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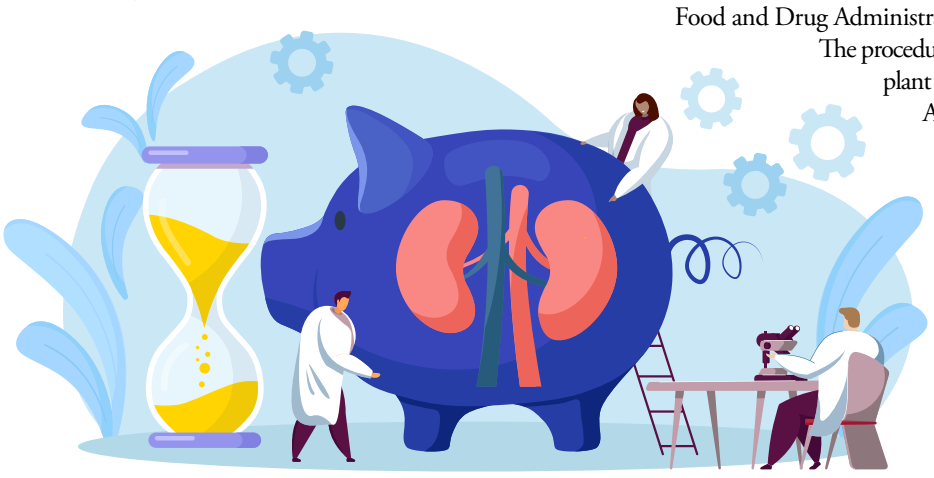
Xenotransplants Make Progress

By Bridget M. Kuehn

In a procedure designed to closely mimic a human-to-human kidney transplant, Jayme Locke, MD, MPH, director of the Division of Transplantation at The University of Alabama, Birmingham, and her colleagues tested the safety and feasibility of transplanting a genetically engineered pig kidney into a human patient with a non-functioning brain.

The results were reported in January 2022 and showed that the genetically modified pig kidneys did not trigger a hyper-rejection reaction, could support human blood pressure, and could produce urine (1). The procedure was one of a string of recent attempts to test the potential of using pig organs as replacements for human organ transplants in preliminary human studies. Last fall, surgeons at New York University (NYU) Langone Health connected genetically modified pig kidneys outside of the body of two deceased donors maintained on ventilators (2). In early January, surgeons at the University of Maryland School of Medicine transplanted a genetically modified pig heart into a living man under a compassionate-use exemption from the US Food and Drug Administration (FDA) (3).



The procedures build on decades of xenotransplant research in non-human primates. According to leaders in the field, this research is progressing toward clinical trials. The hope among Locke and others is that xenotransplantation may help solve the shortage of kidneys available for transplant. Currently, there are approximately 800,000 people living with end stage kidney disease in the United States, but only approximately one-third of them have received a kidney transplant, according to data from the National Institute of Diabetes and Digestive and Kidney Diseases (4). There are approximately 90,000 patients on the waiting list for a kidney, and many will die or become ineligible for transplant during the average 4- to 5-year wait time.

"We're all really humbled to be a small part of this," Locke said. "We all have a common enemy, kidney failure, and we are trying to figure out how we can defeat it and help our patients have access to a cure—kidney transplant."

The pigs used for the kidney transplants at The University of Alabama, Birmingham, and the heart transplant at the University of Maryland were not just any pigs. They were "clinical-grade" animals, raised and housed in highly controlled conditions designed to reduce risk that the pigs could inadvertently spread disease to a human recipient.

Revivicor, a fully owned subsidiary of United Therapeutics, is the company that developed the pigs and leveraged new technologies, including the gene-editing tool CRISPR-Cas9, which genetically engineers the pigs so their organs will be more likely to be accepted by a human recipient. Locke explained that four pig genes encoding carbohydrate antigens were knocked out to prevent the human immune system from immediately rejecting the organ. The pig growth hormone receptor gene was

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Diversity Saves Lives and Drives Excellence in Kidney Health

More Inside

By O. N. Ray Bignall II

You would be hard pressed to find a more capable, resilient, and diverse team of heroes than today's kidney health care workforce. From physicians and nurses to technicians and therapists…from researchers to clinicians to administrative professionals…our field is replete with talented individuals who bring their "all" to achieve equitable, high-quality patient care for the millions of those living with kidney diseases worldwide.

This issue of *Kidney News* is special, because in it, we are highlighting a key ingredient to achieving equitable, high-quality care for children and adults with kidney diseases: our diversity. We acknowledge the ongoing imperative to achieve health equity for racial and ethnic minorities in the United States and beyond. We learn important care considerations for minoritized populations, such as LGBTQ+, rural, and indigenous groups, whose unique concerns are often overlooked by health care teams and society at large. We explore the challenges of delivering high-quality kidney care in low- and middle-income countries, and we even have a special, personal glimpse into the challenges of healing others while seeking healing for oneself.

As you enjoy this special series of articles, it is my hope that you will consider the implications for your own practice and that you will reflect on the power of having diverse teams—around our community and around the world—saving lives, driving for excellence, and working together: united for kidney health. ■

O. N. Ray Bignall II, MD, FASN, is with the Division of Nephrology and Hypertension, Nationwide Children's Hospital, and The Ohio State University College of Medicine, Columbus.

In adult patients with CKD associated with T2D

With KERENDIA, a different pathway leads to different possibilities[1,2]

KERENDIA offers a different path forward

- KERENDIA is the first and only selective MRA with a nonsteroidal structure
- KERENDIA blocks MR overactivation, which is thought to contribute to inflammation and fibrosis that can lead to CKD progression
- In adults with CKD associated with T2D, KERENDIA is proven to slow CKD progression and reduce CV risk

INDICATION:

- KERENDIA is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS:

- Concomitant use with strong CYP3A4 inhibitors
- Patients with adrenal insufficiency

WARNINGS AND PRECAUTIONS:

- ***Hyperkalemia:*** KERENDIA can cause hyperkalemia. The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with KERENDIA and dose accordingly. Do not initiate KERENDIA if serum potassium is >5.0 mEq/L

  Measure serum potassium periodically during treatment with KERENDIA and adjust dose accordingly. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium

MOST COMMON ADVERSE REACTIONS:

- Adverse reactions reported in ≥1% of patients on KERENDIA and more frequently than placebo: hyperkalemia (18.3% vs. 9%), hypotension (4.8% vs. 3.4%), and hyponatremia (1.4% vs. 0.7%)

DRUG INTERACTIONS:

- ***Strong CYP3A4 Inhibitors:*** Concomitant use of KERENDIA with strong CYP3A4 inhibitors is contraindicated. Avoid concomitant intake of grapefruit or grapefruit juice
- ***Moderate and Weak CYP3A4 Inhibitors:*** Monitor serum potassium during drug initiation or dosage adjustment of either KERENDIA or the moderate or weak CYP3A4 inhibitor and adjust KERENDIA dosage as appropriate
- ***Strong and Moderate CYP3A4 Inducers:*** Avoid concomitant use of KERENDIA with strong or moderate CYP3A4 inducers

Learn more about KERENDIA and the FIDELIO-DKD trial

USE IN SPECIFIC POPULATIONS

- ***Lactation:*** Avoid breastfeeding during treatment with KERENDIA and for 1 day after treatment
- ***Hepatic Impairment:*** Avoid use of KERENDIA in patients with severe hepatic impairment (Child Pugh C) and consider additional serum potassium monitoring with moderate hepatic impairment (Child Pugh B)

Please read the Brief Summary of the KERENDIA Prescribing Information on the following page.

CKD=chronic kidney disease; CV=cardiovascular; MR=mineralocorticoid receptor; MRA=mineralocorticoid receptor antagonist; T2D=type 2 diabetes.

References: 1. KERENDIA (finerenone) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; July 2021. **2.** Bakris GL, et al; FIDELIO-DKD Investigators. *N Engl J Med*. 2020;383(23):2219-2229.

Kerendia®
(finerenone) tablets
10 mg • 20 mg

BAYER

PP-KER-US-0016-1 10/21

KERENDIA (finerenone) tablets, for oral use
Initial U.S. Approval: 2021

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Kerendia® is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).

4 CONTRAINDICATIONS

Kerendia is contraindicated in patients:

- Who are receiving concomitant treatment with strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.
- With adrenal insufficiency.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperkalemia

Kerendia can cause hyperkalemia *[(see Adverse Reactions (6.1)]*.

The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with Kerendia and dose accordingly *[see Dosage and Administration (2.1)]*. Do not initiate Kerendia if serum potassium is > 5.0 mEq/L.

Measure serum potassium periodically during treatment with Kerendia and adjust dose accordingly *[see Dosage and Administration (2.3)]*. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium *[see Drug Interactions (7.1), 7.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hyperkalemia *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Kerendia was evaluated in the randomized, double-blind, placebo-controlled, multicenter pivotal phase 3 study FIDELIO-DKD. In this study, 2827 patients received Kerendia (10 or 20 mg once daily) and 2831 received placebo. For patients in the Kerendia group, the mean duration of treatment was 2.2 years.

Overall, serious adverse reactions occurred in 32% of patients receiving Kerendia and in 34% of patients receiving placebo. Permanent discontinuation due to adverse reactions occurred in 7% of patients receiving Kerendia and in 6% of patients receiving placebo. Hyperkalemia led to permanent discontinuation of treatment in 2.3% of patients receiving Kerendia versus 0.9% of patients receiving placebo.

The most frequently reported (≥ 10%) adverse reaction was hyperkalemia *[see Warnings and Precautions (5.1)]*. Hospitalization due to hyperkalemia for the Kerendia group was 1.4% versus 0.3% in the placebo group.

Table 3 shows adverse reactions in FIDELIO-DKD that occurred more commonly on Kerendia than on placebo, and in at least 1% of patients treated with Kerendia.

Table 3: Adverse reactions reported in ≥ 1% of patients on Kerendia and more frequently than placebo in the phase 3 study FIDELIO-DKD

Adverse reactions	Kerendia N = 2827 n (%)	Placebo N = 2831 n (%)
Hyperkalemia	516 (18.3)	255 (9.0)
Hypotension	135 (4.8)	96 (3.4)
Hyponatremia	40 (1.4)	19 (0.7)

Laboratory Test

Initiation of Kerendia may cause an initial small decrease in estimated GFR that occurs within the first 4 weeks of starting therapy, and then stabilizes. In a study that included patients with chronic kidney disease associated with type 2 diabetes, this decrease was reversible after treatment discontinuation.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors and Inducers

Strong CYP3A4 Inhibitors

Kerendia is a CYP3A4 substrate. Concomitant use with a strong CYP3A4 inhibitor increases finerenone exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Kerendia adverse reactions. Concomitant use of Kerendia with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4)]*. Avoid concomitant intake of grapefruit or grapefruit juice.

Moderate and Weak CYP3A4 Inhibitors

Kerendia is a CYP3A4 substrate. Concomitant use with a moderate or weak CYP3A4 inhibitor increases finerenone exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Kerendia adverse reactions. Monitor serum potassium during drug initiation or dosage adjustment of either Kerendia or the moderate or weak CYP3A4 inhibitor, and adjust Kerendia dosage as appropriate *[see Dosing and Administration (2.3) and Drug Interaction (7.2)]*.

Strong and Moderate CYP3A4 Inducers

Kerendia is a CYP3A4 substrate. Concomitant use of Kerendia with a strong or moderate CYP3A4 inducer decreases finerenone exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of Kerendia. Avoid concomitant use of Kerendia with strong or moderate CYP3A4 inducers.

7.2 Drugs That Affect Serum Potassium

More frequent serum potassium monitoring is warranted in patients receiving concomitant therapy with drugs or supplements that increase serum potassium *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Kerendia use in pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal studies have shown developmental toxicity at exposures about 4 times those expected in humans. *(see Data)*. The clinical significance of these findings is unclear.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. 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.

Data

Animal Data

In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of 19 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provide safety margins of 10 to 13 times for the $AUC_{unbound}$ expected in humans.

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provides a safety margin of about 2 times for the $AUC_{unbound}$ expected in humans.

8.2 Lactation

Risk Summary

There are no data on the presence of finerenone or its metabolite in human milk, the effects on the breastfed infant or the effects of the drug on milk production. In a pre- and postnatal developmental toxicity study in rats, increased pup mortality and lower pup weight were observed at about 4 times the $AUC_{unbound}$ expected in humans. These findings suggest that finerenone is present in rat milk *[see Use in Specific Populations (8.1) and Data]*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential risk to breastfed infants from exposure to KERENDIA, avoid breastfeeding during treatment and for 1 day after treatment.

8.4 Pediatric Use

The safety and efficacy of Kerendia have not been established in patients below 18 years of age.

