such measures will harness the model's full potential to alleviate the nephrotoxic effects of cisplatin therapy, propelling the onconephrology field forward. ■

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The author reports no conflicts of interest.

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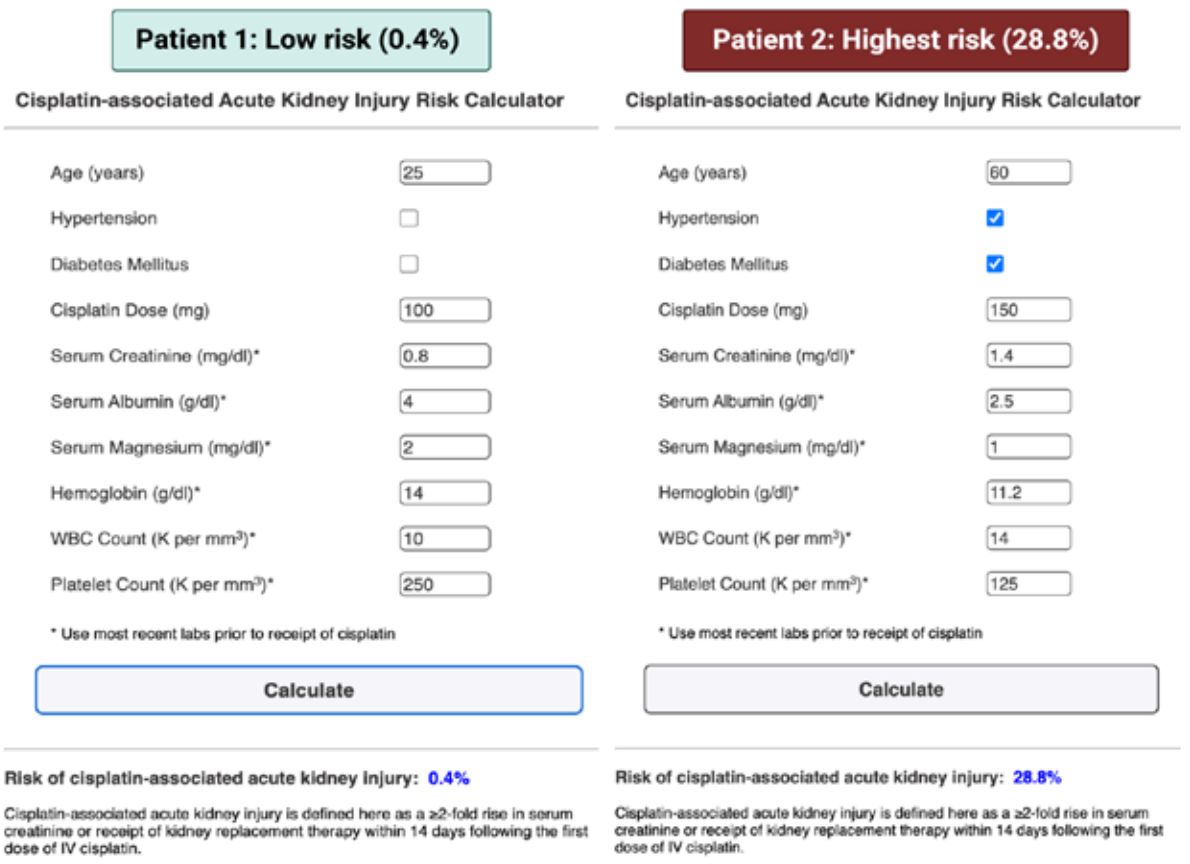
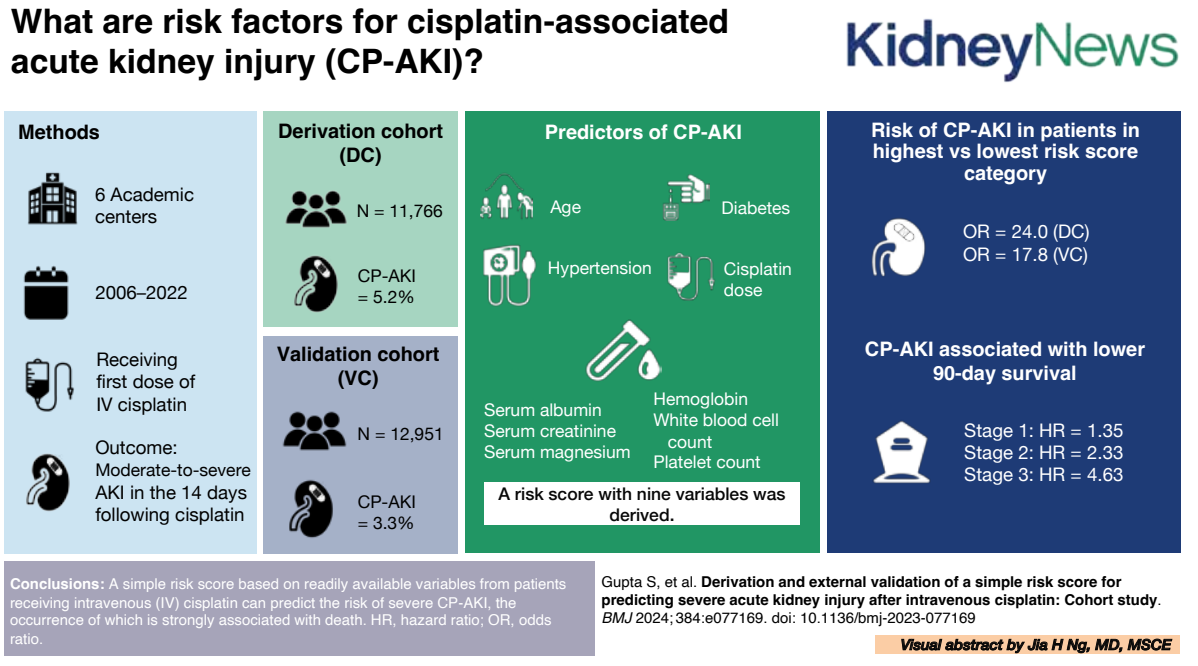
Figure. Results of the CP-AKI risk calculator among hypothetical patients



IV, intravenous; WBC, white blood cell.



ASN President's Update

Bootstraps, Basic Needs, and Kidney Health

By Deidra C. Crews

Dr. Martin Luther King, Jr., said during an interview in 1967, less than 1 year prior to his assassination, that "It's a cruel jest to say to a bootless man that he ought to lift himself by his own bootstraps" (1). I often think of this statement when I ask a patient to be more engaged in their kidney care. Many people at risk for or living with kidney diseases have unmet basic needs like housing, food, transportation, and utilities (such as electricity). Surely these needs would rank higher on their list of concerns than the medications I wish they would take more regularly (if they *can* even access them) or the dietary changes I think they should make. Yet, for most of us in nephrology, our training did not include, nor do our clinical practice structures facilitate, full consideration of these nonmedical basic needs.

Pervasive burden

Unmet basic needs are quite pervasive among the more than 37 million Americans living with kidney diseases. One study found that 30% of a nondialysis-dependent population of people with kidney diseases experienced at least one unmet basic need during the COVID-19 pandemic (2). The burden of unmet basic needs is particularly stark for people with kidney failure treated with dialysis. A pilot study of children receiving dialysis treatment in Indianapolis, IN, and Seattle, WA, identified that 62% lived in food-insecure households, and the majority of them (72%) had experienced worsening of their food insecurity during the pandemic (3). Among a group of adults treated with dialysis in Baltimore, MD, and Washington, DC, 36% reported food insecurity, and 18% reported housing instability (4). Most US studies of this topic have been conducted in urban settings, but the expected burden of unmet basic needs would be even greater for people living with kidney diseases in rural and remote communities throughout the world.

We also know that having unmet basic needs increases the likelihood of experiencing several adverse outcomes related to kidney health (5–7) (Table). Yet, our policies and practices are based in many ways on the false assumption that most patients can meet these basic needs. Take housing, for example. The 2019 executive order on Advancing American Kidney Health included, among three priorities, a focus on increasing patient choice in kidney failure treatment, boldly setting a target that by 2025, 80% of the Medicare beneficiaries who initiate kidney failure treatment do so with a home modality or kidney transplant (8). At present, however, we fail to systematically ask and document whether patients have a stable place to live or the ability to make modifications to their home that would support their being able to dialyze there.

I am reminded of one of my patients who, despite having intermittent transportation needs, has excellent adherence to in-center hemodialysis treatments. She was interested in home hemodialysis because it would allow her to work more regularly and afford to buy the car that she needs, as the engine in her old car died. Unfortunately, her apartment landlord would not approve of the plumbing and wiring changes that would make home hemodialysis feasible for her—and so she has remained a patient of in-center hemodialysis who relies on public transportation.

Now, far upstream from patients being treated for kidney failure are those millions of people worldwide who could benefit from the primary prevention of kidney diseases. Multiple campaigns invite a focus on addressing unmet basic needs in the general population toward preventing morbidity and mortality with messages like "Housing Is Healthcare" and "Food Is Medicine." It sometimes seems—at least to me—a bit outrageous that we need campaigns to call attention to the importance of meeting basic needs to achieve optimal health. Former ASN Secretary-Treasurer Donald E. Wesson MD, MBA, FASN, somewhat rejects the Food Is Medicine mantra, asserting, "Food Is Food." It really should be that simple.

Of course, some would argue that this is not "our lane." According to this perspective, nephrologists and other clinicians should focus on medical treatments and not devote time to understanding and addressing the unmet basic needs of their patients, especially given our expanding medical armamentarium in kidney care. However, these needs may actually be bigger drivers of overall health and kidney health than is medical care itself. Analyses of various health indices in Organisation for Economic Co-operation and Development (OECD) countries and among US states have been more closely, and positively, related to rates of social service spending (on provisions such as housing and food) than with health care spending (9, 10).

Addressing unmet needs

The significance of the problem of unmet basic needs and their impact on kidney health cannot be overstated. Fortunately, there are actions that we can each take to address them. First, clinicians can ask our patients about these needs. Several very brief tools are available, such as the following question about financial resource strain, recommended by the National Academy of Medicine (formerly Institute of Medicine): "How hard is it for you to pay for the very basics like food, housing, medical care, and heat? Very hard? Somewhat hard? or Not hard at all?" (11). These tools have been incorporated into many electronic health records to support documentation, follow-up, and linkage to available services.

Second, once we identify a patient as having unmet basic needs, we can leverage community resources to support patients registering for public and privately funded services that can address their needs. Several health systems have employed community health workers, drawn primarily from the communities they serve, often in partnership with social workers, to help patients navigate community resources. This approach is gaining traction in kidney care (12) and has great promise if barriers to patient enrollment and funding of community health workers can be addressed.

Third, investigators can pursue research into how these unmet basic needs lead to biologic consequences. For example, how does the psychologic stress of financial strain surrounding housing, food, and other needs impact markers of kidney health? What are the underlying mechanisms? And a great need exists for intervention studies examining best practices for identifying, addressing, and monitoring the outcomes of efforts to address unmet basic needs impacting kidney health. Studies on whether approaches should vary depending on the type of kidney disease with which a person lives are also warranted. For example, does an individual with a rare kidney disease, who may need to see multiple specialists, undergo a kidney biopsy, and receive other diagnostic procedures require more intensive support if they have unmet basic needs compared with someone with a more common form of kidney disease requiring a less arduous diagnostic and treatment journey?

Fourth, we can all advocate for "little p" (health system/clinic setting) and "big P" (health and public) policies that could support the basic needs of people with or at risk for kidney diseases. By making use of the "natural experiment" of numerous public policies established during the COVID-19 pandemic to mitigate its economic impact, we can examine whether they had impacts on kidney health. For instance, in March 2020, the US Congress passed the Coronavirus Aid, Relief, and Economic Security Act, which included a moratorium on the evictions of tenants in rental properties that receive federal funding or have federal government-backed mortgages. Many states initially extended this moratorium, but those extensions have since ended. An examination of the impacts on kidney health during this moratorium could reveal data that compel present-day policy changes.

I agree with Dr. King's statement from nearly 60 years ago and believe it would be cruel to ask people who are "bootless" to address their own unmet basic needs that impact their kidney health. Supporting them is *our* responsibility, *our* duty,

Table. Adverse kidney health outcomes associated with unmet basic needs

Unmet basic need	Population(s) studied	Example of adverse outcomes
Housing and/or food insecurity	• Adults	↓ • Kidney disease risk factor control
Housing insecurity	• Adults • Adults with CKD • Older adults on dialysis	↑ • Risk of developing albuminuria • Delays in seeking medical care • Mortality
Food insecurity	• Adults with CKD • Children on dialysis	↑ • Progression to kidney failure • Acute care utilization
Transportation needs	• Adults on dialysis • Transplant candidates	↓ • Hemodialysis treatment adherence • Waitlisting for kidney transplant

and the right thing to do, especially if we are serious about achieving a world without kidney diseases. ■

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

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

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INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

TAVNEOS (avacopan) is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

CONTRAINDICATIONS

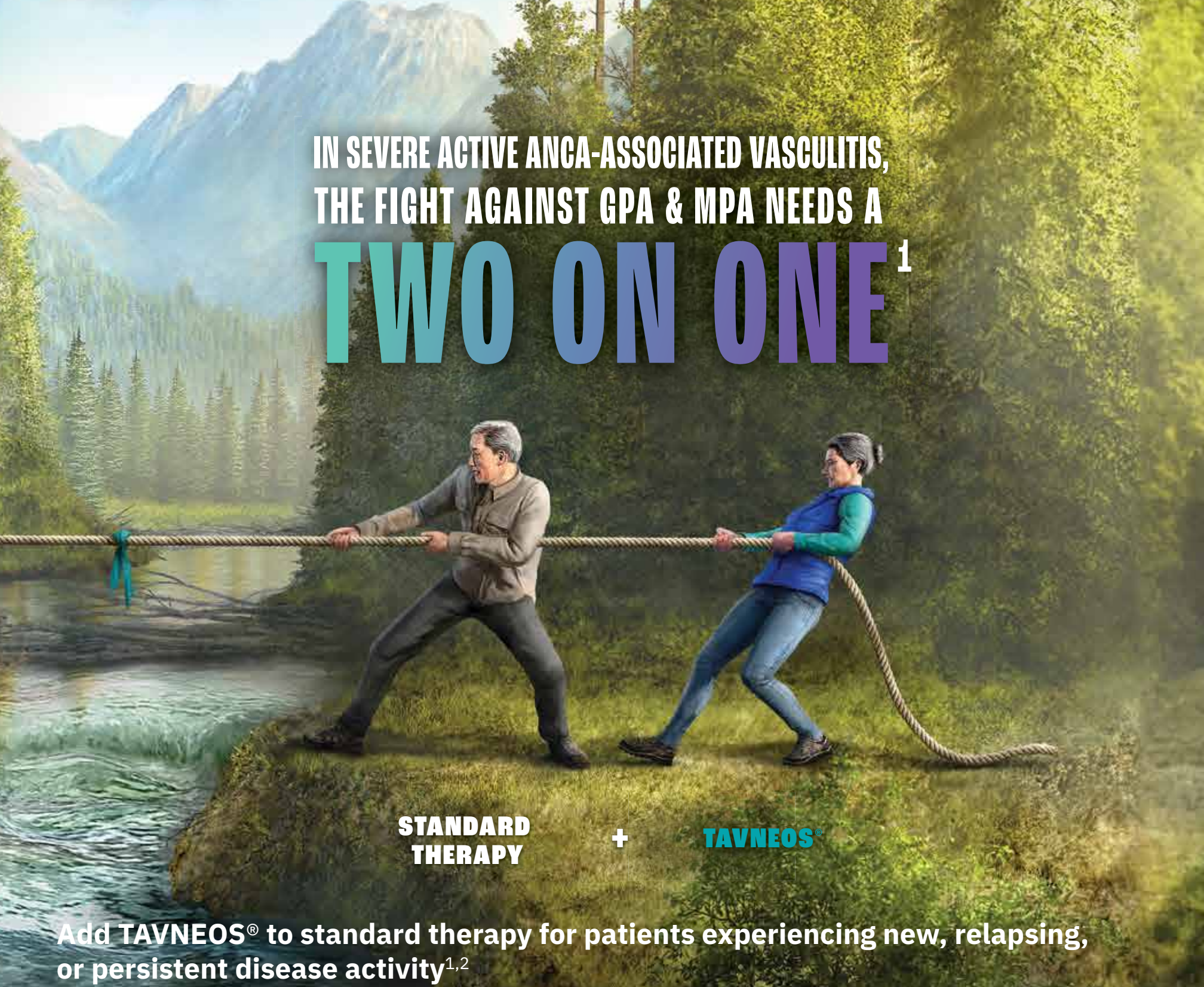
Serious hypersensitivity to avacopan or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Serious cases of hepatic injury have been observed in patients taking TAVNEOS, including life-threatening events. Obtain liver test panel before initiating TAVNEOS, every 4 weeks after start of therapy for 6 months and as clinically indicated thereafter. Monitor patients closely for hepatic adverse reactions, and consider pausing or discontinuing treatment as clinically indicated (refer to section 5.1 of the Prescribing Information). TAVNEOS is not recommended for patients with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risks and benefits before administering this drug to a patient with liver disease.

Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial, including 1 serious event requiring hospitalization. Discontinue immediately if angioedema occurs and manage accordingly. TAVNEOS must not be readministered unless another cause has been established.

Hepatitis B Virus (HBV) Reactivation: Hepatitis B reactivation, including life-threatening hepatitis B, was observed in the clinical program. Screen patients for HBV. For patients with evidence of prior infection, consult with physicians with expertise in HBV and monitor during TAVNEOS therapy and for 6 months following. If patients develop HBV reactivation, immediately discontinue TAVNEOS and concomitant therapies associated with HBV reactivation, and consult with experts before resuming.



Add TAVNEOS® to standard therapy for patients experiencing new, relapsing, or persistent disease activity[1,2]

Serious Infections: Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections. Avoid use of TAVNEOS in patients with active, serious infection, including localized infections. Consider the risks and benefits before initiating TAVNEOS in patients with chronic infection, at increased risk of infection, or who have been to places where certain infections are common.

ADVERSE REACTIONS

The most common adverse reactions (≥5% of patients and higher in the TAVNEOS group vs. prednisone group) were nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia.

DRUG INTERACTIONS

Avoid coadministration of TAVNEOS with strong and moderate CYP3A4 enzyme inducers. Reduce TAVNEOS dose when coadministered with strong CYP3A4 enzyme inhibitors to 30 mg once daily. Monitor for adverse reactions and consider dose reduction of certain sensitive CYP3A4 substrates.

TAVNEOS is available as a 10 mg capsule.

To report a suspected adverse event, call 1-833-828-6367. You may report to the FDA directly by visiting **www.fda.gov/medwatch** or calling 1-800-332-1088.

References: 1. TAVNEOS [package insert]. Cincinnati, OH: Amgen Inc. **2.** Chung SA, Langford CA, Maz M, et al. *Arthritis Rheumatol*. 2021;73(8):1366-1383.

Please see Brief Summary of Prescribing Information for TAVNEOS® on the following pages.

12/23 USA-569-80504

AMGEN®

BRIEF SUMMARY OF PRESCRIBING INFORMATION
TAVNEOS® (avacopan) capsules, for oral use
Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

CONTRAINDICATIONS

TAVNEOS is contraindicated in patients with serious hypersensitivity reactions to avacopan or to any of the excipients *[see Warnings and Precautions (5.2)]*.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. During controlled trials, the TAVNEOS treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events *[see Adverse Reactions (6.1)]*.

Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated.

If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out *[see Adverse Reactions (6.1)]*.

TAVNEOS is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risk and benefit before administering TAVNEOS to a patient with liver disease. Monitor patients closely for hepatic adverse reactions *[see Use in Specific Populations (8.7)]*.

Hypersensitivity Reactions

TAVNEOS may cause angioedema *[see Adverse Reactions (6.1)]*. In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg, in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TAVNEOS. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TAVNEOS treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis, or HBV reactivation during and for six months following TAVNEOS therapy.

In patients who develop reactivation of HBV while on TAVNEOS, immediately discontinue TAVNEOS and any concomitant therapy associated with HBV reactivation, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TAVNEOS treatment in patients who develop HBV reactivation. Resumption of TAVNEOS treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Serious Infections

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections.

Avoid use of TAVNEOS in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating TAVNEOS in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with TAVNEOS should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and TAVNEOS should be interrupted if the patient is not responding to antimicrobial therapy. TAVNEOS may be resumed once the infection is controlled.

ADVERSE REACTIONS

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

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Hepatitis B Virus (HBV) Reactivation *[see Warnings and Precautions (5.3)]*
- Serious Infections *[see Warnings and Precautions (5.4)]*

Clinical Trials Experience

Because the 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 identification of potential adverse drug reactions was based on safety data from the phase 3 clinical trial in which 330 patients with ANCA-associated vasculitis were randomized 1:1 to either TAVNEOS or prednisone *[see Clinical Studies (14)]*. The mean age of patients was 60.9 years (range of 13 to 88 years), with a predominance of men (56.4%) and Caucasians (84.2%). The cumulative exposure to TAVNEOS was 138.7 patient-years. Additionally, two phase 2 trials were conducted in ANCA-associated vasculitis. The cumulative clinical trial exposure from the phase 2 and 3 trials equals 212.3 patient-years.

The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with prednisone were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% TAVNEOS vs. 0.6% prednisone), acute kidney injury (1.8% TAVNEOS vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reaction that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).

The most common adverse reactions that occurred in ≥5% of patients and higher in the TAVNEOS group as compared with the prednisone group are listed in Table 1.

Table 1: Adverse Reactions Reported in ≥5% of Patients and Higher in TAVNEOS Group vs. Prednisone Group in Phase 3 Trial

Adverse Reaction	Prednisone (N=164) n (%)	TAVNEOS (N=166) n (%)
Nausea	34 (20.7)	39 (23.5)
Headache	23 (14.0)	34 (20.5)
Hypertension	29 (17.7)	30 (18.1)
Diarrhea	24 (14.6)	25 (15.1)
Vomiting	21 (12.8)	25 (15.1)
Rash	13 (7.9)	19 (11.4)
Fatigue	15 (9.1)	17 (10.2)
Upper abdominal pain	10 (6.1)	11 (6.6)
Dizziness	10 (6.1)	11 (6.6)
Blood creatinine increased	8 (4.9)	10 (6.0)
Paresthesia	7 (4.3)	9 (5.4)

N=number of patients randomized to treatment group in the Safety Population; n=number of patients in specified category.

Hepatotoxicity and Elevated Liver Function Tests

In the phase 3 trial, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the TAVNEOS group had hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. Study medication was paused or discontinued permanently due to hepatic-related adverse reactions in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. Serious hepatic-related adverse reactions were reported in 6 patients (3.7%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. A serious hepatic-related adverse reaction was reported in 1 patient in the TAVNEOS group in the phase 2 studies.

Angioedema

In the phase 3 trial, 2 patients (1.2%) in the TAVNEOS group had angioedema; one event was a serious adverse reaction requiring hospitalization.

Elevated Creatine Phosphokinase

In the phase 3 trial, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the TAVNEOS group had increased creatine phosphokinase. One TAVNEOS-treated patient discontinued treatment due to increased creatine phosphokinase.

DRUG INTERACTIONS

CYP3A4 Inducers

Avacopan exposure is decreased when co-administered with strong CYP3A4 enzyme inducers such as rifampin *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong and moderate CYP3A4 inducers with TAVNEOS.

CYP3A4 Inhibitors

Avacopan exposure is increased when co-administered with strong CYP3A4 enzyme inhibitors such as itraconazole *[see Clinical Pharmacology (12.3)]*. Administer TAVNEOS 30 mg once daily when coadministered with strong CYP3A4 inhibitors.

CYP3A4 Substrates

Avacopan is a CYP3A4 inhibitor. Closely monitor patients for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with a narrow therapeutic window when coadministered with TAVNEOS *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TAVNEOS in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of avacopan to pregnant hamsters and rabbits during the period of organogenesis produced no evidence of fetal harm with exposures up to approximately 5 and 0.6 times, respectively, the exposure at the maximum recommended human dose (MRHD) of 30 mg twice daily (on an area under the curve [AUC] basis). Avacopan caused an increase in the number of abortions in rabbits at an exposure 0.6 times the MRHD *(see Animal Data)*.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study with pregnant hamsters dosed by the oral route during the period of organogenesis from gestation days 6 to 12, avacopan produced an increase in the incidence of a skeletal variation, described as supernumerary ribs, at an exposure that was 5 times the MRHD (on an AUC basis with a maternal oral dose of 1000 mg/kg/day). No structural abnormalities were noted with exposures up to 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

In an embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 6 to 18, avacopan caused an increase in the number of abortions at an exposure 0.6 times the MRHD (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however, no evidence of fetal harm was observed with such exposures. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.6 times and higher than the MRHD (on an AUC basis with maternal oral doses of 30 mg/kg/day and higher).

In a prenatal and postnatal development study with pregnant hamsters dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

Lactation

Risk Summary

There are no available data on the effects of avacopan on the breastfed child or on milk production. It is unknown whether avacopan is secreted in human milk. Avacopan was detected in the plasma of undosed hamster pups nursing from drug-treated dams *(see Animal Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAVNEOS and any potential adverse effects on the breast-fed infant from TAVNEOS or from the underlying maternal condition.

Animal Data

Avacopan has not been measured in the milk of lactating animals; however, it was detected in the plasma of nursing offspring in a pre- and post-natal development study with hamsters at a pup to maternal plasma ratio of 0.37. This finding suggests that avacopan is secreted into the milk of lactating hamsters *[see Nonclinical Pharmacology (13.1)]*.

Pediatric Use

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

Geriatric Use

Of the 86 geriatric patients who received TAVNEOS in the phase 3 randomized clinical trial for ANCA-associated vasculitis *[see Clinical Studies (14)]*, 62 patients were between 65-74 years and 24 were 75 years or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

Patients With Renal Impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3)]*. TAVNEOS has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Patients With Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (as indicated by the Child-Pugh method) hepatic impairment *[see Clinical Pharmacology (12.3)]*. TAVNEOS has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.tavneospro.com or contact Amgen Medical Information at 1-800-772-6436

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Women in Nephrology Speakers Bureau Initiative

By Niloofar Nobakht, Michelle Rheault, Susanne B. Nicholas, and Mala Sachdeva

Women in Nephrology (WIN) is an international organization that was founded in 1983 by prominent women nephrologists with the goal of assisting women in developing their careers. Over the past 40 years, WIN has expanded its purpose to include advocacy for and mentoring to professionals of all genders in the field of nephrology. In addition, WIN champions within the nephrology community for education and research relevant to women's health (Figure).

Throughout history, women in medicine have been underrepresented in public and leadership roles, including as speakers and moderators at medical conferences and members of conference-planning committees. In fact, a 2017–2018 study showed that only approximately 30% of speakers at medical conferences were women (1). In addition, the proportion of women speakers correlated with their representation on planning committees (1). Over the past few years, some conferences within the nephrology subspeciality have demonstrated strong gains in representation of women as speakers and moderators. Notably, the ASN annual meeting increased its proportion of women speakers twofold, from approximately 20% in 2013 to 40% in 2019. Similarly, women moderators increased from approximately 25% in 2011 to 47% in 2019 (2).

Unfortunately, other national and international conferences within nephrology have not been as equitable in gender representation. Women continue to be underrepresented among invited speakers at departmental grand rounds and named lectureships. A study in 2020 illustrated that women represented only one-fifth of invited speakers for departmental grand rounds, and the proportion of women-named lectureships was approximately 20% or lower (3).

Women also remain underrepresented in the proportion of major awards given by nephrology organizations (4). Although there was somewhat of an increase in 2019, O'Lone and Webster pointed out that major organizations in nephrology awarded fewer than 20% of awards to women over the previous 10 years (4). All of these inequities significantly limit women's ability to achieve proper recognition and obtain leadership roles that would contribute to advancing their professional careers.

Furthermore, women in the field of nephrology face several barriers within their work environments. These challenges include but are not limited to: confronting financial disincentives in which they take on more tasks either without being paid or being underpaid; experiencing pay inequities with lower salaries; facing work/life balance challenges; or being offered fewer opportunities for career advancement compared with their male counterparts (5–7). To address these challenges, O'Lone and Webster recommend four strategies to help women in their career advancement (4).

- Facilitating and prioritizing women to conduct kidney-related research
- Instituting family-friendly policies at conferences and the workplace
- Addressing gender discrimination at an institutional level
- Promoting women through mentorship and increasing opportunities for leadership roles

The WIN social media team has led the way in highlighting and pointing out conferences and seminars in which women have been underrepresented or not represented. When session organizers were asked why this was happening, WIN received responses such as, "We don't know any women who can talk in that area," or "There aren't any women doing that work."

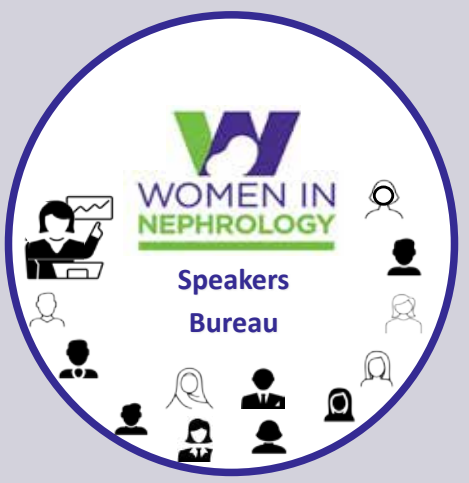
In an effort to reduce the barriers for institutions and organization leaders to identify women speakers who are experts in their field, WIN established the Speakers Bureau, a database comprised of WIN members who can voluntarily register to speak on a specific subject area and offer their expertise as panelists, speakers, or collaborators. Currently, there are 80 women speakers in the WIN Speakers Bureau (https://www.womeninnephrology.org/career/speaker-bureau.aspx), which is publicly and freely accessible through the WIN website (https://www.womeninnephrology.org/). The opportunity to join the database is open to all WIN members.

As women continue to advance in their professional careers, they deserve to be recognized for their knowledge and expertise on a local, national, and global level. There continues to be a need to increase the number of women speakers at departmental grand rounds and conference-planning committees. Through the creation of the Speakers Bureau initiative, WIN has stepped up to address these disparities within speaking opportunities, to provide a conduit for women to advance their careers, and ultimately, to advocate for women across the field of nephrology. ■

Niloofar Nobakht, MD, FASN, is a councilor; Mala Sachdeva, MD, is president-elect; Michelle Rheault, MD, is past secretary; and Susanne B. Nicholas, MD, MPH, PhD, is president of Women in Nephrology, and all serve on its Executive Council.