8.5 Geriatric Use

Of the 2827 patients who received Kerendia in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients. No dose adjustment is required.

8.6 Hepatic Impairment

Avoid use of Kerendia in patients with severe hepatic impairment (Child Pugh C).

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment (Child Pugh A or B).

Consider additional serum potassium monitoring in patients with moderate hepatic impairment (Child Pugh B) *[see Dosing and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of suspected overdose, immediately interrupt Kerendia treatment. The most likely manifestation of overdose is hyperkalemia. If hyperkalemia develops, standard treatment should be initiated.

Finerenone is unlikely to be efficiently removed by hemodialysis given its fraction bound to plasma proteins of about 90%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Finerenone was non-genotoxic in an in vitro bacterial reverse mutation (Ames) assay, the in vitro chromosomal aberration assay in cultured Chinese hamster V79 cells, or the in vivo micronucleus assay in mice.

In 2-year carcinogenicity studies, finerenone did not show a statistically significant increase in tumor response in Wistar rats or in CD1 mice. In male mice, Leydig cell adenoma was numerically increased at a dose representing 26 times the $AUC_{unbound}$ in humans and is not considered clinically relevant. Finerenone did not impair fertility in male rats but impaired fertility in female rats at 20 times AUC to the maximum human exposure.

17 PATIENT COUNSELING INFORMATION

Advise patients of the need for periodic monitoring of serum potassium levels. Advise patients receiving Kerendia to consult with their physician before using potassium supplements or salt substitutes containing potassium *[see Warnings and Precautions (5.1)]*.

Advise patients to avoid strong or moderate CYP3A4 inducers and to find alternative medicinal products with no or weak potential to induce CYP3A4 *[see Drug Interactions (7.1)]*.

Avoid concomitant intake of grapefruit or grapefruit juice as it is expected to increase the plasma concentration of finerenone *[see Drug Interactions (7.1)]*.

Advise women that breastfeeding is not recommended at the time of treatment with KERENDIA and for 1 day after treatment *[see Use in Specific Populations (8.2)]*.

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Xenotransplants Inch toward Clinical Trials

Continued from cover

also removed to prevent the pig organ from outgrowing the available space in its new recipient. Six human genes were also inserted to help modulate the human immune response to the organ, reduce inflammation, and help prevent blood clots.

"[The changes] were designed to humanize the pig enough that the pig kidney could be tolerated with conventional immunosuppressive drugs used after human transplant," Locke said.

Locke and her colleagues also developed an assay to test whether the donor pig and the human recipient were a match and whether the person had preexisting antibodies to pigs. The test predicted a match, which their procedure confirmed without risking a human life, she said.

Within 20 minutes, one of the kidneys was already producing urine, which surprised and excited the team, Locke said. The other organ also produced urine but not as much, and neither achieved creatinine clearance, she said. Locke said she and her colleagues did not expect to achieve either urine or creatine creatinine in a recipient because of physiological changes that occur after brain death. The experiment ended 3 days later after the patient experienced multi-organ failure.

The surgical team at NYU Langone also used pigs developed by Revivicor, but the animals underwent only one genetic change to knock out the pig antigen galactose-α-1,3-galactose (alpha-gal) to prevent immediate rejection, said Robert Montgomery, MD, DPhil, H. Leon Pachter, MD, Professor of Surgery and chair of the Department of Surgery at NYU Langone, who performed the surgeries. That genetic modification was made using a technology called homologous recombination. Additionally, the pig's thymus gland was fused to the kidney before the transplant to help "educate" the immune system, according to the university's announcement (2).

Instead of replicating a transplant procedure, the kidneys were attached outside of the body to blood vessels in the legs of the two recipients to allow close monitoring. Because of the short duration of the procedure—a little over 2 days—the recipients received only steroid medications and the drug mycophenolate mofetil. After both procedures, urine production and creatinine levels were similar to what would be seen after a human transplant, said Montgomery, who is also director of the NYU Langone Transplant Institute. He and his colleagues plan to conduct additional pre-clinical studies with patients who are on life support to monitor for signs of organ rejection over a longer period.

The procedure at the University of Maryland was conducted under a compassionate-use exemption from the FDA, which enables patients with life-threatening conditions to take experimental drugs or undergo experimental procedures (3). The patient was hospitalized with a life-threatening arrythmia and had been on extracorporeal membrane oxygenation for weeks. The patient did not qualify for a human heart transplant and was ineligible for an artificial heart pump.

The patient received traditional immunosuppressive drugs along with an experimental anti-CD40 medication after the pig heart transplant (5). Montgomery noted that many professionals in the field of xenotransplant suspect that anti-CD40 or related anti-CD154 medications will be essential for human xenotransplant based on results from studies in non-human primates.

"This is the culmination of years of highly complicated research to hone this technique in animals with survival times that have reached beyond nine months," said Muhammad Mohiuddin, MD, professor of surgery at the University of Maryland School of Medicine and scientific director of its Cardiac Xenotransplantation Program, in a statement from the university (3). "The successful procedure provided valuable information to help the medical community improve this potentially life-saving method in future patients."

At press time, more than 3 weeks after the procedure, the patient continued to do well.

"Every day that patient continues to thrive is a great day for that patient and a great day for the field [of xenotransplant] in general," said Alfred Joseph Tector, MD, a transplant surgeon and professor of surgery at the University of Miami.

Although the preclinical studies in pig kidney transplantation in patients without brain function and the recent pig heart transplant in a living recipient may help build confidence in the potential of xenotransplants, they will not replace traditional clinical trials, Montgomery said.

A preliminary phase 1 clinical trial in a small number of human patients, who could choose to participate in the trial or choose an alternative treatment, conducted at a few transplant centers would be the necessary next step before more widespread human use, according to Montgomery. Already, several groups, including Locke's team at The University of Alabama, Birmingham, are working toward the goal of launching preliminary clinical trials.

Montgomery predicted the trials could begin in the next year with FDA approval. Such a trial would help determine if there are any other incompatibilities between a pig kidney and a human donor and whether a pig kidney would be able to perform functions beyond just toxin clearance, such as maintaining electrolyte balance, stimulating red blood cell development, and helping control blood pressure.

"All of these things would be watched really closely to see if the pig kidney would fully replace the function of a human kidney," Montgomery said.

David Cooper, MD, PhD, a senior research fellow at the Center for Transplantation Sciences at Massachusetts General Hospital, agreed that preliminary clinical trials are a necessary next step toward xenotransplantation. He noted that studies in human patients without brain function will not be able to provide definitive answers on the function of transplanted pig kidneys in humans, because brain death causes overwhelming inflammation and poor oxygen use, and other hemodynamic and metabolic changes occur that could harm the transplanted kidney. Cooper was awarded a Kidney Innovation Accelerator (KidneyX) award from the US Department of Health and Human Services and the American Society of Nephrology in 2021 to expand his studies of genetically modified pig kidney transplants in non-human primates (6).

"What we need to do now is to be bold and do a few transplants in some patients who are carefully selected by a team that has experience in the [non-human primate] xenotransplant model," Cooper said.

Some patients on dialysis who are waiting for a human kidney transplant might benefit from participating in a pig xenotransplant clinical trial if it could give them a break from dialysis for several months to 2 years, he suggested.

"The potential is there for patients to gain a lot," Cooper said. "Patients always feel much better when they have a functioning kidney than when they are on dialysis."

Tector cautioned that it is important to take all the steps that the FDA requires before moving forward toward a clinical trial—even if further clinical studies in non-human primates will be challenging. Among the necessary next steps are the need to determine the best immunosuppressive regimen to use in clinical trials, which he agrees will likely include anti-CD40 or anti-CD154 antibodies. Tector was also awarded a 2021 KidneyX award as part of a team from Makana Therapeutics (the Regenerative Medicine Division of Recombinetics), which is working on a genetically engineered triple-knockout pig (7).

Tector said the success of human transplants raises the bar for what the public and the FDA will expect from the results of the first xenotransplant clinical trial. He explained that early human-to-human transplants had a high fatality rate, and some patients only lived for a short period of time.

"We have the opportunity to help the first person right out of the blocks," he said.

Cooper said he expects that if the clinical trials are successful then xenotransplants will undergo a steady evolution where they will progressively improve the way human transplants live. He noted that for the first time, using genetically modified pigs creates the opportunity to modify the donor, which could help reduce the need for posttransplant medications.

"It will revolutionize organ transplant," he said.

For Montgomery, the stakes are very personal. He is a heart transplant recipient because of a rare genetic condition that affects members of his family. As such, he knows how difficult it is for patients awaiting a transplant.

"I've spoken to a lot of other patients, and we want to see progress," he said. "It needs to be safe, well thought out, closely monitored, and regulated. But we do want to see this move forward." ■

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Study Examines Use of Palliative Care for Patients with COVID-19 and Acute Kidney Injury

By Tracy Hampton

Historically, there has been low use of palliative care in patients with acute kidney injury (AKI), even when requiring kidney replacement therapy, but does this trend hold true in patients with AKI who also have COVID-19? That's the question posed by a recent study in *CJASN* that analyzed New York University (NYU) Langone Health's electronic health data of COVID-19 hospitalizations between March 2, 2020, and August 25, 2020.

"This research is important because palliative care is often an untapped resource that can help patients and families cope with difficult situations. Serious acute illness is an overwhelming time for patients and families and early referral to palliative care may help alleviate some of this distress," said lead author Jennifer S. Scherer, MD, of the NYU Grossman School of Medicine.

For the study, Scherer and her colleagues analyzed data from three acute care hospitals located in Manhattan, Brooklyn, and Long Island. Among 4276 adults with COVID-19 who were treated there, 1310 (31%) developed AKI.

"We were interested in seeing the role that palliative care played for this patient population, because during this initial surge, there were so many moving parts that went into caring for a patient with COVID-19—new information about the disease was being uncovered every day, and the amount of kidney injury we saw was unexpected and associated with a high mortality," Scherer said.

The team found that compared with patients without AKI, those with AKI received more palliative care consults (42% vs. 7%), but they occurred significantly later (10 days from hospital admission vs. 5 days).

Patients with AKI had a 1.81 times higher odds of receiving palliative care than those without AKI, even after controlling for markers of critical illness, such as admission to intensive care units or the use of mechanical ventilation.

Sixty-six percent of patients with AKI who initiated kidney replacement therapy received palliative care vs. 37% of those with AKI not receiving kidney replacement therapy. Palliative care consults also occurred later for those who were started on kidney replacement therapy compared with those who were not (12 days from admission vs. 9 days).

Even though they had a greater use of palliative care, patients with AKI had a significantly longer length of hospital stay, more intensive care unit admissions, and more use of mechanical ventilation.

Finally, compared with those without AKI, a higher proportion of those with AKI died during hospitalization (46% vs. 5%) or were discharged to inpatient hospice (6% vs. 3%), whereas a lower proportion were discharged home (24% vs. 77%).

Therefore, despite an elevated risk of death associated with AKI, consultation for palliative care in patients with AKI was delayed and was not associated with reduced initiation of life-sustaining interventions.

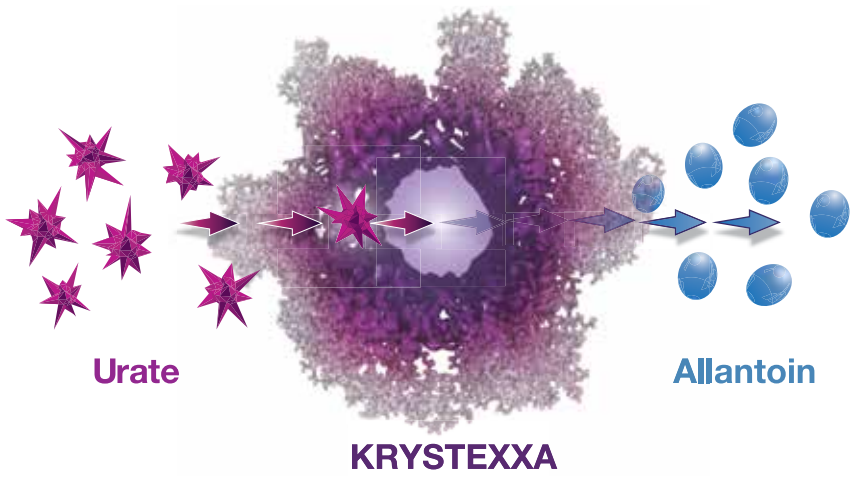
"In this study, we found that, as expected, patients with AKI were seriously ill and had a high mortality rate, but what was not expected was that palliative care was often called later in the hospital course than for those without AKI despite having such a high mortality," Scherer said. "There are several clinical explanations for this, however given the high mortality it does suggest that patients and families could have benefited from earlier support from palliative care." Therefore, AKI might serve as a trigger for proactive and early involvement of palliative care.

Scherer stressed that palliative care supports primary doctors in caring for seriously ill patients by managing emotional and physical symptoms while also assisting in advance care planning. Importantly, it can be incorporated into the care plan of someone who is pursuing curative care and can be helpful in an acute and possibly reversible situation. Perceptions of palliative care as an add-on service rather than a proactive consultation that can provide guidance and support and alleviate physical and emotional suffering can lead to missed opportunities.

An accompanying *Patient Voice* article, written by two members of the national patient and policy leadership team for the American Association of Kidney Patients (Edward V. Hickey, III, and Paul T. Conway), cautions against the generalization or extrapolation of this research, however. "We do not question the sincerity of the authors and their desire to contribute to palliative care deliberations; however, the research lacks quantitative or qualitative patient insight data or patient and family perceptions of palliative care," the authors wrote. "The study does not meet the minimum standards of justification to support any system-wide changes that could interfere with the perceived viability of kidney patients, including AKI patients, and expected care norms during a medical crisis."

The article, titled "Utilization of Palliative Care for Patients with COVID-19 and Acute Kidney Injury during a COVID-19 Surge," and the *Patient Voice* article, titled "COVID-19 and Palliative Care: Observations, Extrapolations, and Cautions," are available at http://cjasn.asnjournals.org/.

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN[1]



Artist's renditions.

RENAL EXCRETION OF ALLANTOIN IS UP TO 10 TIMES MORE EFFICIENT THAN EXCRETION OF URIC ACID[2]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

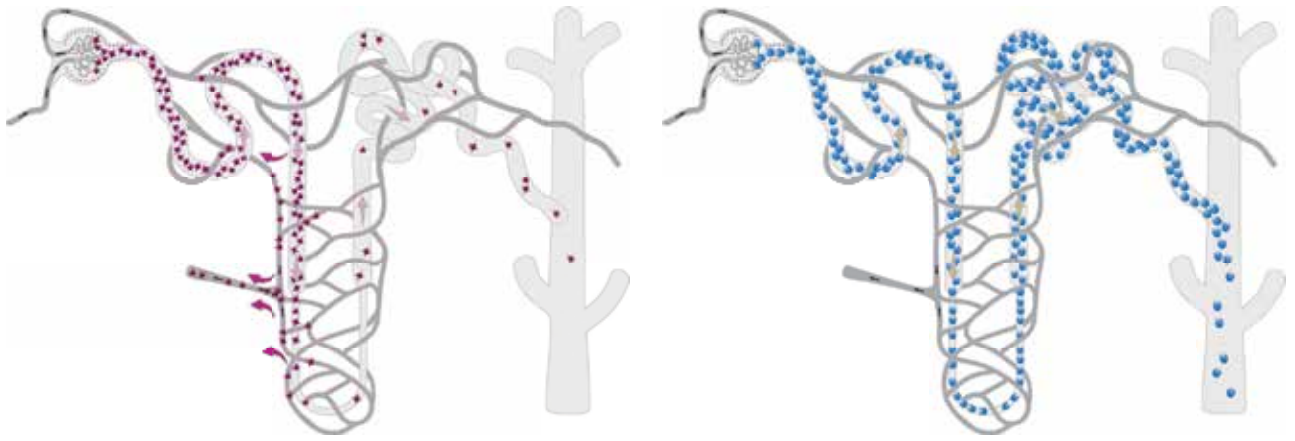
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.

HORIZON

URICASE ENZYME THAT CONVERTS URATE



Only 10% of uric acid filtered through the kidney is excreted[3]

vs

Nearly all of allantoin filtered through the kidney is excreted[2,3]

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

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

CONGESTIVE HEART FAILURE

KRYSTEXXA has not been studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

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

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

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

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

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

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

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

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

Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

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

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

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

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

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

Gout Flares

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

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

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo.

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

The most common adverse reactions that occurred in ≥5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

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

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

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

Immunogenicity

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

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

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

Postmarketing Experience

General disorders and administration site conditions: asthenia, malaise, peripheral swelling have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

No dose adjustment is required for patients with renal impairment. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

Anaphylaxis and Infusion Reactions

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

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

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

Gout Flares

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

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Deerfield, IL 60015

Editorial Commentary

Vaccine Intent versus Uptake—Who? Why? and How Can We Help?

By Valerie S. Barta and Maria V. DeVita

A recent study illustrates the critical role that hemodialysis units can play to break down barriers for patients on dialysis with vaccine hesitancy.

Despite being 2 years into the pandemic, COVID-19 continues to be a top health concern. Our patients on dialysis are at heightened risk of severe illness or death due to lowered immunity and multiple comorbidities. Vaccination remains the most important tool we have against COVID-19. That means breaking down misinformation and systemic barriers contributing to vaccine hesitancy are top priorities.

Recent research from Tummalapalli et al. (1) suggests that although our work can have an extremely positive impact on our patients, vaccine hesitancy remains strong among certain populations, especially among young patients and patients of non-Hispanic Black race.

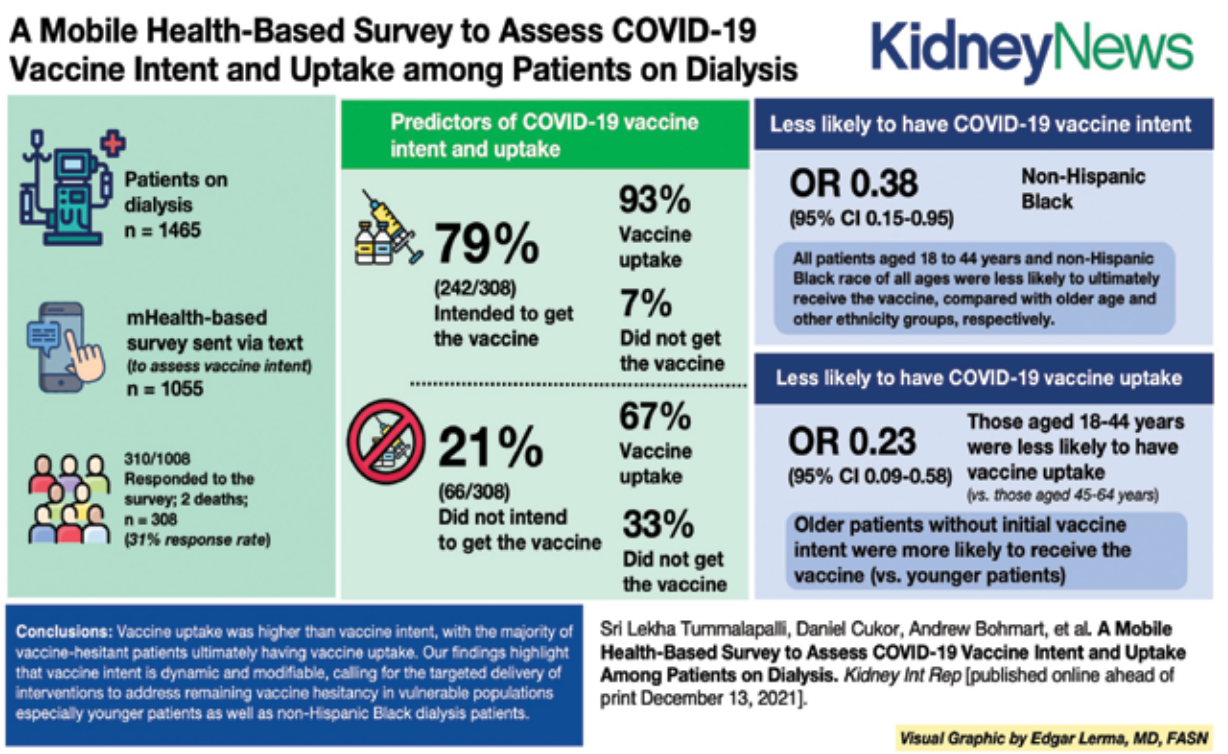
The Rogosin Institute, a non-profit dialysis organization with multiple dialysis centers in New York City, conducted the research within its multiple centers, which included in-center and home dialysis patients (hemodialysis and peritoneal dialysis). The study reports that of 1465 patients at Rogosin facilities, 1055 had cell phone numbers available and were sent a text message. A total of 308 patients participated in this two-part text message survey. The initial survey was sent January 2021, before vaccines were widely available. In response to a single "yes or no" question, 242 (79%) survey participants expressed intent to get vaccinated, and 66 (21%) had no intent. These same respondents received a follow-up survey in June 2021 after vaccines were available widely to this group of individuals. Of those participants who initially said they would get vaccinated, 17 did not, and of those who initially said they would not get vaccinated, 44 (67%) did receive the vaccine, bringing the overall vaccination rate of all survey participants to 87%. In other words, two-thirds of the respondents who did not intend on getting the vaccine had changed their minds.

As part of their study design, following the original January survey, the investigators sent the names of hesitant respondents to their respective dialysis unit. As a result, it was possible for the dialysis team, including physicians, nurses, social workers, and dieticians, to counsel these patients. In addition, after receiving the survey, many patients asked questions about the vaccine, stimulating conversation and shared decision-making. In this manner, the survey served to resolve misconceptions and reduce fears contributing to vaccine hesitancy.

Another important component to breaking down barriers was that vaccines were distributed directly to dialysis centers. This crucial move helped reduce physical and socioeconomic access barriers. In addition, it provided the hesitant patients the chance to see other patients taking the vaccines without issue.

Among older patients on dialysis, these simple interventions were extremely effective in improving vaccine acceptance. Other patient populations, however, remained unconvinced. Race and ethnicity and residential and community context were the most predictive factors affecting patient success in overcoming vaccine hesitancy. Participants of Non-Hispanic Black race were approximately 30% less likely than participants of non-Hispanic White race to initially intend on vaccination, and younger patients (18–44 year olds) were less likely overall to get vaccinated.

We still have work to do; however, these findings demonstrate how conversations with dialysis patients can have a tremendously positive effect on health behaviors. At the same time, we can use this information to increase outreach to our younger and most underserved patient populations. ■



Valerie S. Barta, MD, is Assistant Professor of Medicine with the Division of Kidney Diseases and Hypertension, Lenox Hill Hospital-Northwell Health System, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY. Maria V. DeVita, MD, FASN, Is Chief with the Division of Nephrology; Training Program Director, Nephrology, with Lenox Hill Hospital; and Professor of Medicine with the Donald and Barbara Zucker School of Medicine at Northwell Health, Great Neck, NY.

Dr. DeVita is a Consultant for Vascular Therapies and for Nuwellis. Dr. Barta reports no conflicts of interest.

Reference

1. Tummalapalli SL, et al. A mobile health-based survey to assess COVID-19 vaccine intent and uptake among patients on dialysis. *Kidney Int Rep* [published online ahead of print December 13, 2021]. doi: 10.1016/j.ekir.2021.12.006; https://doi.org/10.1016/j.ekir.2021.12.006

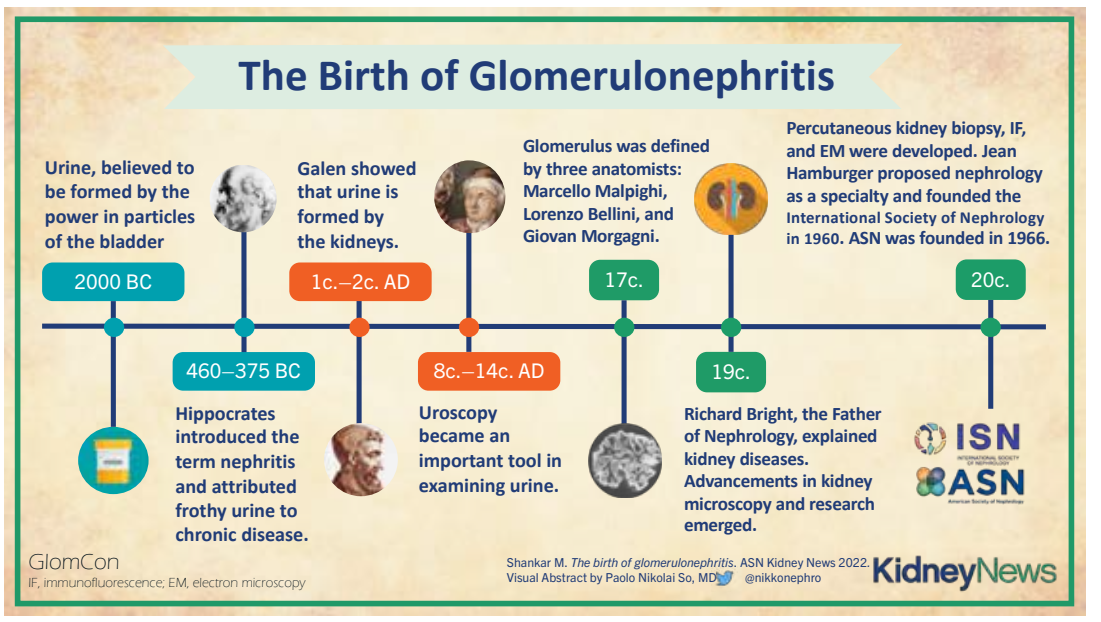
Glomerular Disease Corner

Mythri Shankar's "The Birth of Understanding Glomerulonephritis" in the February *Kidney News* is a comprehensive walk through the history of our understanding of kidney diseases. Pivotal points were the discovery of the glomerulus and subsequent recent insights into the pathobiology and genetics of glomerular diseases.