Figure. Goals of the WIN Speakers Bureau

- Increase visibility for its members on a local, national, and international level
- Increase the number of women speakers at grand rounds and conferences
- Advocate for women
- Assist in career advancement of women in academia and private practice
- Help members develop their niche in nephrology



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In honor of Mental Health Awareness Month, this special section of *Kidney News* focuses on the intersection of mental health and kidney diseases. *Kidney News* thanks L. Parker Gregg, MD, MSCS, FASN, and Itunu Owoyemi, MBBS, FASN, for thoughtfully selecting and coediting these articles.

THE UNIQUE MENTAL HEALTH LANDSCAPE OF KIDNEY DISEASES

By L. Parker Gregg and Itunu Owoyemi

According to the National Institute of Mental Health, one in five adults in the United States lives with a mental illness (1). Patients living with the spectrum of kidney diseases—including nondialysis chronic kidney disease, dialysis-dependent kidney failure, and kidney transplantation—have high rates of mental illnesses and face a complex emotional landscape related both to kidney diseases themselves and their available treatment options. In honor of National Mental Health Awareness Month, this special issue of *Kidney News* is dedicated to shining a light on some of these important concerns, including clinically diagnosed mental illnesses as well as unique stressors and emotional concerns affecting people living with kidney diseases.

Patients with kidney diseases may experience fear, hopelessness, frustration, depression, anxiety, and guilt related to anticipating kidney failure, living with dialysis dependence, and receipt of a transplanted kidney. These feelings, along with the symptom burden and poor quality of life that frequently affect patients with kidney diseases, may contribute to high rates of depression and anxiety. Although kidney transplantation can greatly improve quality of life for patients with kidney failure, it brings its own stressors and emotions. In addition to these concerns, certain populations of patients affected by kidney diseases—including children, Black and Latinx individuals, and undocumented immigrants—face additional sociocultural concerns related to living with chronic illness, access to care, and organ transplantation. For patients receiving dialysis, social and emotional considerations about stopping dialysis treatments can complicate the experience of end-of-life care.

Understanding, or at least acknowledging, these concerns is crucial to enabling patients to communicate with their care team honestly and openly about their mental health. Fortunately, increased attention to research about mental health among patients with kidney diseases has led to important advancements in treatment options. There is now evidence to support the efficacy of some pharmacologic therapies, such as selective serotonin reuptake inhibitors, and nonpharmacologic therapies, such as cognitive behavioral therapy and physical activity, for the treatment of depressive symptoms among patients with kidney diseases. Professional mental health care, a communicative nephrology care team, and peer-support networks can also all reinforce improved well-being.

The articles in this issue of *Kidney News* reflect some of the breadth of mental health difficulties that patients with kidney diseases experience and offer strategies to mitigate these concerns. We hope that readers benefit from the perspectives herein and can carry forward a new awareness to the clinic room and the bedside for the benefit of patients who may be struggling with mental health concerns. ■

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Diagnosis and Management of Anxiety and Depression Among People With Kidney Diseases

By Meredith C. McAdams and S. Susan Hedayati

Mental illness is common among individuals with chronic illnesses, and this holds true among those with chronic kidney disease (CKD) and kidney failure. The prevalence of depression is particularly high, affecting approximately 20% to 25% of patients (1). Dauntingly, depression in individuals with CKD is associated with an increased risk of death, hospitalization, and cardiovascular events (2, 3). Among those with CKD who are not yet requiring dialysis, depression poses an increased risk for progression to dialysis (2). Similarly, symptoms of anxiety are extremely common among those with kidney diseases. It is estimated that approximately 20% of these individuals may have anxiety disorders, and as high as 43% may have elevated anxiety symptoms. People living with kidney diseases experience an increased burden of anxiety when compared with both the general population and people with other chronic diseases, including diabetes mellitus and malignancy (4, 5). Like depression, anxiety is associated with mortality, dialysis initiation, and hospitalization (6). Importantly, depression and anxiety correlate with poor patient-centered outcomes such as decreased quality of life and health care noncompliance (7).

Given the pervasiveness of both anxiety and depression and the overlap in symptoms manifested in later stages of kidney diseases, screening for these disorders is of utmost importance. There are no current guidelines for screening these individuals. Self-report screening instruments can be used for both, but each disorder is formally diagnosed based on *Diagnostic and Statistical Manual of Mental Disorders* criteria, which also allow for identification of concomitant mental health disorders and complications such as suicidal ideation (4).

Few randomized controlled trials exist to guide the pharmacologic treatment of anxiety and depression in patients with CKD (8). A recent observational study of patients with nondialysis CKD stages G3–5 reported a trend toward a higher risk of hip fractures and upper gastrointestinal bleeding that was not statistically significant with initiation of antidepressant medications (9). Despite observational studies suggesting potential safety concerns, sertraline, a selective serotonin reuptake inhibitor (SSRI), was shown in two 12-week randomized trials to be safe, although associated with an increased risk of nausea and vomiting, among patients with CKD and kidney failure who were treated with hemodialysis (10, 11). Even though SSRIs are commonly used to treat anxiety and depression in the general population, data are mixed regarding their efficacy in the setting of kidney diseases. It is reasonable to try SSRIs in people living with kidney diseases, using sertraline as the drug of choice given its safety profile (1). Benzodiazepines and beta-blockers are often used in the general population to treat transient anxiety. Caution is advised with these medications in individuals with kidney diseases, with special consideration given to renal clearance and accumulation of toxic metabolites (5).

Doses for many antidepressants also differ from the general population, and possible adverse effects need to be considered when prescribing these medications (Table) (12). Nonpharmacologic treatments for anxiety and depression include psychologic interventions, of which cognitive behavioral therapy is the most well-studied. Chairside cognitive behavioral therapy was shown to be effective among patients with kidney failure who undergo dialysis. The benefit is less clear for anxiety in patients with CKD, although efficacy was established for the treatment of anxiety in the general population (1, 5).

Given the high prevalence and independent associations with both adverse clinical and patient-centered outcomes, depression and anxiety are important comorbidities to be recognized and managed. Patient preferences and shared decision-making are essential when considering treatments for these conditions. ■

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Table. Dosing considerations of commonly prescribed antidepressants

Medication	Dosing in normal eGFR	Dosing in CKD	Dosing in kidney failure	Cautions
Sertraline	50–200 mg/day	No dose adjustment		Start at the lowest dose, and up-titrate every 1–2 weeks based on symptoms and side effects.
Fluoxetine	20–80 mg/day	No dose adjustment		Start at the lowest dose, and up-titrate every 1–2 weeks based on symptoms and side effects.
Paroxetine	IR: 20–50 mg/day ER: 25–62.5 mg/day	IR: 10 mg/day initial dose; 40 mg/day maximum dose ER: 12.5 mg/day initial dose; 50 mg/day maximum dose		N/A
Citalopram	20–40 mg/day	No dose adjustment if GFR >20	Initial dose, 10 mg/day	Higher doses are associated with QTc prolongation.
Escitalopram	10–20 mg/day	No dose adjustment if GFR >20	Initial dose, 5 mg/day	Higher doses are associated with QTc prolongation.
Venlafaxine	IR: 75–225 mg/day, two to three divided doses ER: 37.5–225 mg/day	Reduce dose by 25%–50%.	Initial dose, 37 mg/day; not to exceed 50% of maximum dose	Accumulation of toxic metabolite
Bupropion	200 mg/day, two divided doses; maximum, 450 mg/day, three to four divided doses	Use with caution; consider 150 mg/day.	Use with caution; active metabolite.	Accumulation of toxic metabolites, wide QRS complex, and increased risk of seizures in kidney failure
Mirtazapine	15–45 mg/day	eGFR <30; initial dose, 7.5–15 mg/day	Initial dose, 7.5–15 mg/day	CNS effects (somnolence and weight gain)
Amitriptyline	75–150 mg/day, one to three divided doses	Avoid tricyclic antidepressants.		QTc prolongation, arrhythmias, and orthostatic hypotension
Trazodone	IR: 150–400 mg/day, divided ER: 150–375 mg/day, single dose	Increase dose carefully.		Start at the lowest dose, and up-titrate every 1–2 weeks based on symptoms and side effects.

CNS, central nervous system; eGFR, estimated glomerular filtration rate; ER, extended release; IR, immediate release; N/A, not applicable; QTc, corrected QT interval.

Navigating Transplantation: Strategies to Promote Wellness

By Erin Dean, Cassandra Abbatemarco, and Joseph Lander

Kidney transplantation is a journey, both physically and mentally, as patients navigate the road from pretransplant to posttransplant life. It is well known that patients with kidney diseases have higher rates of depression compared with the general population and that depression has been associated with increased morbidity and poor quality of life in patients with chronic kidney disease and kidney failure (1–4).

Transplant psychiatrists are often asked to assess patients with advanced kidney diseases and comorbid mental health disorders to determine transplant candidacy. Common indications for transplant psychiatry referral include:

- extensive mental health history
- active and/or unmanaged mental health symptoms
- complicated psychotropic medication regimens
- history of suicidal ideation, suicide attempts, and/or psychiatric hospitalizations
- active substance use or a history of significant substance use
- active concerns or a significant history of nonadherence

Upon review of the literature pertaining to solid organ transplantation, data exist linking pretransplant mental health diagnoses, particularly depression, with posttransplant nonadherence, higher readmission rates, higher risks of acute rejection and graft loss, and decreased survival; however, not all studies showed that these associations were statistically significant (5–7).

Most transplant centers consider active substance use and unmanaged psychiatric illness to be absolute contraindications to transplantation (8). It is important to note that it is unjust to deny a patient transplantation on the basis of psychiatric diagnosis alone, and longer length of psychiatric symptom stability should be considered a positive prognostic indicator.

Kidney transplantation is associated with improved quality of life and lower rates of psychiatric morbidity compared with dialysis therapies (9–11). However, posttransplant recovery is not without risk of psychiatric complications, including but not limited to depression, anxiety, and posttraumatic stress disorder (12). Posttransplant depression has been linked to higher rates of graft failure and death (13).

Managing physical and mental well-being after transplant is crucial, and it is important for patients to use strategies to promote wellness for the best chance of success after transplant (Figure). These strategies include:

- **Building a support system.** Recovering from a transplant can present unexpected feelings and emotions. Patients may express feeling overwhelmed while adjusting to a new posttransplant routine, whereas others may endorse the fear of potential unknowns, including possible organ rejection and medical complications. Some individuals experience survivor's guilt toward their deceased donor. It is crucial to solidify an emotional support team of friends and family who are available to openly conversate and process these feelings.
- **Communicating with the transplant team.** An emotional support team does not need to be exclusive to family and friends; in fact, the transplant team should be an integral part of every patient's support system. Whether it be related to physical symptoms or mental health concerns, it is paramount that patients be communicative and honest with their transplant team to help patients succeed in their recovery. Posttransplant medications can contribute to mood and anxiety, and a dose adjustment may be all that is needed to provide symptom relief.
- **Locating kidney transplant support groups.** Another supportive option is participation in support groups either through an individual transplant program or through a national kidney or transplant organization. Patients may find added validation and understanding by listening to others' journeys who have gone through similar experiences.
- **Seeking professional mental health treatment.** There are circumstances when talking with loved ones or one's transplant team is not enough to provide relief for emotional distress. Meeting with a therapist can provide an additional layer of support while offering a more objective perspective of a patient's situation, or scheduling an appointment with a psychiatrist to determine if psychiatric medications are indicated are both helpful options. Transplant teams are often a good place to start to obtain these referrals.
- **Maintaining healthy diet and exercise.** Preserving a healthy, balanced diet and participating in regular exercise are always important in promoting physical and emotional wellness. Weight management is also important to reduce long-term medical complications.
- **Optimizing quality sleep.** After transplant, some medications, including antirejection medications and steroids, can sometimes cause sleep abnormalities such as insomnia and vivid dreams. Sometimes sleep is affected by anxiety and trauma-related symptoms. Practicing optimal sleep hygiene can help with ongoing physical healing while promoting emotional regulation during the day.
- **Prioritizing adherence.** Following the recommendations of the transplant team is key to success after transplant. This includes adherence with posttransplant medications, attending all medical appointments, and obtaining laboratory work as ordered. ■

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The authors report no conflicts of interest.

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Figure. Strategies to promote wellness after kidney transplantation

Supporting the Mental Health Needs of Adolescents and Young Adults With Kidney Diseases

By Carlos Cesar Becerril Romero

When the Centers for Disease Control and Prevention published the latest results of the Youth Risk Behavior Survey 1 year ago, it raised alarms about the mental well-being of adolescents and young adults (AYA) in the United States. The data showed that 42% of adolescents "experienced persistent feelings of sadness or hopelessness," a significant increase from 28% in 2011 (1).

As pediatric nephrologists, we care for AYA with a chronic illness, including during periods of added vulnerability when they are transitioning care. Their developmental stage (2), combined with the burden of a chronic disease, may increase their susceptibility to mental health disorders. AYA with chronic kidney disease (CKD), on dialysis, or with a kidney transplant experience even higher rates of depression and anxiety compared with their healthy counterparts (3–7). AYA with chronic diseases are also engaging in more substance use, including alcohol, tobacco, or marijuana, compared with AYA without a chronic illness (8). Our patients are struggling, and we must do more to help them.

Mental health disorders may exacerbate the risks of medical complications, leading to worse health outcomes. For example, depression, anxiety, and substance use are associated with medical treatment nonadherence (9, 10). Medication nonadherence among patients who have received transplants can lead to allograft rejection and graft failure (11). Addressing the psychosocial needs of our patients may help improve their long-term survival.

In addition, patients are yearning for additional support to cope during their medical journey. Zhang and colleagues (12) studied the experiences of patients aged 8–21 years with CKD stages 1–5. The study identified that patients felt disadvantaged by the disruption to their self-esteem and identity, bearing the burden alone, and being unable to access psychologic support. Providing psychosocial support to our patients may improve their medical experience and quality of life.

Pediatric nephrologists are often the health care practitioners with whom AYA living with kidney diseases have the closest relationship. They are uniquely positioned to screen and identify patients experiencing mental health issues. When Dawson et al. (13) asked pediatric nephrologists about the importance of providing psychosocial support in their nephrology division, 80% of practitioners across all centers indicated that it was "important" or "very important" to provide holistic care. However, pediatric nephrologists may assume that mental health screening occurs in the primary care setting. In addition, there is a pediatric nephrology workforce crisis, and practitioners are already stretched thin helping patients. Asking pediatric nephrologists also to address the mental health needs of their patients may seem burdensome, out of scope, and unrealistic.

What we can do as pediatric nephrologists is recognize mental health support as treatment to improve kidney health. By including and working with our multidisciplinary team (i.e., social workers, nurses, and child life specialists), we can maximize efforts to support patients and families. We need to screen AYA with CKD regularly for early identification of psychosocial issues that may impact their care. We need to have dedicated psychosocial professionals who can support the most vulnerable patients undergoing nephrology care.