The visual here, prepared by Paolo Nikolai So, MD, pulls it all together. ■

Mythri Shankar, MD, MBBS, is Assistant Professor, Department of Nephrology, Institute of Nephro-urology, Bengaluru, India, and a GlomCon Education Committee Member (2021–2022) and GlomCon Fellow (2020–2021).

Paolo Nikolai So, MD, is a recent graduate fellow in nephrology at Philippine General Hospital, Manila, Philippines, and a member of the GlomCon Education Committee (2021–2022) and GlomCon Pubs Editorial Team (2021–2022).



A Training Program Director's Perspective on Training in the Time of COVID-19

The 2021 ASN Nephrology Fellow Survey

By Roger Rodby

In December 2019, when Chinese authorities alerted the World Health Organization of cases of pneumonia in Wuhan City, for which they were unable to identify a known cause, little did we know that this was just the tip of the iceberg that would leave us with (to quote a Lin-Manuel Miranda song title in "Hamilton") a "world turned upside down."

None of us signed up for this. There was a realistic fear of death to health care workers who were already taxed beyond what anyone could imagine. They may have questioned, "Will my patient die because of a bed or ventilator shortage?" "Will I bring this plague home to my family?" Furthermore, almost everything changed. Shopping, travel, dining, and family holidays had new definitions and restrictions, and social distancing required us to completely rethink how we provided medical education, something that up until now was always done on an in-person, hands-on basis. As a nephrology training program director for 20 years, nothing was more threatening to our fellowship's goals than COVID-19. We had to worry about our fellows' physical safety and mental health, in addition to fulfilling our academic obligation to excellent training. We quickly became experts in video conferencing for lectures and conferences and "virtual" patient visits. In fact, we essentially became a virtual training program.

Not all of these mandatory changes were bad. In fact, I could argue that many were a silver lining to the COVID-19 cloud. Video conferencing made it easier to be present for curriculum activities, and thus both fellow and faculty "attendance" improved considerably. Being in front of our computer screens also allowed each of us to screen-share any information in real time. Additionally, these activities could be easily recorded. Still, we all missed human contact.

The above observations, however, are my perceptions and may not reflect those of our trainees. That is why "Nephrology Training in the Time of COVID-19. The 2021 ASN Nephrology Fellow Survey" is such an important document (1, 2). Although a number of topics were explored in the survey (Table 1), as a program director, I was most interested in fellows' perception of how the pandemic affected their training. Additionally, I was very concerned about the mental health of the fellows who I believed were at risk of some form of posttraumatic stress disorder.

From the standpoint of training, 83% of the respondents felt that their education was successfully maintained, and 87% felt they would be prepared for independent practice upon graduation. Only approximately 10% felt that their educational training was not sustained. These are encouraging data and speak to the resiliency and flexibility of faculty and fellows. From my personal experience, our fellows were extremely helpful in making this virtual transition. In fact, because of the ease of providing lectures and conferences over the internet, their suggestions led to an increase in our curriculum's teaching activities.

Fellow mental health was reported as a Resident Well-Being Index (RWBI), a measure of "burnout" and general mental quality of life. For this RWBI metric, we are presented data from 2020 and 2021, and the pandemic has clearly taken its toll. Over this single, 1-year period, fellows considered at a "distress level" went from 17.5% to 27.2% for women and from 12.6% to 17.7% for men. Whereas the long-term impact of this is not known, this may be the most important message from the survey and stresses the need for an open dialog between faculty and fellows that requires regular inquiry into fellows' level of stress, anxiety, happiness, and sense of workload. This must remain a priority even after the pandemic and emphasizes the need for training institutions to have easily accessible and confidential free counseling.

Finally, I want to end this on a more optimistic note. Figure 12 of the survey (see Figure 1 below) demonstrates that since 2014, despite the doom and gloom of decreased nephrology fellowship match success and the less-than-optimal nephrology board pass rates over this time period, there was a persistent increase in the percent of fellows who would recommend nephrology to medical students and residents, from a low 70% to a high 80%.

Indeed, we did not ask for this, but we are doing better than I would have predicted. Still, we cannot let down our guard. But as it now appears in early 2022, there is light at the end of this dark pandemic tunnel, and it just may lead us to a better educational place. ■

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The author reports no conflicts of interest.

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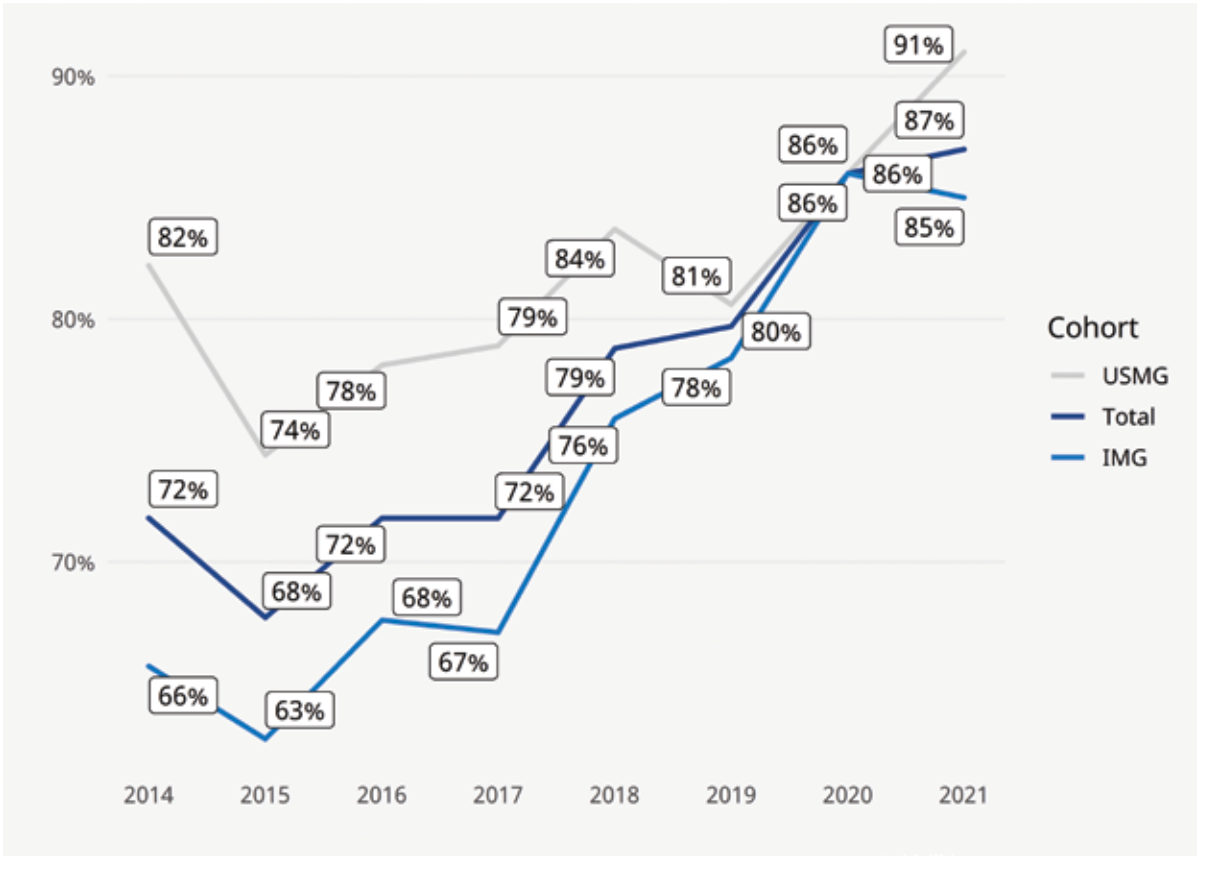
Figure 1. Proportion of fellows recommending nephrology



USMG, US medical brief citation graduate. Adapted from American Society of Nephrology Alliance for Kidney Health (1).

Table 1. Main findings of the national nephrology fellow survey

1 More than 80% of fellow survey respondents felt that despite the pandemic, their program was able to sustain their training and that they would be ready for "Independent Practice" (the American Board of Internal Medicine's standard) upon graduation.
2 Telemedicine was used at some point either exclusively or for the majority of outpatient visits by more than 80% of fellows.
3 Fellows suffered from a decreased sense of well-being; this was worse for women and for fellows in their first year of fellowship training.
4 The perception of the job market as a whole was good except for jobs close to where fellows were receiving their training.
5 87% of fellows would recommend nephrology to medical students and residents.
6 90% of graduating fellows will be practicing clinical nephrology with a median starting base salary of $200,000. Although international medical graduates (IMGs) had a slightly higher starting salary, there were no differences between men and women.
7 Although there were several reasons for choosing a specific practice to join, the number 1 reason that a fellow chose his or her job was income guarantee (43%).
8 The decision to go into nephrology happens most of the time in residency (years 2–3).
9 Only 14% reported that they will be responsible for placing dialysis access lines or performing renal biopsies in their job following fellowship graduation.

Diversity, Equity, Inclusion, and Justice
Yesterday, Today, and Tomorrow

ASN Executive Vice President's Update

By Tod Ibrahim

In 1960, my father immigrated to the United States to avoid religious persecution, experienced racism in Ohio, overstayed his student visa, and was considered "illegal." My mother—whose family has deep, often racist, roots in the United States—eloped with my father, helped him become a US citizen, experienced sexism (especially in the workplace), worked for two female members of Congress, and volunteered as a counselor during the AIDS crisis.

Their individual and shared experiences shape my commitment to diversity, equity, inclusion, and justice. The American Society of Nephrology (ASN) was a pacesetter—and is now an advocate—in this arena because its members, leaders, and staff share the same commitment.

Valuing people from different races, ethnicities, cultures, and gender identities and expressions makes an organization diverse. An equitable organization treats everyone fairly, impartially, and justly. By involving, accommodating, and embracing people who have historically been excluded, an organization is inclusive. Starting (essentially) at "square one" a decade ago, ASN has increasingly promoted diversity, equity, and inclusiveness "to enhance the nephrology profession and the lives of people with kidney diseases through improved health care, research, and education" (1).

Of the more than 37 million people with kidney diseases in the United States, a disproportionate number are Black or African American, Hispanic or Latinx, Indigenous or Native American, Asian American, and Native Hawaiian or other Pacific Islanders. Disproportionately, people with kidney diseases also have lower socioeconomic status. As is well documented, the kidney health of these Americans is unacceptable (2). Achieving health care justice for them requires the following:

- Identifying opportunities to promote fairness in health care and society
- Influencing social determinants of health, particularly in populations at risk for and overburdened with kidney diseases
- Acknowledging that all kidney health policy should be rooted in the principle of justice
- Making it incumbent on all kidney health professionals to seek just, equitable social conditions for their patients, their colleagues, and their communities (3)

Teams, medical specialties, and associations that embrace diversity, equity, inclusion, and justice make better decisions, are more innovative, perform at a higher level, experience less turnover, are considered more satisfying workplaces, and are financially more profitable (4). Compelling data underscore this reality. Such a culture also reveres empathy. As the poet Lucille Clifton observed, "Every pair of eyes facing you has probably experienced something you could not endure" (5).

Promoting diversity, equity, and inclusion among kidney health professionals depends on "some of the same solutions" as health care justice but often necessitates "different sets of strategies—at the levels of federal and local policies, multisector and community-academic partnerships, institutional policies and practices, individual and social group attitudinal and behavioral change—and targeted interventions to address not only organizational but also broader social and environmental influences on health," according to ASN Secretary Deidra C. Crews, MD, ScM, FASN, and colleagues (6).

By making a public commitment, examining the society, establishing a presence, funding the next generation, continuing to learn, and addressing policy issues, ASN has created a strong foundation in diversity, equity, inclusion, and justice (Table 1). The society's leadership, staff, and I are committed to building on this bedrock in 2022 and beyond.

In addition to continuing many of the 26 activities listed in Table 1, ASN has identified five priorities centered on diversity, equity, inclusion, and justice for 2022. First, ASN must continue working with the National Kidney Foundation (NKF) to implement recommendations from the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases. ASN is responsible for addressing the legislative and regulatory issues related to the task force's recommendations, including the need to encourage and fund "research on [glomerular filtration rate] GFR estimation with new endogenous filtration markers and on interventions to eliminate racial and ethnic disparities" (7). This recommendation compels KidneyCure (established in 2012 as the ASN Foundation for Kidney Research) to enhance its grant portfolio as well.

> **ASN has increasingly promoted diversity, equity, and inclusiveness "to enhance the nephrology profession and the lives of people with kidney diseases through improved health care, research, and education."**

Last month, ASN participated in a workshop, "Designing Interventions That Address Structural Racism to Reduce Kidney Health Disparities." The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) held the workshop to review how structural racism contributes to health and health disparities for people with kidney diseases, as well as to "identify feasible areas for intervention," including "study designs needed to evaluate potential interventions" (8). NIDDK will summarize the results of the workshop in the near future.

Second, the society launched the ASN Health Care Justice Committee in March 2021. Recently, the ASN Council discussed the committee's first set of recommendations. In the coming months, ASN will announce specific plans to pursue justice in medical education, scholarship, clinical care, innovation, and advocacy. Following the committee's advice, for example, Kidney Week 2022 will include a "Health Equity" abstract category.

In 2020, I served as president of the Council of Medical Specialty Societies (CMSS), a coalition of 47 medical specialty societies (including ASN) that represents more than 800,000 US physicians. Last year, CMSS partnered with the Accreditation Council for Graduate Medical Education to launch "Equity Matters: A Diversity, Equity, Inclusion, and Antiracism Initiative for Physicians and Medical Leadership."

ASN's third priority is to initiate a "capstone project" with other specialty societies as part of "Equity Matters." This project will result in concrete recommendations for increasing the pool of US medical school applicants who identify as underrepresented in medicine, improving the likelihood of their acceptance and enrollment, and reducing barriers to their successful graduation to residency training and beyond.

CMSS also plays a key role in ASN's fourth priority. Earlier this year, CMSS worked with the American Medical Women's Association, Executive Leadership in Academic Medicine, and other leading groups to establish a new alliance: the Gender Equity in Academic Medicine and Science Alliance (GEMS Alliance). The GEMS Alliance will work collectively to ensure that "all women achieve their full potential in advancing medicine and science" (9).

As its fifth priority, ASN responded last month to a request from the US Centers for Medicare & Medicaid Services "seeking public comment that will help to inform potential changes that would create system-wide improvements, which would further lead to improved organ donation, organ transplantation, quality of care in dialysis facilities, and improved access to dialysis services" (10). In its 71-page response, ASN provided specific suggestions to the federal government and emphasized: "Developing system-wide improvements that address inequitable access to kidney transplantation and home dialysis could have a strong and lasting positive impact for patients with kidney failure."

To strengthen, target, and increase the likely success of its current and future initiatives to promote diversity, equity, inclusion, and justice, ASN is enhancing the collection of member demographic information and under-

standing of its members. In the future, ASN plans to:

1. Publish an anti-racism toolkit on its website.
2. Continue to refine the ASN Loan Mitigation Pilot Program. All six of the program's first participants will start nephrology fellowships on July 1, 2022.
3. Seek options for assessing workplace culture.
4. Facilitate conversations among the US Food and Drug Administration, commercial entities, the society's members, and other stakeholders on setting guidelines and developing tools to promote increased diversity of participants in clinical trials.
5. Engage with Historically Black Colleges and Universities, Hispanic-Serving Institutions, and others to reach potential health professionals, researchers, and scientists from groups underrepresented in medicine.

A pacesetter yesterday. An advocate today. An innovator tomorrow. ASN is fully committed to promoting diversity, equity, inclusion, and justice in nephrology, health care and science, and broader society. ■

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Table 1. ASN's activities for promoting diversity, equity, inclusion, and justice

Make a public commitment
1. Dedicating goals in ASN's Strategic Plans (2016–2020 and 2021–2025) to increasing diversity, achieving equity, embracing inclusion, and pursuing justice
2. Producing "ASN Values Statement on Diversity and Inclusion"
3. Issuing an ASN statement against racism and signing the AAMC and CMSS statements against racism
4. Facilitating a webinar on "Going Beyond the Statement: Dismantling Systemic Racism in Nephrology"
5. Testifying during the House of Representatives Ways and Means Committee Hearing on the "Disproportionate Impact of COVID-19 on Communities of Color"
Examine the society
6. Improving demographic data collection from members by increasing participation and expanding and advancing inclusiveness
7. Requesting that all ASN committees examine their demographic data
8. Requiring implicit/unconscious bias training for ASN leaders, including committee members
9. Launching midcareer awards to recognize clinicians, researchers, educators, mentors, and leaders
10. Establishing the ASN Diversity, Equity, and Inclusion Committee and the ASN Health Care Justice Committee
11. Reevaluating every aspect of the annual process for identifying, nominating, and selecting candidates to run for the ASN Council to ensure diversity, equity, and inclusion
Establish a presence
12. Providing administrative support to Women In Nephrology
13. Featuring regular sessions at ASN Kidney Week related to diversity, equity, inclusion, and justice, including the annual in-person Wesson-Himmelfarb Diversity and Inclusion Lunch (and virtual gatherings throughout the year)
14. Holding an annual LGBTQ+ and Allies Members Reception at Kidney Week (and virtual gatherings throughout the year)
15. Convening a KHI "Member Town Hall: Diversity in Clinical Trials"
16. Exhibiting at the AMSA, APSA, LMSA, and SNMA Annual Meetings
Fund the next generation
17. Partnering with the RWJ Foundation to fund ASN-Harold Amos Medical Faculty Development Program Scholars
18. Providing travel support for members to attend the NIDDK Network of Minority Health Research Investigators Annual Workshop
19. Launching the ASN Loan Mitigation Pilot Program to attract people who are underrepresented in medicine to careers in nephrology
Continue to learn
20. Proposing sessions at Kidney Week on caring for underserved populations (such as patients who are LGBTQ+ and people with physical disabilities)
21. Publishing perspectives on caring for diverse patient populations (such as appropriately identifying and supporting individuals who are of NHPI background and highlighting the need to support individuals who live in rural parts of Hawaii)
22. Examining perceptions of visa issues for nephrology fellows who are IMGs
23. Launching a multi-pronged approach to position nephrology as attractive to and inclusive of osteopathic students and physicians, as well as mitigating potential biases
Address policy issues
24. Partnering with NKF to form the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases, which resulted in nephrology being the first specialty to recommend removing race from a major clinical algorithm
25. Advocating for Congress to pass the Health Equity and Accountability Act of 2020—legislation to address disparities in health care
26. Joining "Equity Matters: A Diversity, Equity, Inclusion, and Antiracism Initiative for Physicians and Medical Leadership," a collaboration between ACGME and CMSS
Organizations and Acronyms
Accreditation Council for Graduate Medical Education (ACGME)
American Medical Student Association (AMSA)
American Physician Scientists Association (APSA)
Association of American Medical Colleges (AAMC)
Council of Medical Specialty Societies (CMSS)
International Medical Graduates (IMGs)
Kidney Health Initiative (KHI)
Latino Medical Student Association (LMSA)
Lesbian Gay Bisexual Transgender and Queer or Questioning and Others (LGBTQ+)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Kidney Foundation (NKF)
Native Hawaiian and Other Pacific Islander (NHPI)
Robert Wood Johnson (RWJ) Foundation
Student National Medical Association (SNMA)

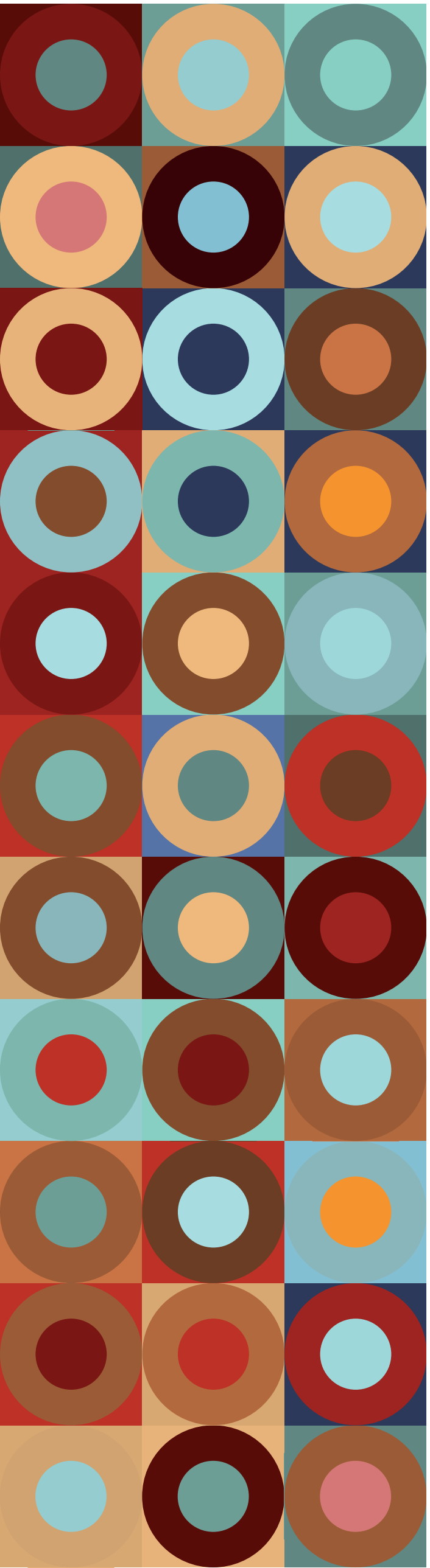
THANK YOU

The American Society of Nephrology thanks you, the Kidney Care Team, for your extraordinary efforts caring for kidney patients throughout this pandemic.

We're United 4 Kidney Health

ASN
American Society of Nephrology

For more information visit www.asn-online.org/covid-19. To access a module on mental wellness, scan the QR code.



IT TAKES A VILLAGE:

Addressing Structural Racism as a Barrier to Health Equity in Kidney Care

By Christel Wekon-Kemeni and Keisha L. Gibson

With more than 37 million people in the United States affected, chronic kidney disease (CKD) is arguably one of the largest threats to public health outside of the current COVID-19 pandemic. The American Society of Nephrology (ASN) aims to create a world without kidney diseases. To achieve this goal, health equity for all patient populations must be realized, which requires the vanquishing of racial and ethnic disparities in kidney health.

Much like the realities revealed by the COVID-19 pandemic, race-associated disparities in prevalence, morbidity, and mortality outcomes in people with CKD are glaring. These disparities stem directly from structural racism—a system of structuring opportunity and assigning value based on the social interpretation of how one looks (e.g., their race)—which unfairly creates disadvantages for some individuals and communities and advantages for other individuals and communities, according to Camara Phyllis Jones (1). Structural racism saps the strength of the entire society by suppressing a portion of its human resources. This social framework is embedded in the fabric of both society and health care. The recognition of structural racism's influence on children and adults with kidney diseases is the shared responsibility of all kidney health professionals.

One malignant consequence of racism in medicine lies in the historic acceptance of race essentialism, the belief that races are biologically distinct groups due to the presence of intrinsic genetic differences (2). Because of the historic, widespread acceptance of this belief, erroneous conclusions were established and implemented into medical practice. The inclusion of race in clinical algorithms is an example of this, and the clearest instance in nephrology is the longstanding presence of a Black race modifier in the Chronic Kidney Disease Epidemiology Collaboration equation to estimate kidney function. Over time, this has ultimately led to the under-diagnosis of CKD in patients of Black race and the disproportionate level of access to home dialysis treatment and kidney transplantation that this patient population experiences. The inclusion of ethnicity as a risk factor in the kidney donor profile index is another example of the harm that race essentialism can inflict on minoritized populations (3) (Figure 1).

Both race essentialism and racism as a whole are dire threats to rigorous science and health equity. Race essentialism minimizes the role that structural racism plays in perpetuating health disparities by exaggerating the link among biology, race, and health outcomes. It fails to specify that health disparities are a result of the inequities of social determinants of health, such as governing processes and economic and social policies.

As an organization, ASN focuses on not only promoting diversity and inclusiveness within the society but also on enhancing the nephrology profession and the lives of people with kidney diseases through improved health care, research, and education (4). ASN's partnership with patients and organizations, such as the National Kidney Foundation (NKF) and others, has been critical in moving forward efforts to dismantle the effects of structural racism in nephrology. Growing efforts among our government partners are additionally vital in these efforts. One welcome example is the recent work of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases, which in 2021 recommended the elimination of a "race modifier" in equations for estimated glomerular filtration rate (eGFR) and published new, validated equations for eGFR, which do not include race (5). Another example of designing interventions that address structural racism to reduce kidney health disparities is the recently held virtual workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (6).