Addressing the mental health needs of patients is no easy task. Clinicians may feel uncomfortable discussing mental health concerns, and the nephrology team may not have adequate resources to help their patients. Do not let this stop you from checking on your patients. Simply asking how they are coping can make a difference. ■

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Improving Mental Health in Marginalized Communities With CKD

Historically marginalized and underserved populations with kidney diseases are vulnerable to unique challenges when it comes to mental health and kidney health. In the next few articles, we dive into these issues and the opportunities to improve care for patients in some of these communities.

Issues Impacting Care in Latinx Populations

By Flor Alvarado, Vanessa Evans, and Lilia Cervantes

One in five Hispanic or Latino/a/e/x (herein Latinx) individuals in the United States is affected by mental illness, yet among those affected, only 36% received mental health services (compared with 52% of White individuals with mental illness) (1). In the limited research exploring mental health in individuals with chronic kidney disease (CKD), Latinx individuals were at greater risk of experiencing depressive symptoms compared with non-Latinx White individuals; however, they were less likely to be treated for depression (2, 3).This raises a critical concern about the availability of appropriate mental health services for Latinx individuals with CKD.

Barriers to mental health support

The accessibility of mental health services in Latinx individuals in the United States may be impacted by the maldistribution of social determinants of health, including structural (i.e., the sociopolitical and economic context impacting access/quality of health care, socioeconomic status, and exposure to structural racism and discrimination) and intermediary (i.e., social risk factors, sociocultural context, and personal lived experiences) determinants (4) (Figure).

In terms of structural determinants, Latinx individuals compose the minoritized group with one of the largest uninsured healthcare coverage rates in the country (18%), significantly affecting their access to care (5). Even with insurance, it is challenging for Latinx patients to find a mental health practitioner who is culturally and language concordant. Many Latinx individuals also experience challenges that include personal experiences with discrimination in clinical encounters or fear of deportation; they have also witnessed racism and discrimination shared by the media. All of these examples may understandably foster a general lack of trust in the US health care system (6).

Regarding the intermediary determinants, the Latinx population is disproportionately impacted by social risk factors including food insecurity, housing instability, and financial strain, further affecting health care access (6–8). Furthermore, the pervasive stigma surrounding mental health persists in many Latinx communities and may lead to a reluctance in accessing care (8, 9). Other cultural beliefs and values may affect willingness to seek mental health care, such as *fatalismo* (attitude that a person's plight is religiously based or fate), *machismo* (attitude associated with exaggerated masculine pride), and *marianismo* (attitude associated with self-sacrifice and putting the needs of others first) (10). Traditionally, family relationships have been an important aspect of the Latinx culture (i.e., *familismo*), although it is important to note that family dynamics can serve as both a source of support or stress (8–10). The latter may occur in the context of multigenerational households in which adults have extended caregiving and financial responsibilities, delaying their own health needs. There may also be a desire to downplay symptoms to avoid burdening or causing shame to one's family (10).

Strategies to promote mental health well-being

To promote the mental health well-being of Latinx individuals with CKD, the nephrology community can implement diverse strategies (Figure). Health care teams can screen for mental health well-being, inquire about coping mechanisms and social-emotional support (e.g., family, religion, or other spiritual support), and direct patients to culturally responsive mental health services and resources. Future research should assess the associations between mental health disorders and CKD outcomes, identify barriers to mental health screening, and develop culturally responsive and community-based interventions to improve mental health well-being of Latinx individuals with CKD. ■

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Figure. Potential barriers to obtaining mental health services among Latinx individuals with kidney diseases and strategies to improve care access and quality

Barriers to obtaining mental health services	Strategies to improve care access and quality
Structural Determinants Access and quality of health care • High uninsurance rates • Language and cultural discordance between clinicians and patients • Limited availability of language-access services Socioeconomic status • High poverty rate • Disparities in educational attainment impacting Latinx individuals Structural racism and discrimination • Discriminatory public policies toward Latinx immigrants **Intermediary Determinants** Social risk factors • High rates of food insecurity, housing instability, and financial strain Sociocultural context • Stigma surrounding mental health • Family-related concerns; downplaying mental health symptoms to avoid burdening or shaming family • Other historical cultural beliefs/values: *fatalismo*, *machismo*, and *marianismo* Personal lived experiences • Discrimination during clinical encounters	✓ Talk openly and normalize mental health wellness. ✓ Provide culturally responsive resources to promote mental health well-being (e.g., contact information of local and online bilingual mental health clinicians, educational materials about mental health well-being). ✓ Use multidisciplinary teams (i.e., inclusion of social worker, community health worker) to screen for mental health well-being, and link patients to community resources. ✓ Inquire about coping mechanisms and social support (e.g., family, religion/spiritual, or other); screen for social isolation/low social support. ✓ Enhance social/emotional support as needed (i.e., provide information about in-person and online peer support groups, refer to peer-to-peer programs). ✓ Demonstrate empathy; provide sufficient time for open dialogue and questions.

Issues Impacting Care in Latinx Populations

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Addressing Mental Health in Undocumented Immigrants Living With CKD

By Sri Shyamkumar, Dominique Pean, and Rajeev Raghavan

People who suffer from chronic kidney disease (CKD) are twice as likely to have self-reported fair or poor health status compared with those without CKD (1). The World Health Organization defines "mental health" as a state of well-being that enables people to cope with the stresses of life, realize their abilities, learn and work well, and contribute to their community (2). The mental health of marginalized groups, particularly undocumented immigrants, is further strained by cultural systemic barriers to their mental health including language barriers, health care coverage, disease characteristics, differences in beliefs, and trust with the health care team. Practicing cultural sensitivity with undocumented immigrants can give health care professionals a better idea of how to provide better care to patients with CKD (3).

Language barriers

Undocumented immigrants often face a language barrier to care, with nearly 50% reporting a lack of English proficiency (4). This challenge compounds the stress of expressing health concerns during vulnerable moments, contributing to mental health strain. This may erode trust with primary care physicians or the nephrology care team. Using a medical interpreter during conversations may improve care.

Residency status and health care coverage

Undocumented immigrants are often excluded from government, state, or employer-based insurance plans, which may limit access to affordable and preventive health care (4, 5). Undocumented immigrants residing in states that do not provide scheduled dialysis rely on emergency dialysis treatments; this is known to increase anxiety, morbidity, and mortality (5–7). Undocumented immigrants with kidney failure report an exceptionally low quality of life when surveyed using the validated Kidney Disease Quality of Life survey (8, 9). Physicians should be familiar with resources that support mental health and well-being for undocumented immigrants. One example is El Futuro, a nonprofit organization that provides advice, education, and support groups in the Latinx community (10).

Disease characteristics

CKD is a silent disease. Diagnosis requires laboratory testing, and symptoms manifest only in late stages. Nephrology care teams should acknowledge limitations such as medication costs and access to primary care that disproportionately affect undocumented immigrants. These limitations may accelerate progression of diabetes mellitus and hypertension, the leading causes of CKD.

Addressing beliefs

Discussions around diet and medications often overlook cultural preferences, such as fasting or dietary restrictions, leaving patients feeling overwhelmed rather than empowered. Kidney care practitioners should inquire about patients' cultural or religious preferences as they relate to treatment, and customize treatment plans to fit their patients' unique needs. We note that this is not unique to undocumented immigrants and should be considered for all patients.

Next steps

A viable approach to address mental health in undocumented immigrants with CKD might mirror strategies studied to improve mental health for patients with kidney failure. This includes establishing a patient-navigation program tailored to meet the cultural and linguistic needs of a patient. A portion of the clinical visit should be dedicated to discussing this patient population's unique mental health challenges. Nephrologists should also familiarize themselves with resources offered on a community and state level to alleviate the mental health burden of chronic health conditions on the undocumented immigrant population. These strategies, along with use of a multidisciplinary team, can be utilized to provide high-value care to undocumented immigrants. ■

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Know Better, Do Better: Mental Health Support for Black Americans With CKD

By Denise Thomson and Tanjala S. Purnell

A rocky foundation

For more than 400 years, resilience for people of the African diaspora was essential for survival. The concept of "Black resilience" recognizes the need for "extraordinary strength of mind and body for the sake of psychological and physical survival" (1). The stigmatization of mental illness within the Black community has also been linked to American slavery and scientific racism by historians with a dichotomy of thought: Black people were deemed "subhuman, incapable of mental illness," and having such an illness showed weakness (2). Because of this stigma, mental illness was often concealed or explained away by an outside, remediable source such as stress or physical ailments, which created barriers to treatment and help-seeking behaviors (3).

The National Institute of Mental Health estimates that 21.4% of Black Americans live with a mental illness (4). In addition, 2021 data from the United States Renal Data System estimate that the overall prevalence of chronic kidney disease (CKD) was highest among Black individuals (18.8%), and a 2022 study found that US adults with self-reported CKD were more likely than those without a chronic illness to experience mental illness (5, 6).

Barriers to appropriate care

The disproportionate burden of CKD and mental illness among Black Americans contributes to health disparities. For individuals willing to seek care for mental health, disparities in access remain a significant barrier, with 10% of Black Americans not having any health insurance compared with 5.2% of White Americans (7). Additional socioeconomic barriers, such as high out-of-pocket costs or unfathomable waiting times for outpatient appointments, often portend emergency departments becoming the main source of mental health care, leading to care fragmentation. Among patients with CKD, the widespread use of race-based clinical equations, such as those used to estimate glomerular filtration rate—until very recently (8)—may also contribute to disparities in timely diagnosis, referral to subspecialty care, access to transplantation, and medical trust among Black patients.

To compound this issue, the scarcity of Black mental health professionals may discourage patients from seeking care due to fear of medical mistreatment or concerns about a lack of cultural familiarity and common ground of the assigned clinician (9). Data from the American Psychiatric Association show that only 2% of the estimated 41,000 psychiatrists in the United States are Black, and just 4% of psychologists are Black (10). As clinicians, we are charged to enter each patient encounter culturally aware, remembering to check our own biases at the examination room door. Unfortunately, we often fall short. One study from 2004, albeit dated, found that physicians speaking with Black patients were 23% more verbally dominant and engaged in 33% less patient-centered care when compared with White patients (9). The complexities of gender/gender identity, sexual orientation, mental health, and chronic diseases merge with these implicit racial biases.

Navigating a path forward

The path forward to advancing mental health equity among individuals living with CKD requires inclusivity among care teams and a recognition of the importance of cultural sensitivity. Recognizing the historical origins of mental health stigma and the vital roles of patients' family and social and faith communities in treatment decision-making is an important first step in understanding the Black experience in any chronic disease. Extended family and shared faith partners are often integral stakeholders in the decision-making process. Continued efforts to promote workforce diversity among kidney care and mental health professionals are needed. Nephrologists should also make every effort to work collaboratively with culturally sensitive mental health professionals to enhance overall care for Black patients living with both CKD and mental illness. Useful resources include the Black Virtual Wellness Directory (11) and the National Alliance on Mental Illness (12).

In conclusion, let us strive to live by the words attributed to the brilliant poet, Dr. Maya Angelou, "Do the best you can until you know better. Then when you know better, do better." Much is yet to be mastered on this subject; however, we have enough knowledge now to indeed do better. ■

The path forward to advancing mental health equity among individuals living with CKD requires inclusivity among care teams and a recognition of the importance of cultural sensitivity.

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It's Not All About the Meds: Nonpharmacologic Management Strategies for Depression in People Living With Kidney Diseases

By Claire Carswell

People living with chronic kidney disease (CKD) are at significant risk of developing mental health conditions, such as depression and anxiety, particularly in the later stages of CKD (1). Symptoms of depression and anxiety can include fatigue, loss of motivation (avolition), loss of pleasure (anhedonia), sleep disturbances, changes in appetite, feelings of hopelessness, and thoughts that life is not worth living (2). These symptoms can make it substantially more difficult for people to adhere to treatment and self-management strategies for CKD aimed at preventing progression. Unsurprisingly, depression is therefore an independent predictor of mortality in people with CKD (3).

Typical treatment for depression and anxiety can include the use of antidepressant medication. Although prevalent antidepressants are not known to be nephrotoxic, there are some limitations in the evidence base for using them as monotherapy to manage depression in people with CKD. One large trial of antidepressants for people with depression and CKD showed that sertraline was no more effective than a placebo at reducing symptoms of depression but did have higher rates of adverse effects (4). This is an important consideration, particularly for people living with kidney failure who are already experiencing substantial symptom and treatment burdens. Concerns about needing to take additional medication and the associated side effects can act as a barrier to people with CKD seeking help for their mental health (5). Therefore, it is important to consider alternative approaches to managing depression in this population.

There is mounting evidence that nonpharmacologic interventions could be an acceptable and effective option for people with CKD and depression. Cognitive behavioral therapy, an evidence-based psychotherapy focused on supporting people to restructure thoughts and change behavior, has shown initial promise in small studies of people with CKD and depression (6). Lower-intensity alternatives, such as peer support groups, physical activity interventions, and behavioral activation, have been recommended for people with mild to moderate depression and long-term conditions and may be appropriate for people with CKD (7).

Overall, there is a need for interventions that account for the profound psychosocial impacts that result from living with CKD. Mental health support for people with depression and CKD should be provided within a collaborative care model underpinned by multidisciplinary communication (7). Research must continue in this area so that people with CKD can receive high-quality, evidence-based care to improve their mental health. ■

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The Role of Physical Activity in the Management of Mental Health Conditions in People With Kidney Diseases

By Matthew P. M. Graham-Brown and James O. Burton

Approximately one-quarter of people living with chronic kidney disease (CKD) are affected by symptoms of depression, and this statistic is even higher in patients on dialysis (1). The prevalence of pervasive symptoms of anxiety is similar (2, 3), and early neuro-cognitive decline is common (4). Importantly, the presence of mental health disorders is associated with poorer patient outcomes (5). Prescription of appropriate pharmacotherapy for mental health conditions is low in patients with CKD (6), and given the pharmacokinetics of the drugs, their effectiveness in CKD is likely to be reduced.

In the general population, there are clear relationships between exercise behaviors and mental health burden (7); it is commonly espoused that physical activity and exercise are good for mental health. Exact definitions vary, but physical activity can be defined as "any bodily movement produced by skeletal muscles that results in energy expenditure," whereas exercise is a subcategory of physical activity that is planned, structured, and usually repetitive with at least one goal related to improving or maintaining a physical fitness component (8). The term "exercise" tends to be associated with formal exercise training or activities, such as going to the gym, running, or bike riding, with the aim of becoming fitter or stronger. For many patients who are physically deconditioned or unfit, these activities or environments are incredibly off-putting, yet structured programs of exercise have often been the focus of rehabilitation programs in patients with CKD. Indeed, our research group showed that a structured program of intradialytic cycling led to prognostically important improvements in cardiac structure and function (9). As important as these findings are, just as important is the lack of effect that the program had on health-related quality of life or measures of depression and anxiety—findings that were corroborated by the PEDAL (Prescription of Intradialytic Exercise to Improve Quality of Life) study (10). Neither of these studies made patients feel better and had no effect on mental health or well-being.

For mental well-being, formal exercise may not be the answer. Instead, we need to think and talk about how we can support patients to become more physically active. Physical activity regimens can be more easily personalized to fit in with patients' lives and what they enjoy doing, without the targets or pressure of a formal program and physiologic testing. We can be confident that if people can achieve close to 150 minutes of moderate to vigorous physical activity each week, then health outcomes will likely improve (11); it really does not matter how this is achieved. Results from the Kidney BEAM trial support this view. The study showed that for patients with CKD, on dialysis, and who underwent a transplant, engagement with a personalized program of exercise and activity, in a way that was convenient for them, led to important improvements in health-related quality of life and mental well-being (12).

This is the message that we need to convey to our patients. If we as clinicians can support them to become more physically active in a sustainable and enjoyable way, they will likely experience improvements in their mental well-being, and their physical health outcomes should improve. ■

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Patient Perspectives: A Dialogue on Mental Health and Kidney Diseases

Living with kidney diseases brings unique challenges and concerns that can profoundly affect mental health and well-being. *Kidney News* is grateful to Austin Lee and Jackson Goodrich, two individuals living with kidney diseases, for sharing their personal experiences of managing their mental health alongside their kidney health.

Austin Lee is a member of the Kidney Health Initiative Patient and Family Partnership Council.

Jackson Goodrich is the head of teen outreach at the Dent Disease Foundation.

KN: How has kidney disease impacted your mental health?

Lee: As a two-time kidney transplant recipient, living with kidney disease has had a significant impact on my overall mental health. I was diagnosed with acute renal failure in 2007 after my first transplanted kidney went into rejection. After this diagnosis, I have lived with the fear of my second transplant rejecting and me having to undergo peritoneal dialysis for the third time in my life. It can be a challenging and stressful condition to manage along with everyday living arrangements such as school and work. Kidney disease often requires frequent medical appointments as well as dietary restrictions.

Goodrich: Having Dent, a rare kidney disease, has added something to my plate. I have to be mindful of my diet like few people I know. It is often uncomfortable for me to talk to people, such as event coordinators, about my dietary needs or to tell my friends that I cannot eat out at most restaurants because of the high salt content.

KN: What was your emotional experience during major transitions in your kidney disease (e.g., chronic kidney disease to dialysis, dialysis to transplant)?

Lee: I initially felt a deep sense of hopelessness when I was assigned to peritoneal dialysis for the second time. At the time that I was experiencing the symptoms of renal failure, I had no idea that my condition would lead to dialysis if it progressed. I had prior familiarity with dialysis but never really understood what it was that made me feel very frustrated when I was told that my kidney progression had reached its ending point. During my senior year in high school, my mental health was substantially impacted. Kidney disease caused me to feel depressed because of how my physical features changed. Additionally, the physical symptoms of kidney disease, such as fatigue, pain, and difficulty concentrating, have been a challenge that I continue to overcome in my life.

Goodrich: While I have been blessed to not require dialysis or a transplant yet, I have been increasingly anxious about my kidneys as time has gone on and as I have matured. I know that every bite of food I eat and every drop of water I drink have enormous impacts on the rest of my life. This sometimes makes me experience anxiety about what I eat. Another factor is that a transplant will require a kidney from my younger sister. I do not want her health to be possibly jeopardized because I did not take care of my condition. This has made me feel anxious and sometimes scared about what might happen in the future. Even through all of this, I know that whatever happens is up to God, and that has been the greatest help to my mental health.

KN: Do you feel comfortable raising concerns about your mental health with your nephrologist? Why or why not? What advice would you have for your clinicians to help you feel more comfortable talking about these concerns?

Lee: I have grown to become more comfortable raising concerns about my mental health with my nephrologist, but I often believe that I have to explore other personal care options such as a therapist to help guide me through how I feel with kidney disease. It is important for individuals with kidney disease to prioritize their mental well-being and seek outside support from support groups and counselors. Clinicians should begin with understanding the environments that patients come from to have a better understanding of their mental health issues and so that patients feel supported and cared for throughout their journey with kidney diseases.

Goodrich: My mental health in terms of my kidney disease is connected with what I know about the condition of my kidneys. When I have questions about my diet, medication, or a new phenomenon related to my condition, I feel comfortable asking my nephrologist about it. Sometimes, I felt guilty about telling my nephrologist about a new phenomenon, because I feel responsible for my health. Over time, I realized that the more I talked to him, the more confident I got with his care, and the more I understood my kidneys. Eventually, knowing more about how I can take care of my kidneys helped me have more peace and feel like I had more control over my condition. Only by maintaining this confident relationship with my nephrologist was I able to maintain this positive outlook.

My advice to other clinicians would be this: Build trust with your patients. If your patients are not comfortable in sharing concerns or asking questions that could change the status quo of their care, it will be harder to help them, and they will have more anxiety and a worse state of mind as the condition develops. This can be easily avoided if the patient knows that talking more freely to their clinician will help them—if not now, then in the future. ■

Existential Challenges at the End of Life for People Receiving Dialysis

By Catherine R. Butler

The right to die in dignity is a problem raised more often by medicine's successes than by its failures.

–Joseph Fletcher (1)

Millennia of philosophic, religious, and artistic traditions provide guidance on the profound existential questions that arise at the end of life. However, in the past decades, medical technologies have transformed our relationship with death and dying. Dialysis for kidney failure presents an especially poignant manifestation of this broader pattern as one of the first organ replacement therapies and now the most common.

Hemodialysis first became an option for treating kidney failure in the 1960s. In light of the miraculous opportunity to live with what was previously a fatal disease, patient requests to withdraw from treatment were perceived to represent a form of psychopathology or suicidality (2). Over the past several decades, there is increasing awareness of burdens and sometimes low quality of life for many people on dialysis, especially for the growing population of older adults and people with multiple comorbidities. These insights underline the importance of tailoring decisions about initiating and withholding dialysis to individual patient circumstances and goals (3) (Table).

An increasing emphasis on shared decision-making around initiating and withholding dialysis is intended to support patient autonomy (3). However, this shift also brings new and complex existential challenges about the meaning and character of the end of life for people receiving dialysis. These themes are reflected in an extensive body of qualitative work from social scientists Russ, Shim, and Kaufman who conducted interviews and observed care for older adults receiving dialysis (4). The very presence of a "choice" about how much time is left or when one will die is a relatively new phenomenon that confers responsibility and perception of control to a patient or their family over what has traditionally been a mysterious and uncontrolled event (5). A choice to stop dialysis may provoke moral distress, anxiety, and guilt among patients and family members (6). Patients and families may be overwhelmed by existential questions and defer active decisions (4), in which case care reverts to a strong system default to continue dialysis. However, although dialysis treatment can extend life, it also "cannibalizes the quality of the time it creates," and some patients describe feeling trapped in a prolonged experience in which "living and dying increasingly shade into one another" (4).

Although the end of life has always presented existential questions, advances in medical technology have changed the character of these questions, and patients with kidney failure report significant gaps in existential and supportive care needs (7). Clinician education on spiritual practices and interventions such as meditation exercises (8) may offer tools to actively support patients, and screening questions, including "Are you at peace?" (9), may serve to open a dialogue. More flexible approaches to palliative dialysis may alleviate a false dichotomy of choice between dialysis or hospice that rarely aligns with overlapping goals for both longevity and quality of life (10). Of course, no intervention will address the profound existential challenges inherent to the human condition, but simply understanding and acknowledging this complex experience for people with kidney failure represent important steps toward more person-centered care. ■

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Table. Support for patients with kidney diseases in navigating existential challenges at the end of life

Topic	Key messages and references for practical resources
Prognostication and advance care planning	• Offer honest prognostication about longevity and quality of life. Consider using a conceptual framework, such as "best case/worst case," to communicate likelihood and range of possible futures (11). • Engage in an ongoing discussion about future care centered on understanding values, treatment preferences, and goals (12). This activity may include, but is not limited to, completion of advance directives and identification of surrogate decision-makers.
Shared decision-making	• Support culturally competent shared decision-making about treatment options for kidney failure tailored to individual care needs and goals (3, 13). • Involve family and/or other close persons in discussions and planning.
Symptom management, palliation, and spiritual support	• Incorporate symptom management and support functionality across the spectrum of kidney diseases (14). • Offer flexible treatment options for kidney failure to uphold overlapping values around longevity and quality of life, including conservative kidney management and palliative dialysis (10, 15). • Elicit needs, and offer emotional and spiritual support for contending with challenges at the end of life (9, 16).

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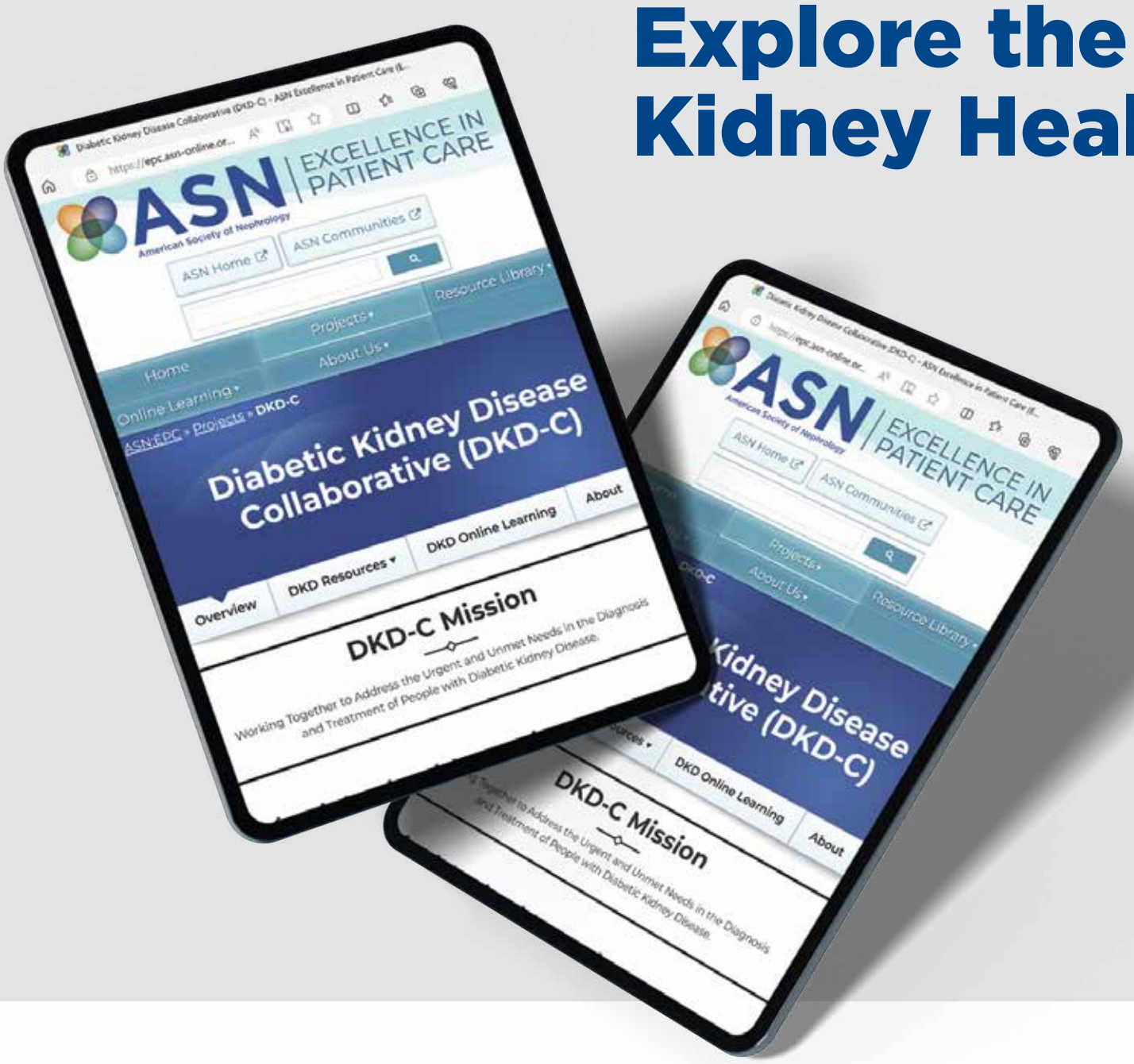

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Serving the Underserved

The following article is the final part of a five-issue series focused on caring for patients in underserved populations. Inspired by several sessions at Kidney Week 2023, this series has featured unique patient and physician perspectives, explained legal protections and limitations, and has sought to identify opportunities to improve kidney care for these communities. In this final article, we focus on the mental and emotional well-being of clinicians—pivotal in effectively caring for patients with kidney diseases and their mental health.

Bolstering Clinician Mental Health and Well-Being

By Bridget M. Kuehn

Justin Bullock, MD, MPH, a nephrology fellow at the University of Washington, is very open about living with bipolar disorder with his colleagues and patients. He wears a jacket that identifies himself as a "doctor with a disability," which often opens the door to positive patient conversations. "Patients seem so much more comfortable after they ask me about it," Bullock said in an interview with *Kidney News*. "It makes them feel I'm more of a human, less of a robotic doctor."

He says that feeling like he can be himself at work and open about his mental health makes him a better physician. He uses the intense focus and ability to sometimes operate on less sleep that comes with his condition, and he is also able to better connect with patients with kidney diseases who are often facing enormous health challenges and coping with their own mental health struggles.

During a Kidney Week 2023 presentation, Bullock shared his view that nephrology can leverage clinician mental wellness to serve patients better (1). His advocacy reflects a growing reckoning in medicine with how systems and culture may impair clinician well-being, fueling burnout, attrition, and poor patient care. The US Surgeon General (2) and the National Academy of Medicine (3) have published reports highlighting the need to better support clinician wellness and have provided roadmaps for institutional change. Some training programs and workplaces are already implementing changes at their institutions to streamline administrative burdens, give physicians greater autonomy, and emphasize clinician wellness.

"When physicians feel like they're working for an organization that has values consistent with their own values, that decreases burnout and increases professional fulfillment," said Mickey Trockel, MD, Director of Evidence Based Innovation for the Stanford University School of Medicine WellMD Center. "When physicians are working in an environment with policies and procedures that make sense and increase efficiency, they're less likely to experience burnout as well."

Preexisting conditions

Burnout, exhaustion, and moral distress were preexisting conditions in the health care workforce when COVID-19 hit, driving many clinicians closer to the breaking point, according to the US Surgeon General's advisory (2). A 2019 National Academy of Medicine report found that 34% to 54% of nurses and physicians and 45% to 60% of medical students and residents reported symptoms of burnout (4). "Physicians are more likely to reduce their hours or leave their place of practice if they are burnt out," Trockel said.

Burnout and poor work environments contribute to work–personal life conflicts and higher rates of anxiety and depression among clinicians, according to the Surgeon General's report (2). Patient care often suffers, with studies linking burnout, poor clinician well-being, and resulting sleep disturbances with more patient complaints and medical errors that cause patient harm (5, 6).

Nephrologists are not immune to these challenges. A 2020 survey found that 30% of first- and second-year nephrology fellows reported burnout; 28%, emotional exhaustion; and 14%, feelings of depersonalization (7). Women and fellows who reported work–life conflicts or dealing with disruptive behavior from other physicians were more likely to experience burnout. "Nephrology is unique in requiring collaborative efforts with so many other health care professionals," said the survey's lead author Varun Agrawal, MD, FASN, associate professor of medicine (nephrology) at The Robert Larner, M.D., College of Medicine at the University of Vermont in Burlington. "There are a lot of opportunities for differences of opinion or disagreements in nephrology."

Approximately one-third of fellows also reported depressive symptoms in the survey. Factors linked with depressive symptoms were lack of social support and strong department leadership and a poor work–life balance. In a 2021 survey, nephrology fellows also frequently reported moral distress—when a physician feels they cannot take the ethically appropriate action (8). Providing dialysis care that they felt was futile or not beneficial to the patient was a source of moral distress for three-quarters of the trainees. Moral distress contributes to burnout; almost 30% reported that they had thought about leaving their fellowships, and 1 in 10 was considering quitting when they completed the survey. In fact, 2022–2023 Accreditation Council for Graduate Medical Education data show that nephrology fellows account for one in five of the internal medicine fellows who withdraw before completing their fellowships (9).