Achieving health equity in kidney care is going to take the collective effort of all kidney health stakeholders, and the ongoing collaborative momentum across our broad community must continue. ■

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Dr. Wekon-Kemeni reports no conflicts of interest. Dr. Gibson reports consulting agreements with Travere Therapeutics and Aurinia Pharmaceuticals and previously with Reata Pharmaceuticals and is also the current Treasurer for the American Society of Nephrology.

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It Takes a Village

Continued from page 17

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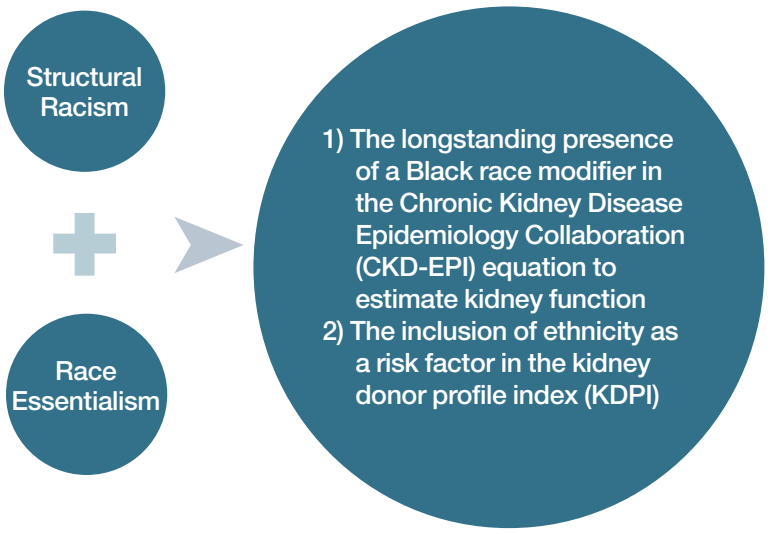
Figure 1. Roles of structural racism and race essentialism in perpetuating health disparities



	Definition	Intervention examples
Structural racism	A system of structuring opportunity and assigning value based on the social interpretation of how one looks (which is what we call "race"), that unfairly disadvantages some individuals and communities, unfairly advantages other individuals and communities, and saps the strength of the whole society through the waste of human resources (1)	The sponsoring of a virtual workshop by the NIDDK that is aimed at designing interventions to address structural racism to reduce kidney health disparities
Race essentialism	The belief that races are biologically distinct groups due to the presence of intrinsic genetic differences	The elimination of a "race modifier" in estimating equations for glomerular filtration rate (eGFR) by the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases and the publication of new validated equations for eGFR that do not use race

The Imperfect Hero

By Justin L. Bullock

It had only been 5 years into my taking lithium when my urine turned from golden yellow to a consistent translucent lemonade. As an internal medicine resident and incoming nephrology fellow living with bipolar disorder, I had hoped to have at least 20 years before any renal concentrating deficits began. Lithium had always been my "hero," albeit imperfect, and hand tremors and nausea seemed a paltry price to pay for the drug's mood-stabilizing and anti-suicidal effects (1). Ironically, soon after choosing the field of nephrology, my polyuria and nocturia began.

For many years, I have been intentionally transparent about my struggle with mental illness. Bipolar disorder is a lifelong journey, and each person's journey is unique. I have not triumphed over bipolar disorder; rather, I strive to live vibrantly while navigating my disease. Therapy and medications help to control my mood fluctuations. Still, sometimes the suffering wins. My ascents typically signal impending plunges. When depressed, I have physically hurt myself so that my outside pain matches my inside pain. During some periods of intense suffering, suicide feels seductive because it offers peace. I know that I am not alone in my internal battle against mental illness and against its stigma in medicine: through writing and speaking about my mental illness, hundreds of physicians, nurses, therapists, and social workers have shared their personal experiences of mental illness with me.

I feel optimistic in pursuing a career in nephrology because as I interviewed for fellowship, I met many successful nephrologists who openly shared their own personal connections with mental illness. One critical factor in being a successful provider with mental illness is to be affiliated with a workplace that allows me to openly step back, when necessary, without fear of repercussions. Too often, medicine discourages transparency. This is unfortunate, because like lithium, health care providers are imperfect heroes. We suffer from conditions, such as depression, anxiety, posttraumatic stress disorder (PTSD), substance-use disorders, and kidney disease, just as our patients do. Why would we as health care providers be any less human than our patients? Medicine often struggles to accept this concept.

This denial has deleterious implications on the care that we provide. Patients with chronic kidney disease (CKD) suffer from high rates of mental illness, which is associated with increased mortality (2). Our patients—the teacher, the mother, the cashier, the doctor—are all imperfect heroes. Mental health is within the purview of kidney health providers because it deeply impacts the care we provide. We must not focus solely on the kidneys at the cost of sacrificing the person. When done thoughtfully and intentionally, bringing one's authentic self into medicine can provide powerful healing for both patient and provider. Disclosure is not the only way to genuinely connect with someone else's suffering, but I believe it is an effective way. I have found it powerful to exist together as my true self with my patients and colleagues. Personal and professional need not be mutually exclusive lifestyles; medicine opens the door to many intimate conversations. We can convey humility, strength, support, and power by saying, "I share in some of your experiences. I have taken these medications too. I've struggled with these side effects and found these ways to help mitigate them." ■

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The author reports no conflicts of interest.

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Advancing LGBTQ+ Kidney Health Equity

By Dinushika Mohottige and Mitchell R. Lunn

Lesbian, gay, bisexual, transgender, queer or questioning, and/or other sexual and gender minority (SGM) individuals (LGBTQ+) represent a diverse range of people who experience disparities in health outcomes and other health-promoting resources and opportunities and are served by kidney care professionals (1–3).

Although there have been advances in civil rights legislation, including same-sex marriage equality aimed to equalize some sociopolitical opportunities, there are innumerable persistent social, economic, legal, health, and health care-related disparities facing SGM individuals (2, 4). These challenges are exemplified by a patchwork of non-discrimination policies across the United States that do not universally prohibit discrimination based on sexual orientation and gender identity (SOGI) in public accommodations, including in health care centers, such as dialysis facilities (5).

SGM people face a disproportionate burden of suboptimal and discriminatory health care due to implicit and explicit bias, as well as inadequate education regarding inclusive care (6–9). Furthermore, the national dialogue regarding the problematic use of race in clinical algorithms, including in kidney function estimation (i.e., estimated glomerular filtration rate [eGFR]), has galvanized discussions about the most precise method for estimating kidney function among individuals who are transgender and particularly among those receiving gender-affirming hormone therapy (10–12). Each issue presents opportunities for kidney care professionals to advance health justice and equitable health outcomes for all.

The National Kidney Foundation and American Society of Nephrology led a joint task force to address the use of the Black race coefficient in kidney function estimation (13, 14). Race is a sociopolitical variable without biologic meaning and exemplifies the problematic nature of race essentialism, which is a flawed belief that race captures biological distinctions and defines characteristics that are unique to an individual (15–17). The comprehensive re-evaluation of eGFR calculation provides an important opportunity for kidney care professionals to examine the role of the "female" sex coefficient as it pertains to transgender individuals/gender-expansive individuals who may have a higher prevalence of acute kidney injury (AKI) and chronic kidney disease (CKD) (18). Inaccurate eGFR calculations may contribute to kidney care disparities because of bias and/or systemic eGFR overestimation, and further investigation is needed to clarify the role of gender-affirming hormone therapies (e.g., estrogen and testosterone) on AKI and CKD (18). Overestimation of eGFR results in delays in referring patients to nephrology care and kidney transplant, as well as, for example, inadequate medication dosing (10, 19–21).

There is a lack of comprehensive data regarding the bias introduced by using the sex coefficient in eGFR calculation among individuals using gender-affirming hormone therapies, which impact muscle mass and creatinine production, versus cisgender people who are not utilizing these therapies.

First, affirming standard practices for obtaining SOGI data is essential to ensure a comprehensive understanding of a patient's sexual and gender identity. These details influence the patient's health care needs and our evaluation of laboratory tests (e.g., hemoglobin and eGFR) (10–12, 17, 18, 21, 22). SOGI data collection is needed to determine long-term kidney outcomes associated with sex hormones and other gender-affirming therapies (10, 22).

Second, as kidney care professionals seek greater precision to estimate kidney function and predict kidney failure, we must include populations with a range of sexual and gender identities (including individuals on gender-affirming hormone therapies) to ensure measurement optimization and validation (including the use of cystatin C in lieu of creatinine).

Furthermore, in situations in which there is clinical ambiguity regarding the use of a female sex coefficient for eGFR, we encourage providers to estimate GFR more precisely using additional tools (e.g., 24-hour urine creatinine and urea measurements and measured iothalamate/iohexol clearance) and to assess eGFR at baseline before initiation of gender-affirming therapy. Finally, we recommend that nephrology providers engage multidisciplinary teams (e.g., endocrinology, psychology, social work, and other SGM-affirming care experts) whenever complex decisions regarding gender-affirming hormone therapy occur (e.g., the discontinuation of estrogen therapies when considering kidney transplant and spironolactone use in advanced CKD). These discussions must account for the vital nature of these medications to the improved quality of life and psychological outcomes among many transgender/gender-expansive individuals (10, 23, 24).

SGM people, and especially transgender and gender-expansive individuals, are more likely to lack a usual source of care, health insurance, and a routine checkup in the prior year, as well as to have unmet medical care needs due to cost (among other barriers to care), compared with their cisgender and heterosexual counterparts (5, 25). To address these persistent inequities, kidney care professionals can advocate for and implement non-discrimination policies that explicitly prohibit bias due to sex, gender identity, gender expression, sexual orientation, and gender, while educating ourselves regarding the evolving, inclusive language and culturally humble best practices (e.g., recording and using a patient's pronouns and demonstrating signage and informational materials for CKD/transplant education that are inclusive at dialysis facilities and transplant centers). These practices should be embedded into continuing medical education (CME)/graduate medical education (GME) and are essential for earning trust by ensuring barriers to optimal care are addressed (e.g., access to appropriate preventive screenings) and by enhancing the quality of care we provide. Thus, by focusing on inclusive approaches that ensure affirming care and thoughtful attention to SOGI data collection, protecting all patients through comprehensive and inclusive policies, and enhancing CME, which highlights novel advances to improve care provision, we can achieve the equity we seek in kidney care. ■

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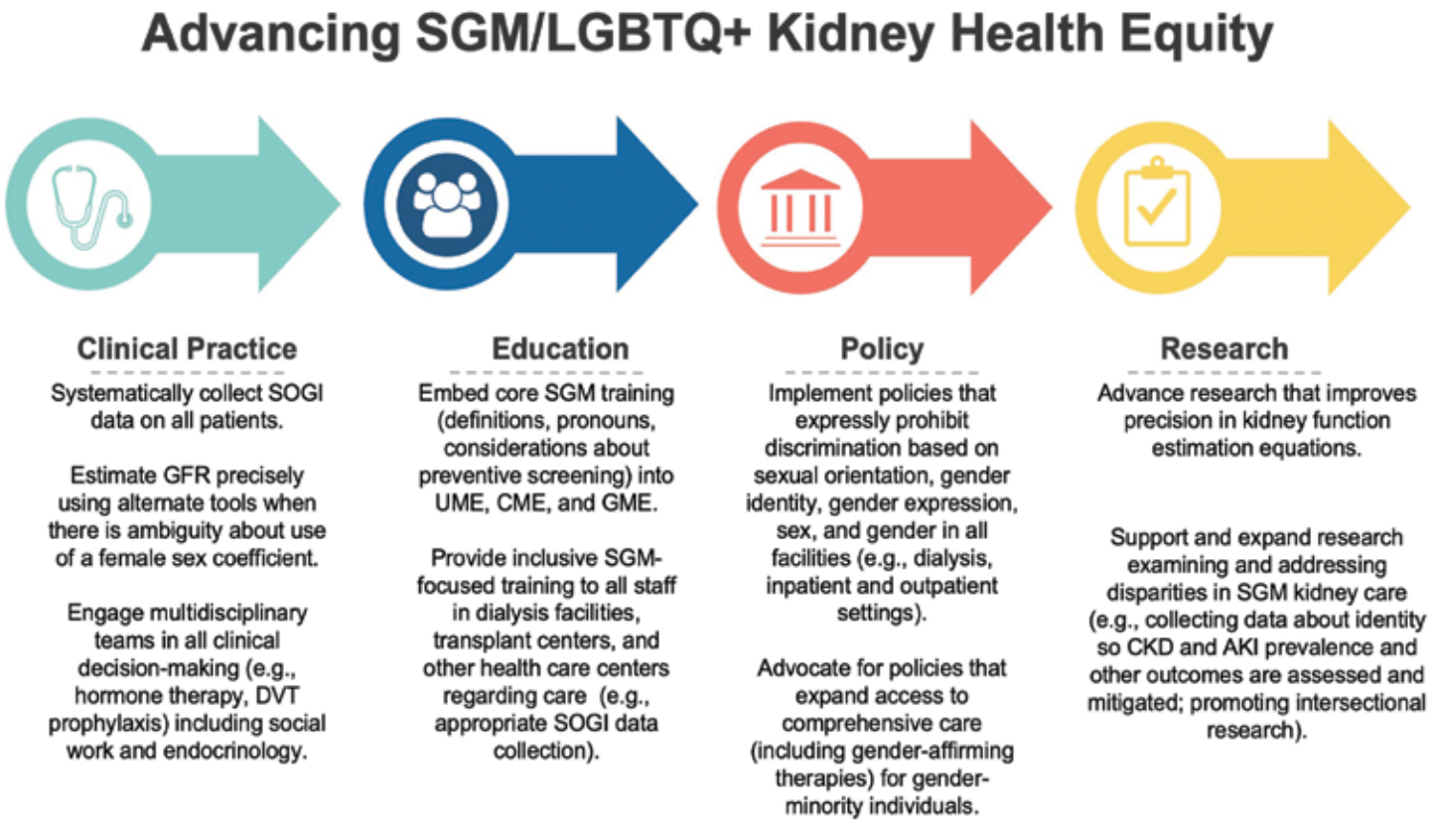

SGM, sexual and gender minority; DVT, deep vein thrombosis; UME, undergraduate medical education.