"Burnout and depressive symptoms in nephrology fellows highlight the need for optimal support of mental health and well-being," Agrawal said. "One may wonder if burnout in nephrology plays any role in fewer residents wanting to get into nephrology, fellows staying in training, or attendings leaving nephrology practice, when compared with other specialties."

Another survey of 457 nephrologists, published in 2022, found that one in four reported experiencing burnout; 21%, emotional exhaustion at least once a week; 9%, depersonalization at least once a week; and 7%, both emotional exhaustion and depersonalization both weekly or more often (10). Those who reported burnout said their work hours, burdensome electronic medical record requirements, lack of time with family and friends, and clinic workloads were the main drivers. Other contributors described a decreased sense of autonomy, lack of sense of purpose or connection with work, low reimbursements or the financial strain, and lack of focus on patient well-being.

Trockel reflected that the culture of medicine may contribute to burnout. He noted lack of self-compassion—a culture that condemns errors or imperfections rather than supporting growth—and that perpetually deferring self-care affects physicians more than other fields.

Additionally, physicians face a greater likelihood of work–life conflict. All of these factors can contribute to burnout or poor mental health. "Doctors are humans, and humans experience depression," Bullock said.

But the culture of medicine or stigma associated with mental health conditions in the field can be barriers to seeking help, Bullock explained. Physicians often pride themselves on pushing through difficult situations, and physicians are often portrayed in the media as being unaffected by the difficulties they experience, which may discourage help-seeking, he noted. "We're often praised for being great in some way; it makes people very hesitant to want to ask for help and get help. What turns out to be a small problem can amplify to a bigger problem because there's societal judgment around mental illness, but then there's certainly judgment [in the field of medicine] that's on top of that," Bullock said.

Culture of care

Fostering cultures that emphasize care for physicians and their well-being can help. Trockel noted that when Stanford began offering a specialized mental health service for residents and fellows over 1 decade ago, approximately 50 to 60 trainees took advantage of the service the first year (11). But last year, 300 used the service. He noted that increased awareness and reduced stigma have led to greater uptake. "The difference in stigma comes from people getting help, then telling their friends, and seeing the fears they had about bad things happening are unfounded," he said.

One fear that has held some physicians back from seeking mental health is that they may worry it could affect their licensure. However, Trockel explained that most states have updated their licensure requirements to prevent this, and he is not aware of any trainees who have used the service and encountered problems with licensure. Dozens of medical associations are also lobbying for reauthorization of the 2022 Dr. Lorna Breen Health Care Provider Protection Act, which made $103 million available to 44 health care organizations to implement clinician well-being programs and for additional changes to protect physicians who seek mental health help (12). The law honors an emergency department physician who died by suicide during the pandemic.

The 2020 survey results also point to potential factors that may protect nephrologists against burnout or poor mental health (7). For example, this survey of nephrology fellows found that having social support, good work–life balance, and strong program leadership were associated with lower rates of burnout or depressive symptoms. Agrawal and coauthors noted that some fellowship programs are experimenting with new models, such as having "nephro-hospitalists" who focus on handling in-patient consultations for a specific part of the hospital, restructuring how fellows manage night calls, or adding nonteaching clinicians such as nurse practitioners or physician assistants to help support the nephrology service. "Program directors have to come up with novel, creative ways of supporting fellows through the nephrology program and helping them achieve a good balance between their work and personal lives," he said.

Bullock said that he paid careful attention to how programs treated their fellows when choosing a program. He had selected his fellowship program at the University of Washington because he felt comfortable being open about his bipolar disorder during the application and interview process. He also felt supported by Cary Paine, MD, program director of the Nephrology Fellowship Program at the University of Washington, who became the director of the fellowship program shortly before Bullock's arrival and worked with him to develop a plan for managing any issues related to his condition. "It felt like he cared about 'Justin' as a person," Bullock said. Creating environments in which fellows feel like they can be their authentic selves and are comfortable asking for what they need is essential, he reflected.

Paine said that the program prioritizes fellow and faculty well-being. If someone needs time off, he prioritizes that over staffing. That approach is made possible by institutional and division leadership support, staffing redundancy, and a jeopardy coverage pool, he said. He also noted that it is essential that the division is not overly reliant on the fellows. He said attendings in the program are willing to step in and do not feel fellows' work is beneath them. "It's important for fellows to be integral to the team, but the system has to be able to operate and not crumble when a fellow is absent," Paine said.

Bullock said not being able to do things that are important to you is a big driver in burnout in fellows. But feeling that your requests are taken seriously and granted, when possible, helps and makes it easier to accept when the answer is no. "When you feel like your team will go to bat for you, then you'll go to bat for your team," he said.

Many resources are available for programs and program directors who want to improve the well-being of faculty and trainees. Trockel highlighted the Surgeon General's report and recommendations (2). The National Institute for Occupational Safety and Health's Impact Wellbeing program, which was developed in coordination with the Dr. Lorna Breen Heroes Foundation, details evidence-based interventions to help institutional leaders build health systems in which health care workers thrive (13). Programs like Stanford's WellMD program (11), which studies and advocates for institutional approaches to improve clinician well-being, and conferences like the American Conference on Physician Health or the International Conference on Physician Health also provide information on best practices and emerging research.

Bullock emphasized that taking these steps is essential to improving patient care: "If we cannot care for the mental and physical health of [ourselves and our colleagues], then I don't believe that it is ever possible to be able to do so effectively for patients." ■

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Send your idea to the ASN *Kidney News* Fellows First column at kidneynews@asn-online.org

ASN Advocacy Makes Early Progress in United States and Abroad

ASN advocacy delivered early progress on an ambitious policy agenda as 2024 began. Building upon a year of historic accomplishments, including the first significant steps to reform the US transplant system since its establishment over 40 years ago, ASN's 2024 policy priorities (1) set a course to build on this progress and achieve kidney health for the more than 850 million people living with kidney diseases internationally, including 37 million people in the United States.

Massive funding increase for transplant modernization

On March 23rd, President Joe Biden signed into law the fiscal year 2024 (FY24) Labor, Health and Human Services, Education, and Related Agencies (LHHS) appropriations bill, which included funding for several ASN priorities, particularly a large $23 million funding increase to continue transplant modernization.

The LHHS appropriations bill includes the majority of health programs funded by the federal government, including the entirety of the US Department of Health and Human Services (HHS). HHS had been operating under a series of temporary funding agreements or continuing resolutions since the start of the federal FY24 on October 1, 2023, hampering the ability of HHS to enact important policy reforms such as the Securing the US Organ Procurement and Transplantation Network (OPTN) Act and the Health Resources and Services Administration (HRSA) OPTN Modernization Initiative—twin policy initiatives supported by ASN in 2023 to transform the US transplant system (2).

The final FY24 LHHS funding bill signed by Biden included a total of $59 million to implement the reforms called for in the Securing the US OPTN Act and proposed as part of the HRSA OPTN Modernization Initiative, a $23 million increase over the prior FY, and the largest increase ever in the program's history. HRSA has requested increases in funding to establish an independent OPTN board, invest in core systems, as well as build out information technology systems that use modern technology and are more capable of meeting the needs of patients and health professionals.

ASN advocates had repeatedly stressed the importance of funding these generational improvements to the transplant system in the lead-up to passage of the legislation. In 2023, 27,000 kidney transplants were performed in the United States, far short of the nearly 100,000 person-long kidney transplant waitlist. Despite this need, more than one in four kidneys are wasted, even though data suggest that many of these unused organs would benefit patients. ASN representatives noted the urgency of increasing transparency and navigability of the transplant system for patients and physicians, particularly through modernizing information technology systems, among other key reforms.

ASN leaders are already encouraging continued investment in the US transplant system in FY25 to continue building on this historic progress. Members of the ASN Council, Policy and Advocacy Committee, Quality Committee, and Transplant Workgroup met with their congressional delegations on April 18th to call for an $8 million increase to continue implementing the Securing the US OPTN Act and the HRSA OPTN Modernization Initiative to help ensure that Congress keeps transplant transformation a priority for FY25 and beyond.

Shaping the HRSA OPTN Modernization Initiative

In addition to advocating for funding, ASN has been engaging extensively with the Biden administration as it designs and implements the HRSA OPTN Modernization Initiative to ensure that it addresses the society's transplant-related policy priorities. The broad strokes of the reform efforts—increased transparency, strengthened transplant system accountability, and an emphasis on equity to improve system performance and allow more patients access to kidney transplant—share a great deal of resemblance to what ASN has advanced. Moreover, the specific policy changes that have come into focus also reflect ASN advocacy efforts. For example, HRSA will soon initiate data collection regarding the period between when a patient is referred for transplant and when a waiting list decision is made, including reporting on referrals to transplant centers and time to patient evaluation—key ASN requests in recent years. These data will help ASN identify and resolve unnecessary barriers to waiting lists that affect patients who would benefit from a transplant.

Complementing this effort, the Centers for Medicare & Medicaid Services (CMS) also recently announced similar transplant-related

changes to the 2728 form for which ASN had advocated, including the addition of data points such as when and to which transplant centers patients are referred. Together, the CMS and HRSA changes will allow ASN to gain a holistic understanding of the referral and evaluation process. This advancement is crucial, as more than half of people with kidney failure under 40 years old with no other major comorbidities are *not* waitlisted, even though many would likely be excellent candidates. By collecting this information, ASN, through policy changes, can design a system that better serves them.

Other changes that ASN is advancing and aiming to see addressed through the HRSA OPTN Modernization Initiative include greater transparency for patients regarding details like program acceptance criteria and facilitating shared decision-making, such as retrospective information about organs offered and declined on their behalf. ASN is also urging HRSA and CMS to align metrics for transplant centers across the two agencies as well as to share crucial CMS patient data (particularly graft survival and mortality data) with HRSA and the Scientific Registry of Transplant Recipients.

In line with the changes made possible by the Securing the US OPTN Act, HRSA will be allowing multiple vendors to support the many functions of the OPTN for the first time in its nearly 40-year history, ushering in competition and ensuring that patients are served by the best-in-class expertise in every aspect of the transplant system. HRSA is expected to issue these Requests for Proposal in the second quarter of 2024.

Reaffirming commitment to diversity, equity, and inclusion in medical education

On March 26th, the American Medical Association and the Council of Medical Specialty Societies—to which ASN belongs—and other health care organizations issued a statement (3) on improving health through diversity, equity, and inclusion, noting: "Excellence in patient care cannot exist until we have a physician workforce capable of caring for our patients and their needs holistically, and until the profession of medicine is accessible to all qualified individuals." ASN will continue to advocate for achieving diversity, equity, and inclusion in the kidney health workforce, for funding medical education, and for nonintervention in the patient–physician relationship.

On April 12th, ASN joined members of the American College of Physicians in support of actions to achieve diversity, equity, and inclusion in medical education. Responding to recent proposals to ban federal funding for medical education that includes reference to such a commitment, ASN and 24 other health professional organizations highlighted research showing the importance of achieving diversity, equity, and inclusion to improve patient outcomes and to strengthen the health workforce—commitments risked by eliminating federal funding for medical education.

New milestones in kidney innovation

On March 27th, the Advanced Research Projects Agency for Health (ARPA-H)—a newly established agency to invest in breakthrough health care technology—announced a program to develop artificial kidneys and other organs using biotechnology and regenerative medicine (4). Building off the success of KidneyX (Kidney Innovation Accelerator) in de-risking the development of an artificial kidney, this announcement marks the first time ARPA-H has invested in kidney innovation.

The announcement follows a March 20th House Ways and Means Committee hearing in which Representative Suzan DelBene (D-WA), cochair of the Congressional Kidney Caucus, pressed HHS Secretary Xavier Becerra on several ASN priorities, including the importance of funding the US transplant system, supporting living donors, and ensuring that people with kidney failure have access to innovation. During the exchange, DelBene secured Becerra's commitment to continued support for cutting-edge innovation in kidney health, including through ARPA-H (5).

Continued provision of oral-only medications by pharmacies

On March 20th, the full House Energy and Commerce Committee reported out—on a 36-to-10 bipartisan vote—an amended Kidney PATIENT Act (6). As passed by the committee, this legislation would extend current policy to keep oral-only medications in Medicare Part D (and distributed by pharmacies) for 2 more years and require HHS to report on outstanding questions surrounding the implementation of this policy. Initially proposed as a 10-year exclusion that faced opposition, the 2-year compromise solution was brokered by DelBene after speaking with members of the kidney community and was passed out of the House Ways and Means Committee earlier in March. The legislation now awaits action on the House floor and in the Senate before becoming law.

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Ensuring success of voluntary kidney payment models

On March 29th, ASN and the Renal Physicians Association (RPA) sent joint organization letters to leaders in Congress and HHS requesting a commitment to addressing increased financial risk facing participants in the Comprehensive Kidney Care Contracting (CKCC) model that is jeopardizing their continued participation. Due to a decision by CMS to apply a retrospective trend adjustment to participation years 2022 and 2023, nephrologists and nephrology practices are facing an unexpected increase in financial risk for prior years and may decide to drop out entirely by the April 30th deadline.

Previously, ASN called for risk corridors within the voluntary models to be capped, one of several solutions offered in the joint ASN and RPA letters to stabilize risk and avoid a drop in participation. The CKCC model incentivizes care coordination, delayed progression of kidney diseases, and increased rates of transplantation—goals shared by ASN to improve the health of people with kidney diseases. ASN will continue to promote improvements to the model to ensure continued participation by nephrologists.

Developing international goals for kidney health

On April 3rd, *Nature Reviews Nephrology* published a landmark international consensus statement by ASN, the European Renal Association (ERA), and the International Society of Nephrology (ISN) titled, "Chronic Kidney Disease and the Global Public Health Agenda: An International Consensus" (7). The three societies emphasized that, despite the growing global problem of kidney diseases—including their disproportionate impact on populations with limited resources, vulnerabilities, and marginalization and being a major contributor to premature death and disability—they are not explicitly included in the major noncommunicable diseases identified by the World Health Organization (WHO). ASN, ERA, and ISN noted that kidney diseases, the third fastest-growing cause of death, have not received adequate attention beyond WHO from governments, multilateral organizations, the media, or health systems.

The consensus statement explains that the increasing rise of kidney diseases is the result of a confluence of factors including but not limited to environmental, social, and medical drivers of the disease. The growth in prevalence around the world can be explained in part by the impact of population growth, aging, diabetes, heart disease, hypertension, and environmental factors such as climate change, toxins, and air pollution, all coupled with a general lack of early detection and awareness among those living with kidney diseases.