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Advancing LGBTQ+ Kidney Health Equity

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Promoting Kidney Health among American Indians and Alaskan Natives

By Stephanie Mahooty

In the United States, diabetes is the leading cause of kidney failure, and the prevalence of diabetes among American Indians and Alaskan Natives (AIs/ANs) is one of the highest among any racial and ethnic group. In the United States, diabetes accounts for 69% of new cases of end stage renal disease (ESRD; diabetes-associated ESRD [ESRD-D]) among the AI/AN population (1).

The roots of this disparity began in the 1950s and 1960s, when the epidemic of diabetes among the AI/AN population was soon followed by a dramatic increase in diabetic kidney disease and subsequent kidney failure, first described in the 1980s (2). From 1982 to 1996, ESRD-D among AIs/ANs increased substantially and disproportionately compared with other racial and ethnic groups (1). In 1996, the incidence rate of diabetes among the AI/AN population was approximately 4 times the rate of Americans of European ancestry (2). As a result, the Indian Health Service (IHS) implemented a systemic approach to diabetes care using evidence-based interventions and later established the IHS Kidney Disease Program. These diabetes standards of care were revised in the early 1990s to include screening, identification, and treatment of chronic kidney disease (CKD), which became a part of primary care delivery to indigenous communities served by the IHS (2). The systematic implementation of diabetes and CKD standards of care has contributed to the decreased incidence of ESRD-D among AI/AN adults by 54% from 1996 to 2013—a triumph for kidney health equity. Among adults with diabetes, ESRD-D incidence was the same in AIs/ANs as in White Americans by 2013 (1).

Despite the decrease in incidence in ESRD-D, the prevention of diabetic kidney failure continues to be a challenge. Personally, I come from a small AI community with a huge burden of diabetic kidney disease and ESRD-D. I have experienced my own father and paternal grandmother affected by diabetes and ESRD-D. Thus, this issue is very close to my heart and a primary reason for my decision to pursue a career as a kidney health professional.

There are several important considerations for health care professionals who provide care to this population. First, as a nurse and provider, I have learned that it is important to approach an AI/AN patient who has been newly diagnosed with CKD or ESRD-D with sensitivity, even if the provider is unaware of a particular culture. Many AI patients from the Southwest tribes, for whom I have provided care, associate the terms "kidney disease" or "dialysis" with a negative connotation, such as shameful or a death sentence. Patiently educating these individuals is an important first step to building trust and diminishing stigmas.

Second, it may help to start a conversation with a new patient by simply asking, "How much do you know about kidney disease?" This question can help clear up misconceptions, fears, or myths about kidney disease. It is not uncommon for AI/AN patients from a small community to know of a family member, relative, friend, or neighbor who is or has been on dialysis, but that experience may interfere with the patient's proper understanding of his or her own kidney disease.

Many AI/AN individuals live in multigenerational households, where family members collectively provide encouragement and support for their loved ones with kidney disease. Educating the patient and family together about kidney disease and care is crucial. I feel this gives the patient empowerment and hope and helps him or her to be more receptive to interventions offered to slow the progression of CKD and prevent ESRD-D.

Through patient education and adherence to evidence-based practice, all kidney health professionals can work together to narrow the disparities faced by AI/AN patients and their families. ■

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Challenges and Opportunities to Champion Women in Nephrology

By Andrea Kattah

The challenges for women in medicine are well documented: Women get paid less than men (1, 2). Women are under-represented in leadership positions at academic institutions (3, 4). Women bear more of the burden at home in dual professional households (5). The headlines are so familiar that it can be difficult for one to muster outrage. Although there are increasing victories in the struggle for equality, such as the inclusion of female voices on academic panels, systemic changes are needed to level what has historically been an uneven playing field. In an era when recruitment to nephrology is a struggle, and burnout is high (6, 7), we want medical students, residents, and fellows of all genders and backgrounds to see aspirational figures at the top of their fields. We should be intentional in selecting women for nominations, promotions, and speaking opportunities. Although groups, such as Women in Nephrology, have driven many effective changes in this area, the burden of championing women should not rely on women alone.

The COVID-19 pandemic has demonstrated how much societal burden rests on women, with large numbers of women leaving the workforce nationwide—including in health care—due to an inflexible system (5, 8). Particularly in academia, there is one path that has been established, which starts with scant financial support just out of fellowship and high expectations in the early stages of one's career that then sets the stage for future success. Does this inflexible model make sense? This uncompromising system imperils many clinicians and researchers who may stumble into competing priorities at various stages of life, whether it be raising children, caring for elderly parents, or attending to one's own health. It is possible that many would consider an alternate career path once any of the aforementioned competing priorities might occur. Thus, facilitating mid-career entry into research tracks would allow more clinician scientists—men and women—the chance to advance the science of our field.

Transparency is also critically important in driving change. This includes establishing concrete goals for the percentage of women proceeding through academic promotion and allowing practice members access to the salary information of their peers. Making gender equality an explicit goal of the practice may help drive additional conversations and changes that are unique to each setting. Examples include developing a sensible parental leave policy, building in time to busy clinic calendars for lactating women, and not penalizing physicians who may choose to work part-time when their children are young and need more direct care at home. Anecdotally, many women early in their career feel guilt or anxiety about asking for what they feel is "special treatment" when it comes to issues surrounding motherhood. That is why it is so critically important to state these policies explicitly and to provide safe venues for communicating what is and is not working.

Increasing recruitment, building the next generation of nephrologists, and supporting our colleagues through their varied life paths will benefit all nephrologists, regardless of gender (Table 1). Not every woman has the same desires or demands on her time. Not every woman has a family or wants to focus her energies on raising one, and that choice should not influence how she is perceived and what her options are. Women are as varied as we are capable, and it is time the structures of health care shifted to meet our needs. ■

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Table 1. Challenges and opportunities for women in nephrology

Challenges	Opportunities
Salary gap between men and women	Transparency in salaries
Fewer leadership opportunities	Representation on panels and in conferences
Increased household burden	Sensible parental leave policy
Inflexible route to academic promotion	Mid-career entry into research tracks
Fear of asking for special treatment	Flexibility in scheduling; equitable effort for men and women

Addressing Kidney Health Disparities among Rural Populations

By Kiri Bagley and Brianna Borsheim

Twenty percent of Americans live in rural areas. Many face health disparities caused by geographic isolation, transportation limitations, and a lack of access to local specialty health care (1, 2). Americans living in rural areas also are more likely to be uninsured, to have lower rates of access to preventive health services, and to engage in unhealthy behaviors (such as tobacco use) (2–5). They also have greater incidence rates of potentially preventable diseases, including heart disease and stroke, and higher mortality rates than their urban counterparts (2, 4, 5). Likewise, children living in rural America experience higher rates of poverty and obesity and are less likely to obtain preventive health and dental examinations (6). Rural hospital closures pose another obstacle: increasing patients' travel distances to receive medical services (7). These closures reached a record high in 2020, when the COVID-19 pandemic-related financial strain compounded underlying hardships that rural safety-net institutions already faced (8, 9).

These inequities have significantly impacted kidney health, as evidenced by the greater incidence of kidney failure in rural areas (10). People with chronic kidney disease (CKD) and kidney failure who live in rural areas have difficulty accessing nephrology care. A recently published systematic review by Scholes-Robertson et al. (11) elaborates patient and caregiver perspectives on access to kidney replacement therapy in rural communities. In 18 studies of populations worldwide, rural patients with CKD identified numerous difficulties in accessing care. These included the financial and scheduling burdens incumbent in traveling for care, separation from family and community while receiving care, and other associated sacrifices. Additionally, rural patients frequently reported discomfort with health care systems, stemming from an unfamiliarity with the systems' language and cultural norms. Although the review by Scholes-Robertson et al. (11) included studies from 8 countries (including the United States), a study of rural North Carolinians' perspectives about kidney disease reflected similar themes (12). This concordance of findings suggests that kidney disease presents a profound challenge for affected rural populations, domestically and globally.

The COVID-19 pandemic has amplified these rural inequities (13). In addition to rural hospital closures, limited access to home health and broadband presents ongoing barriers for those living in rural America. Rural dialysis centers' lower patient volumes and profit margins suggest they may be more vulnerable to closure, leaving rural patients to bear a significant travel burden if their home dialysis centers close. Moreover, the disruptions in transportation access for rural dialysis patients during the pandemic further highlight their vulnerability to care discontinuity (10, 14). Caregivers in rural communities, also feeling the impact of the COVID-19 pandemic, are more than twice as likely to report increases in caregiver burden than their urban counterparts (15).

Studies have shown mixed findings when assessing outcomes for patients with CKD and kidney failure in rural areas (16–22). This may be, in part, because rural populations, although less heterogeneous than urban populations, are diverse. As such, it is important to recognize that racial and ethnic disparities also occur within rural communities (23). For example, among rural patients with CKD, patients of Black race are less likely to receive early nephrology and dietician care than their White counterparts (18). It is important to identify and address the racial or ethnic disparities within rural communities, in addition to addressing the overall rural-urban disparities between communities.

Rural populations, like many marginalized and underserved groups, are often overlooked. This article highlights the susceptibility, social vulnerability, and substantial health disparities experienced by people with CKD and kidney failure living in rural communities. Currently, there are gaps in the literature investigating rural-urban health disparities. To combat these disparities and inform future policy decisions, additional research assessing the efficacy of different mitigation strategies will be critical. Additionally, improving rural population health is essential to ASN's commitment to health equity and its focus on engaging with social determinants of health to target upstream factors and root causes of disparities (24). As such, rural populations must be a priority in research. Policymakers should continue exploring innovative policy solutions to improve rural health. Clinicians, investigators, and the broader nephrology community should continue to invest in progress toward high-quality care for all. ■

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Health Disparities and Inequity in Access to Kidney Care: A Review of Literature on Kidney Care in Jamaica and Other Low- and Middle-Income Countries

By Nadia McLean and O'Neal Malcolm

Chronic kidney disease (CKD) is a significant cause of morbidity and mortality worldwide. The global burden of CKD is estimated at 500 million people worldwide, with the majority of people with CKD (80%) living in low- and middle-income countries (LMICs) (1). In 2017, 1.2 million people died from CKD, with the all-age mortality rate increasing 41.5% between 1990 and 2017 and a global prevalence of 9.1%. The global all-age prevalence of CKD also represented an increase of 29.3% since 1990 (2). Along with the noted increases, there is inequity in the distribution of CKD; people living in LMICs are disproportionately affected more than people living in high-income countries (HICs) (1). Stanifer et al. (1) noted that although CKD in 2016 represented the 19th-most common cause of death worldwide—an 82% increase since 1990—the annual death rate attributed to CKD is growing more than 5% per year.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative introduced a framework for the definition of CKD. The aim of the model is to depict risk factors that could be associated with progression to more severe stages of CKD (3). CKD was initially defined based on the presence of kidney damage or a reduction in glomerular filtration rate for more than 3 months (3). In 2004, Kidney Disease: Improving Global Outcomes (KDIGO) endorsed this framework, noting that proteinuria worsened the progression of CKD (4). By standardizing the definition of CKD and offering treatment guidelines, these models have presented an important basis for the diagnosis and management of kidney diseases in LMICs, such as Jamaica, and help us to elucidate the scope of the challenge in delivering expert kidney care to adults and children in this setting by providing a standardized basis for data collection, analysis, and policy recommendations.