The statement featured the following key recommendations:

1. **Improved access to care:** Enhancing the availability of affordable and accessible health care services is paramount to addressing the diagnostic, treatment, and preventive needs of individuals with chronic kidney disease (CKD) and acute kidney injury, especially in resource-constrained settings.
2. **Better prevention strategies:** Effective strategies for preventing CKD and acute kidney injury must be developed through multidisciplinary research and community engagement, with a focus on understanding risk factors and tailoring interventions to local contexts.
3. **Development and scaling of care models:** Implementing balanced, scalable, and sustainable models of care requires collaborative efforts with stakeholder communities and innovative approaches such as task-sharing, digital technologies, and online platforms for training and supervision.
4. **Greater awareness and education:** Awareness campaigns are essential to educate both individuals and primary care practitioners about the importance of early diagnosis and management of CKD, thereby reducing its progression and associated complications.
5. **Addressing social determinants of kidney health:** Recognizing and addressing social determinants of health, such as poverty and lack of access to basic amenities, are crucial steps in mitigating the burden of kidney diseases, particularly among communities that are marginalized.
6. **Increased funding for research and development:** Adequate funding is needed to support research initiatives aimed at developing new treatments, improving understanding of kidney diseases, and addressing global disparities in health care access and outcomes.
7. **International cooperation and coordination:** Collaborative efforts at the international level are vital for promoting effective policies, programs, and knowledge-sharing to prevent, detect, and manage kidney diseases worldwide.
8. **Greater engagement with patient communities:** Meaningful involvement of patient communities is essential for designing patient-centric policies, programs, and services that address the diverse needs and priorities of individuals living with kidney diseases.

The kidney community must continue to advocate that WHO prioritizes global kidney health by listing kidney diseases on its list of major noncommunicable diseases.

In the meantime, ASN will continue to call for improved access to and the novel models of care, better prevention and increased awareness strategies, more funding for research, and greater engagement with patient communities to effectively combat the burden of kidney diseases. A forthcoming article in *JASN* will review ongoing initiatives that ASN has already undertaken to address the causes of kidney diseases in an effort to reduce disease burden and ultimately save lives.

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Use of the Kidney Failure Risk Equation in Clinical Practice

By Heba Elgubtan and Navdeep Tangri

Patients with chronic kidney disease (CKD) and their practitioners and caregivers want to know the risk of kidney failure requiring dialysis to help them make decisions about referral, treatment, and access or transplant planning. The kidney failure risk equation (KFRE) is the most widely used prediction model in nephrology to assess the risk of kidney failure among individuals with CKD (1, 2). Developed in 2011, the equation provides an estimated probability of progression to kidney failure over a 2- and 5-year period (1, 2). The four-variable model includes age, sex, estimated glomerular filtration rate (eGFR), and the urine albumin-to-creatinine ratio and is integrated in clinical practice guidelines (1–3). The eight-variable model includes the initial four variables in addition to serum albumin, serum bicarbonate, serum calcium, and serum phosphorus (Figure). The KFRE's utility lies in its ability to seamlessly integrate into electronic medical record (EMR) systems to guide clinical decision-making for health care professionals to identify high-risk patients with CKD for targeted interventions. It has demonstrated its accuracy across diverse populations and has been validated in over 30 countries worldwide (4).

In a recent article, "Implementation of the Kidney Failure Risk Equation in a United States Nephrology Clinic," by Patel et al., the authors used a mixed-methods design to explore the implementation of the KFRE in nephrology clinics (5). Their findings included an increase in the documentation of KFRE scores over time, reaching 25% of the eligible outpatient nephrology clinic notes by the study's end. However, the adoption of KFRE documentation varied widely among practitioners, with some incorporating scores in more than 75% of notes, whereas others did so in less than 10%. Surveys and focus groups uncovered disparities in utilization of KFRE for clinical decisions, highlighting practitioners' uncertainty about the risk-based thresholds in guiding clinical care (5). Practitioners' perspectives suggested that KFRE scores could have remarkable impact, especially for specific subsets of individuals with CKD, emphasizing the need for additional education to maximize its use.

One of the key takeaways from this study is that it highlights the versatile utility of the KFRE, with aims of extending its relevance beyond nephrology to other disciplines, including the transition from primary care to nephrology. Since its initial validation, independent researchers have confirmed the accuracy of the KFRE, demonstrating its superiority over the subjective opinion of patients or health care practitioners (6–8). Nonetheless, implementation remains mixed due to a lack of trust in prediction equations by some practitioners, along with limitations of the equation in early stages of CKD or in patients with unavailable information about albuminuria (9).

To further aid implementation, we agree with the study's authors and advocate for strategies to fully integrate the KFRE into EMR systems along with the largest laboratory organizations in the United States and worldwide. Specifically, we urge EMR vendors and laboratory groups to automatically report KFRE whenever an individual's eGFR falls below 60 mL/min/1.73 m^2. The study underscores the ongoing need for efforts to optimize KFRE implementation, concentrating on enhancing education of our peers, inside and outside of nephrology, on its interpretation and application.

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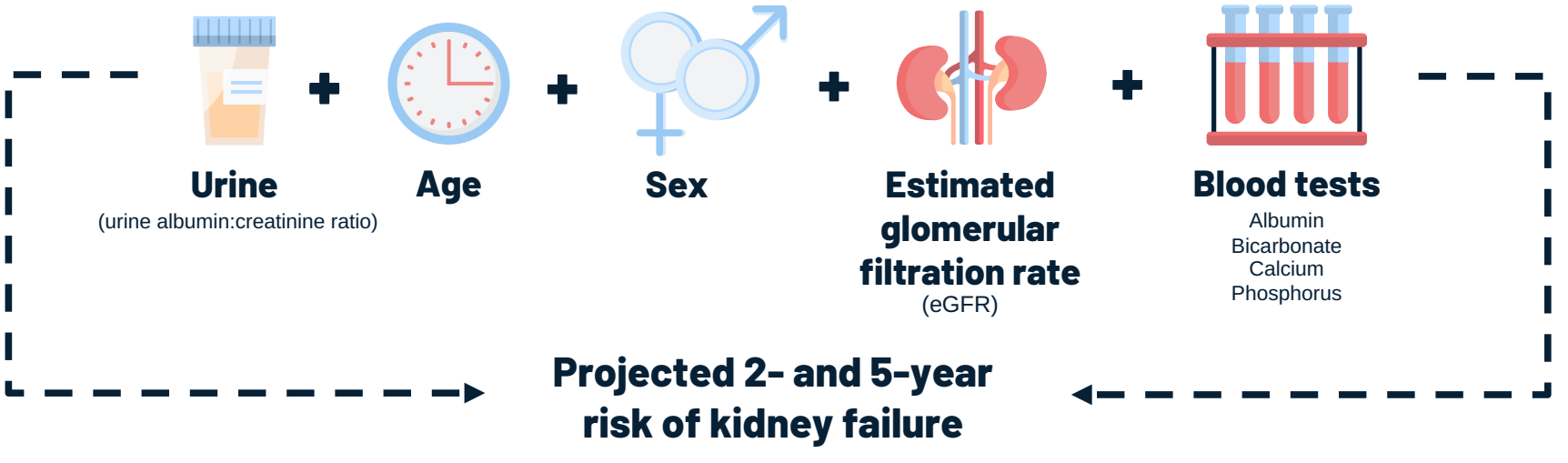
Figure. Eight-variable KFRE model to calculate risk of kidney failure



Importance of Including Nephrology Professionals in Planning for and Responding to Emergencies: Pandemics and Disasters, Both Natural and Manmade

By Matthew Sinclair, Nancy Welder, Vineeta Kumar, and Joseph Kessler, on behalf of the ASN C-ET Lessons Learned and Preparing for the Future Workgroup

The COVID-19 pandemic started in Wuhan, China, in late 2019 and quickly spread worldwide. The first reported patient to die from COVID-19 in the United States was a patient undergoing maintenance hemodialysis in Washington state. Outbreaks in major metropolitan areas in early 2020 threatened the ability of overwhelmed health care delivery systems. The need to save lives and prevent the spread of the infection among patients with chronic kidney disease and health care workers caring for them presented great challenges because these individuals could not isolate at home, and information available from authorities was conflicting. Individuals with the SARS-CoV-2 infection receiving hemodialysis had a worse prognosis than the general population who had the infection. The mortality rate for patients undergoing dialysis was 37% higher in April 2020 compared with the same calendar weeks in 2017–2019 (1). Furthermore, patients who were immunosuppressed because of a transplant or treatment of other chronic diseases were particularly vulnerable to infection and its complications, due to, in part, an associated higher burden of comorbidities (2, 3). Additionally, when health care resources became overwhelmed, transplant and dialysis access surgeries were considered elective.

Expertise from nephrology professionals can aid in making important decisions regarding elective versus essential life-sustaining procedures, reopening health care facilities, restarting immunosuppressive medication protocols for patients who are infected or in close contact with individuals who are infected, and organ procurement safety. The timeline of when a natural disaster or worldwide pandemic will occur is usually unknown; therefore, nephrology professionals should be included in and contribute to preparation activities and be privy to disaster intelligence during actual events. Nephrology professionals can provide coordination and collaboration to ensure that adequate staffing models, equipment, dialysis solutions, filters, and appropriate personal protective equipment are available regardless of where patients receive care—home, hospital, or outpatient.

It is now evident that nephrology professionals were an essential part of responding to many crises during the COVID-19 pandemic. However, the specialized training of nephrology professionals during emergencies is not limited to pandemics. Many emergencies requiring nephrology professionals include but are not limited to weather, fire, mass casualties, earthquakes, terrorist attacks (both biologic and technologic), and building collapses. Emergencies may result in individuals developing acute kidney injury requiring life-sustaining treatment that may result in an unnecessary system burden when advanced preparation is not in place. In addition to individuals with newly diagnosed kidney injury, patients already living with kidney diseases require ongoing life-sustaining therapies; therefore, coordination between emergency services and outpatient dialysis facilities is essential to protect those patients and the people caring for them. Similarly, discharge from acute facilities among patients who are newly diagnosed and medically stable requiring maintenance dialysis in an outpatient setting is critical to reduce the burden on overcrowded hospitals. Coordination of emergency preparedness activities with outpatient facilities is essential to ensure that there is capacity to accommodate the acute influx of patients during a crisis. Similarly, during any crisis, patients undergoing a transplant will need to have access to practitioners and pharmacies to continue receiving critical transplant medications and treatments.

Each emergency, including pandemics and disasters, both natural and manmade, may pose unique challenges that nephrology experts need to plan for in advance, and it is critical that nephrology professionals are included in emergency intel during actual events and allowed to contribute to emergency plan refinement.

To learn more about the profession of nephrology and access additional information and resources, visit ASN Excellence in Patient Care (EPC) online at epc.asn-online.org. The Figure delineates how the COVID-19 and Emerging Threats (C-ET) Workgroup fits under the EPC umbrella, in addition to highlighting completed and ongoing actions of this workgroup. Be sure to review the C-ET and the Emergency Preparedness Initiative pages. You can contact a member of the EPC staff via email at EPC@asn-online.org. Ensure your health care system, community, state, and nation are prepared for the next emergency by informing leaders at all levels of the importance of having nephrology professionals included in emergency preparedness. ■

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Figure. C-ET Workgroup organization and actions

COVID-19 and Emerging Threats

Action	Accomplishment
COVID-19 After-Action Meeting *Learn more:* https://bit.ly/COVIDMEETING	Brought together patients, clinicians, and partners from many areas of government to review the impact of the pandemic and successes and to discuss opportunities.
COVID-19 Virtual Summits *Lessons learned and call-to-action to be published in Fall/Winter 2024:* bit.ly/ASNCET	Bring together community partners from ESRD Networks, CMS, state, and regional officials to review the impact of the pandemic and successes and to discuss opportunities.
Multi-Drug Resistant Organism (MDRO) Compendium *Coming summer of 2024 with the first organisms* Candida auris *and tuberculosis:* bit.ly/ASNCET	Provide knowledge, practical pearls, precautions, and resources to safely care for patients infected or colonized with an MDRO.
Communication channel for the nation's dialysis companies	Share data and experience during regular meetings with clinical leadership of dialysis companies and medical officers from the CDC under the auspices of ASN.
Preparing for a surge blueprint *Coming summer of 2024:* bit.ly/ASNCET	Provide nephrology professionals with foundational steps to prepare for biologic threats.
Leadership in Uncertainty and Crisis Training Module *Coming summer of 2024:* bit.ly/ASNCET	Prepare nephrology professionals with skills and knowledge to lead teams during times of emergencies.

CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare & Medicaid Services; ESRD, End-Stage Renal Disease.

Scan the QR code to view a video companion to this article.

Genetic Alterations Causing Structural Changes of the Diaphanous Inhibitory Domain in Inverted Formin 2 May Contribute to Podocyte Infolding Glomerulopathy

By Liwu Guo, Kenar D. Jhaveri, and Ming Wu

Podocyte infolding glomerulopathy (PIG) was originally reported in 1992 and then proposed as a new disease entity in 2008 (1). There are approximately 160 cases reported globally (2, 3). PIG is characterized by the presence of microtubules and microspheres within the glomerular basement membrane (GBM), podocytic membranous infolding, and foot process effacement. The pathogenesis remains to be illustrated. The largest case series (116 cases) was recently reported by Hong et al. (3). The authors established that a variety of diseases can present with the phenotype of PIG. Additionally, they analyzed alterations in the biochemical constituents of the GBM using laser microdissection and mass spectrometry. Kudose and Stokes (4) reviewed this most recent report and commented that there could be "population-based genetic or epigenetic" alterations that play important roles in the pathogenesis of PIG since most PIG cases are reported from Japan and China. Based on our clinicopathologic observation and currently available literature related to the genetic alteration, we hereby try to understand and explore the possible mechanism that may cause PIG.

The sequence of events leading to podocyte injury begins with the effacement of foot processes, indicating disarray within cytoskeletal structures, including actin filaments and microtubules. This disorganization suggests a potential imbalance in the synthesis and degradation of the cytoskeletal components. Furthermore, a thickened GBM, along with the presence of microtubules and microspheres, as well as the intrusion of the podocyte membrane into the GBM, points to a disruption in the physiologic regulation of substance transport between the podocyte and the GBM. These processes, although seemingly distinct, are actually interrelated steps in a progressive sequence of pathologic changes.

The cytoskeleton dynamics in the podocyte, including the foot process, is intricately regulated by approximately 20 genes, including *ARHGDIA*, *AVIL, CDK20*, *INF2*, *FAT1*, *MAGI2*, and *PODXL*. Genetic alterations causing an even slight impairment of the podocyte cytoskeletal apparatus can result in structural changes in the foot process as well as the slit diaphragm, leading to proteinuria and glomerular disease (5, 6).

The formins family is a group of proteins controlling cellular adhesion, cell shape changes, and morphogenesis by remodeling the actin and microtubule cytoskeletons. As a member, inverted formin 2 (INF2) may play a critical role in the formation of adhesion-associated actin structures adjacent to the extracellular matrix involving cellular protrusions (such as filopodia and lamellipodia), cell migration, and tissue morphogenesis. It also has been reported that INF2 plays roles in actin polymerization and depolymerization as well as microtubule formation (7). Feng et al. (2) reported INF2 genetic alterations (multiple single nucleotide polymorphisms and a nonframeshift deletion) in exon 8 in patients with PIG using whole exome sequencing, although in a very limited number of patients.

INF2 carries the following domains (a simplified scheme from the N to C terminus) and functions: G domain: binding to Rho GTPase; diaphanous inhibitory domain (DID): interacting with the diaphanous autoregulatory domain (DAD); formin homology 1 (FH1) and formin homology 2 (FH2) domains: nucleating G actin and growing the actin filament, also serving the actin filament and promoting formation of stabilized and bundled microtubules; and DAD: binding to the G domain and inhibiting biologic activity of INF2 (Figure, A). In the wild-type, when DID interacts with DAD, this interaction closes the INF2 protein as an inactive status; when Rho GTPase competitively interacts with the G domain, the DID–DAD interaction will be disrupted, opening the INF2 protein in a catalytically active form (Figure, B). When the DID is mutated, it may lose or weaken its capacity to interact with DAD, leaving the mutated INF2 in an active form, letting the FH1 and FH2 to constitutively polymerize actin molecules and stabilize synthesized microtubules (Figure, C) (6).

These excessively synthesized actin filaments and microtubules can accumulate inside the podocyte, physically interact with each other, and eventually be mislocalized. (For example, microtubules will migrate into the foot process and coexist with actin filaments in both filopodia and lamellipodia.) These disorganized microtubules–actin filaments in excessive amounts in the foot process can provide force to extend and deform the membrane lipid bilayer toward the GBM, causing membrane invagination, protruding and abandoning actin filaments, microtubules, and other cellular contents into the GBM (Figure, D). It has been reported that the mutations in the DID, originating from exons 2 to 6, lead to focal segmental glomerulosclerosis (8). We are interested in finding the causative effects of genetic alterations in exon 8 or even exon 7 in PIG.

The podocyte is specifically terminally differentiated, and its gene expression profiling is unique. It would be interesting to isolate and purify the podocyte/foot process (9, 10), then check whole exon expressions, and identify all PIG-related variants using whole exome sequencing. In addition to INF2, genetic alterations from other genes (5, 6) that involve in actin polymerization and severance, the microtubule's stabilization, bundling, or severance can also cause the cytoskeleton changes in the podocyte/foot process.

If the aforementioned hypothesis is proven to be true, it could be easier to decide whether or not PIG is a new disease entity. When PIG is induced by the genetic alterations that lead to the destabilization of the podocytic cytoskeleton, it can be counted as the primary PIG and of course a new entity; if PIG is observed in other diseases (pathogenic immune reactions and inflammation) due to the interruption of the podocytic cytoskeleton organization, it could be categorized as acquired PIG. ■

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The authors report no conflicts of interest.

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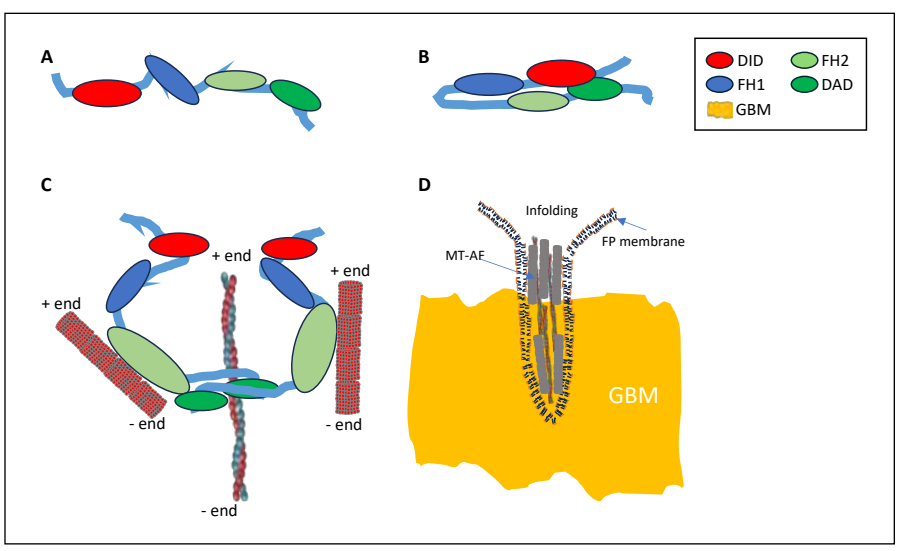
Figure. Pathogenesis of PIG



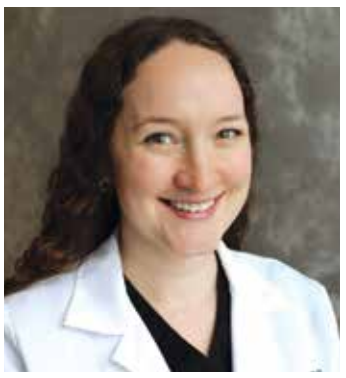
(A) Schematic domains of INF2. (B) Inactive status of INF2 (wild-type). (C) Active status of INF2 (either an activated form of wild-type INF2 or a mutated INF2). (D) Membranous invagination/infolding. AF, actin filament; FP, foot process; MT, microtubule.

Nephrologist "Walks the Walk," Becomes Life-Saving Living Kidney Donor

By Lisa Schwartz

In January 2024, Anna Gaddy, MD, FASN, a nephrologist at Froedtert Hospital and Medical College of Wisconsin, Milwaukee, created quite a buzz on X (formerly Twitter) after her altruistic living kidney donation. Trending hashtags included #Hero, #Walkthewalk, and #SavingALife, and Gaddy was referred to as an angel, a superhero, incredible, and inspiring. Gaddy did not know the person who would be receiving her spare kidney, which continues to spark the conversation about the importance of living organ donation and how directed and nondirected living kidney donations save the lives of those with chronic kidney disease (CKD) and kidney failure.

Gaddy remains a substantial proponent for living kidney transplants and bringing awareness to the topic of live organ donation—something many people, even in the medical community, are not aware of. In the end, she hopes that her selfless act continues to inspire others to "walk the walk" by exploring living kidney donation.



Anna Gaddy, MD, FASN

Q: Why did you decide to become a living kidney donor?

A: Seeing patients [who] I have developed a rapport with day in and day out whose conditions could continue to decline no matter what I do to treat them is very difficult. We've seen several medical advances such as SGLT2 [sodium-glucose cotransporter-2] inhibitors and new treatments for glomerulonephritis over the past few years that help nephrologists improve and prolong the lives of patients. That's hopeful for the future of CKD treatment. Being a living kidney donor, however, was one of the few things I could do now that would improve the life of someone with CKD. We can live with one healthy kidney, and donating the spare kidney is truly lifesaving.

Q: Were you concerned about giving up a kidney that a family member or loved one may need later in life?

A: No, this wasn't a concern. I went through the National Kidney Registry (NKR), which is an amazing organization that helps increase the number of living kidney donor transplants while protecting living donors. I participated in the Family Voucher program [https://www.kidneyregistry.org/for-centers/voucher-program/], which is for donors who give a kidney to a stranger, often for a transplant chain. So, if one of my family members ever needs a kidney transplant in the future, they receive prioritization for a kidney donation. Learning about NKR and that as a nondirected donor, my family will be covered if they ever need a kidney in the future made me feel at peace with my decision. It's like a backup plan, a "just in case."

Q: Was the donor testing process arduous?

A: NKR made testing very easy. [The organization] sent boxes for the bloodwork to my house. I had the choice to go to the lab or to have a phlebotomist sent to my home to do the bloodwork. I had my bloodwork and other tests done where I work at the Medical College of Wisconsin, which is also a kidney transplant center. The process was simple and streamlined.

Q: To dispel any fear, doubts, or even misconceptions that people may have about living donation, can you explain your surgery and recovery process?

A: In the scheme of things, the surgery was relatively easy. The procedure was performed laparoscopically, and one kidney was removed through a 3-inch incision in my abdomen. I was only in the hospital for one night and was up and moving the next day, albeit a bit slowly, which helped my recovery. I managed any discomfort with just [acetaminophen]. As with any surgery, I wasn't allowed to lift anything heavy for a few weeks but was able to shower, cook, and care for myself with no issues almost immediately after the surgery. I took 3 weeks off work to recover but was back at work 2 weeks postsurgery, and to be honest, I could have gone back to work even earlier than that!

Q: As a physician who is used to taking care of others, what was it like being the patient?

A: The good thing was, I was a patient in my own hospital. I love my colleagues and know they're great, empathetic [practitioners], but it was nice to see just how well they cared for me and my loved ones throughout the transplant process. Being a patient and a donor helps me explain the logistics to my own patients going through the transplant journey. I have a better understanding and appreciation for everyone's role in the process.

Q: Has this experience changed the way you approach your job as a nephrologist?

A: I have several patients who will need a kidney transplant in the near future. I share my experience as a living donor with them because it's important for them to see how healthy I am after my surgery. Many transplant recipients feel guilty about taking a kidney from a loved one. I've always been open and compassionate with my patients, and now I feel like I can advocate more for living donation since I've been there myself. I can be more open to helping my patients realize that yes, living donation is a "big ask," but people are more open to that "big give" than they would think.

Q: What do you hope to see in the future of CKD?

A: One of the biggest issues in CKD is that even if we had an unlimited number of kidneys to give to people in need, there are still so many patients, who, by the time they get to us, are no longer transplant candidates. Many people have other chronic but preventable conditions that affect not only their kidneys but the rest of their body. I'm not only an advocate for living kidney donation but also for access to quality, affordable preventive care so that people can better manage their health to limit [CKD] and improve transplant outcomes.

Q: What do you want others to know about living kidney donation?

A: In life, we don't get many chances to do something good. Being a living kidney donor is a way to save and change someone's life even if it is someone we don't know. We donate our money and time to causes we believe in, so why not donate our health if we're able to? I've walked the walk, so to speak, and I'm not asking people to consider doing something I haven't done myself. Living donation is not something healthy people often think about or even know about. Now that I have been through the process, I want more people to understand how doable it is. I never thought about sharing my good health, but what a blessing it has been. ■

Gila Monster Wins NephMadness 2024

By Matthew A. Sparks

NephMadness 2024 has come and gone. The 12th iteration of NephMadness produced some surprising and memorable moments.

NephMadness began in 2013 as a way to celebrate World Kidney Day, educate people on important aspects of kidney diseases, and have fun in the process. Based on the annual US college basketball tournament March Madness, the hottest nephrology topics compete in NephMadness each year with an ultimate winner selected by a Blue Ribbon Panel of nephrologists, trainees, physicians, and patients.

The winning team of NephMadness 2024 was the Gila Monster hailing from the Animal House region. Nephrology boasts a rich tradition of leveraging the intricacies of nature and physiology to unearth therapeutic interventions and unravel the complexities of pathophysiology (think angiotensin-converting enzyme inhibitors and pit vipers or the bark of an apple tree and sodium-glucose cotransporter-2 inhibitors). The Animal House region of NephMadness highlights the kidney physiology of animals, which helps us understand and improve human health. Team Gila Monster (*Heloderma suspectum*) is the latest example and the first time an Animal House region member has won NephMadness in its 4 years in the competition. Team Gila Monster continues to ride the wave of impressive cardiovascular and weight reduction, as well as improved kidney outcomes, derived from its hormone (exendin-4) isolated from its saliva. Exendin-4 is a potent agonist of the glucagon-like peptide 1 receptor (https://ajkdblog.org/2024/03/05/nephmadness-2024-they-may-look-cute-but-are-all-animals-sweet/), which has ushered in a revolution in diabetes and obesity care with medications like semaglutide and tirzepatide.

One of the true joys of NephMadness is seeing the parties that take place all over the world. This year did not disappoint with a neon theme, cookies, cakes, and costumes. The winner of the best party category was the General Hospital of Mexico in Mexico City.

Thanks to everyone who participated and helped make the 2024 tournament a success. The NephMadness Executive Team is already constructing the 2025 tournament. What topics will make the field, and what surprises await in 2025?

Matthew A. Sparks, MD, FASN, is an associate professor of medicine; program director of nephrology fellowship; and lead, Society for Early Education Scholars program, Department of Medicine, Duke University, and staff physician, Durham VA Health Care System, Durham, NC. He is the cocreator of NephMadness and serves as communications editor for the ASN journals.

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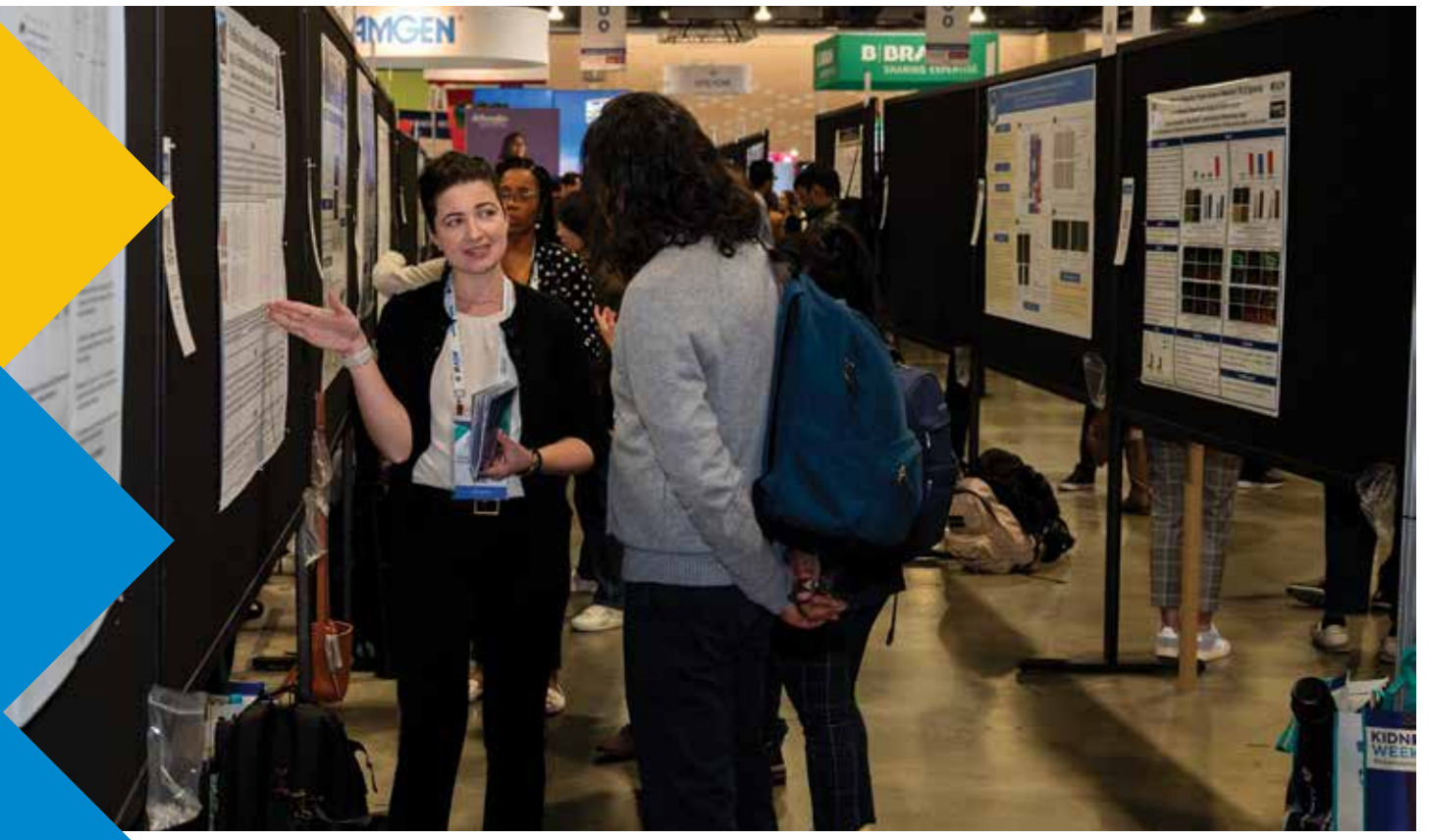

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