The characterization of the scope of kidney diseases in Jamaica is foundational to an understanding of the burden faced by patients and providers, including lack of care and resources, workforce shortages, and chronic disease burden (5). With results from a survey of a specialist diabetes clinic in Jamaica, Ferguson et al. (6) estimated the prevalence of CKD to be 22%. Of note, moderate and severe albuminuria, known to advance CKD, was present in 82.6% of the population (6). The Caribbean Renal Registry, established in 2006, highlighted the difference in patterns of CKD and end stage kidney disease (ESKD) in LMICs. These patterns included high rates of health care demand compounded by a lack of trained nephrologists throughout the Caribbean region. As with other LMICs, such as those in Asia and parts of Africa, there was also inequitable access to kidney replacement therapies (KRTs), including peritoneal dialysis, hemodialysis, and kidney transplantation (5).

Inequity among adults also translates to the pediatric population of LMICs. In 2016, Miller and Williams (7) noted that between 2007 and 2012, 27 children developed CKD, with a cumulative annual incidence per million child population of 7.83 for children under age 12 years and 1.67 for the average population. The study also noted a paucity of pediatric data in LMICs and lack of access to KRTs.

A meta-analysis by Plumb et al. (8) noted an increased risk of late presentation among the pediatric population from LMICs. These children tended to be older and already hospitalized under emergent situations, which increased their risk of poor health outcomes, including mortality. The study pointed to the need for policy focus on reducing modifiable barriers to improve access to care, such as consensus definitions, protocols focused on risk stratification, and early specialist intervention (8).

It has been established that the burden of kidney failure in LMICs approaches that of HICs, but relatively few patients in LMICs receive KRTs (9). Currently, children throughout Jamaica primarily receive KRTs in the capital, Kingston. Major challenges for the pediatric population residing outside of Kingston, including rural areas, are distance, travel duration, and transportation availability. The inequity in access to care extends to the most rural and often resource-limited parts of the country where transportation is unreliable and costly.

White et al. (9) proposed a framework for reducing the global burden of ESKD and improving access to KRTs. This model included a national registry of dialysis and transplant patients, national policy and budgetary planning about KRT delivery and eligibility, retention and training of skilled personnel, and education at the community and regional levels. This framework and call to action were echoed by Ameh and colleagues in 2019 (10). Their review highlights factors hindering the prevention of CKD progression in LMICs. These components include poor funding of health care, struggling health care systems, lack of local data, and costs of screening systems—all of which prevail among the population in Jamaica (10).

We hope to highlight the inequity as it relates to access to diagnosis, expert care management, and KRTs faced by adults and children living in rural parts of Jamaica, a LMIC. It is our hope that data from this article will represent the basis for recommendations to increase access to care for this vulnerable population and to improve health care outcomes and reduce morbidity and mortality. ■

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The authors report no conflicts of interest.

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Hypocalcemia: Parsabiv® lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv®. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv®.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv®. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv®.

Concurrent administration of Parsabiv® with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv® should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv®. Closely monitor corrected serum calcium in patients receiving Parsabiv® and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv®. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv®. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv®. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv® clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv® for worsening signs and symptoms of heart failure.

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Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv®. Monitor patients for worsening of common Parsabiv® GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv® therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv® to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
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2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred with PARSABIV *[see Adverse Reactions (6) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Monitoring Serum Calcium and Patient Education

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

Management of Hypocalcemia

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials 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 clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is 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

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7- and 7-fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

AMGEN®

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Patent: http://pat.amgen.com/Parsabiv/

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Protecting the Careers of International Medical Graduates on Visas: What Can Be Done?

By Harish Seethapathy

According to 2019 Association of American Medical Colleges (AAMC) data, international medical graduates (IMGs) comprise 23% of all actively practicing doctors in the United States (1). In nephrology, that number rises to 51% and in the coming years, is expected to grow, given that IMGs now make up nearly 60% of trainees entering the specialty. In the most recent fellowship match (appointment year [AY] 2022), 38% of all matched applicants were non-US IMGs, and most are likely to be on visas (2). The growing number of IMGs on visas (J-1 and H1-B; Table 1) entering practice face unique career and immigration challenges. Nephrology societies should consider instituting specific measures aimed at career development and preservation of the IMG workforce (Figure 1).

Recruitment into fellowship

Program directors and recruitment committees should be realistic and transparent during the fellowship interview process. IMGs envisioning themselves as physician scientists have a steep mountain to climb, and many applicants may not have fully considered nor been aware of the implications of choosing to pursue such a pathway. Society or foundation research grants and bridge funding (division clinical funds or extramural non-federal funds) will be required to support research careers until permanent residency or citizenship criteria can be obtained and US National Institutes of Health (NIH) funding mechanisms can be unlocked. Programs should clearly state their capacity to support such applicants and be transparent with applicants seeking such research pathways. J-1 applicants are obligated to serve a 3-year, full-time (1.0 full-time equivalent [FTE], at least 40 hours/week) clinical commitment in an underserved area (also known as a J-1 waiver) before they can even apply for permanent visas and hence, do not qualify for protected research time. Special efforts must be taken to preserve the research interests of such individuals (3).

Awareness of the immigration process

Division chiefs, clinical directors, and practice leaders should take steps to understand and learn the basics of physician immigration, such as the following:

- Waiver of home requirement (only for J-1): Also known as a J-1 waiver, this process has strict timelines and multiple steps that vary by state. Leaders should understand the legal steps in the waiver process and identify waiver catchment areas—practices and service areas that qualify as waiver sites within their practice base (4).
- Pathway to permanent immigration (J-1 and H1-B): Obtaining a green card through employment-based (EB) categories. There are two main EB categories: EB-1 requires an outstanding and exceptional ability that comes with stringent criteria, and EB-2, for which all physicians qualify, has become an impossible path to permanent residency for individuals from India (wait time >150 years) and China (wait time 5–8 years) since green card allotment is based on country of birth (5). Understanding the paperwork and basic criteria will enable nephrology leaders to provide valuable guidance to their trainees as they move forward in their careers.

Workgroup for formulation of guidelines on visa hires

There is concern over new graduates signing contracts at potentially malignant and predatory practices. Because nephrologists who are IMGs are entirely dependent on visa sponsorship through the practice, they are particularly susceptible to mistreatment. This could include a variety of situations that are averse to growth and development of a successful career.

- *Practice oriented*: excessive work hours, higher frequency of calls
- *Career oriented*: impediments to attaining partnerships, compensation increases not offered despite meeting requirements
- *Immigration oriented*: delay or non-processing of visa and immigration paperwork either from maleficence or lack of understanding of processes

J-1 trainees, whose initial waiver contract is for 3 years, have binding clauses that make it nearly impossible to switch or change jobs. Trainees with any visa waiting for a green card after submission of immigration paperwork face similar hurdles and as such, are vulnerable to practices looking to profit from their labor.

Although there are no resources or legal ways for our national societies to hold nephrology groups accountable for misleading practices, they can formulate guidelines on hiring an immigrant physician and recommend that practices advertise to trainees on visas that they follow appropriate procedures. Such guidelines shall broadly include the following:

- Prompt processing for a visa waiver (if applicable) or work visa, as well as application for permanent visas, including covering legal fees
- Specifying work hours or a schedule in the contract, compensation in line with median salary within the group, and bonuses (if applicable) in line with others in a similar role within the practice
- Offering partnerships, compensation hikes, and opportunity for joint ventures through the usual schedule within the practice

National database

To research and maintain standards, national societies need to establish and maintain a database of trainees and their practice locations in the first 5 years of practice and conduct yearly surveys to assess whether the aforementioned obligations were met by the practices that hired them. Identifying systemic problems will help our leaders form clear targets for improvement and focus resources on high priority issues.

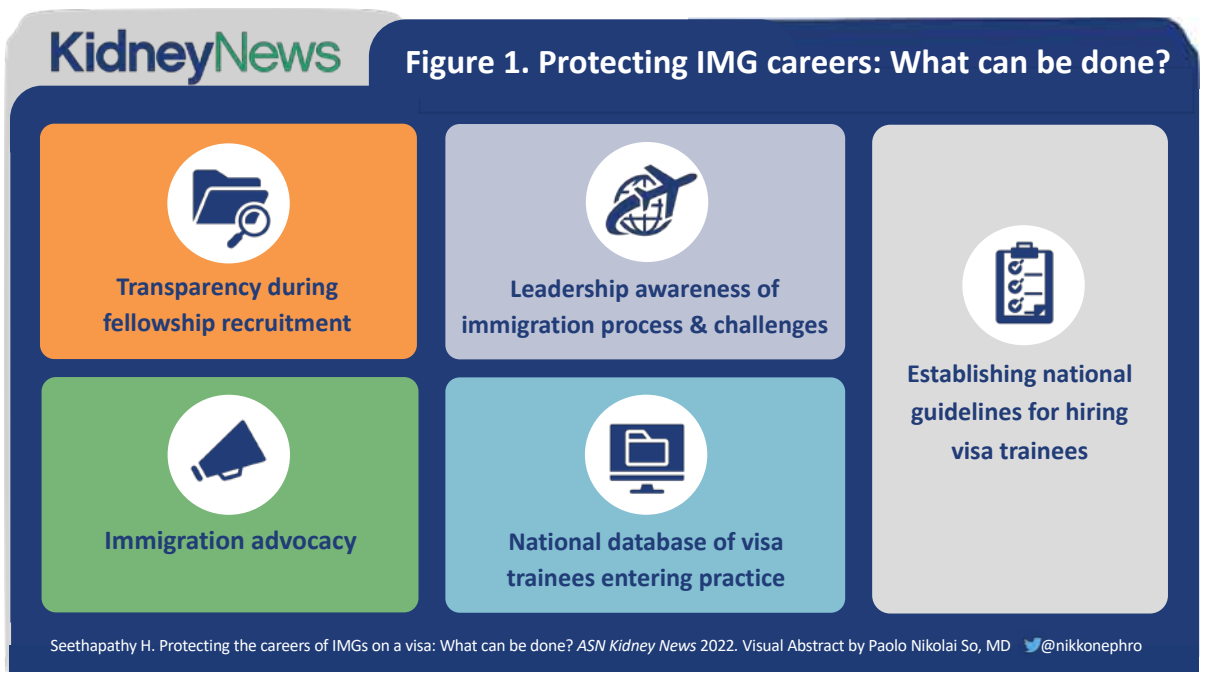
Immigration advocacy

The ASN Policy and Advocacy Committee and other societies in nephrology play leading roles in advocating for legislation that improves the care of kidney patients. In addition, increased representation of IMGs on the ASN Policy and Advocacy Committee and advocation for bills that ease immigration rules and the transition of physicians from immigrants to permanent residents, in concert with other organizations (such as the American Medical Association) that

Table 1. Comparison of J-1 and H1-B visas

	H1-B	J-1*
Sponsor	Training program	ECFMG
Requirements	Step 3 in addition to ECFMG certificate	ECFMG certificate (USMLE steps 1 and 2, credentialing)
Cost for the program	Few thousand dollars	None
Maximum duration of visa**	6 years	7 years
Transition to permanent visa after training	EB-1 and EB-2 pathways to a green card	J-1 waiver (3 years) followed by EB-1 and EB-2 pathways

ECFMG, Educational Commission for Foreign Medical Graduates; USMLE, United States Medical Licensing Examination.
*H1-B visas are not possible for many applicants due to various reasons, including but not limited to 1) previously on a J-1 visa (typically for research), 2) many residency and fellowship programs do not offer H1-B visas, and 3) step 3 not completed on time.
**Should have permanent visas in process before the time limit expires. Individuals on J-1 visas seek J-1 waivers (3-year requirement), which automatically transitions them to a H1-B, thereby beginning the 6-year time limit for H1-B.



play a pivotal role in advocating for immigration reform, are warranted (6). ■

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The author reports no conflicts of interest.

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Findings

Organ Transplant Recipients Show Lasting Immunity after COVID-19

Solid-organ transplant recipients can maintain peripheral immunity for up to 6 months after SARS-CoV-2 infection—especially with greater clinical severity—reports a pre-proof paper in *Kidney International*.

The researchers evaluated serologic and functional T-cell and B-cell immune memory against major immunogenic SARS-CoV-2 antigens. The cross-sectional study included two groups of COVID-19 convalescent patients: 53 solid-organ transplant recipients (38 kidney recipients) and 49 immunocompetent patients.

In both groups, patients were classified as having severe COVID-19, requiring hospitalization and supplemental oxygen; mild COVID-19, not requiring hospitalization; or asymptomatic infection. Immunologic assessments included SARS-CoV-2-specific serologic memory and immunoglobulin G (IgG)-producing memory B cells and SARS-CoV-2-reactive cytokine-producing memory T cells.

At a median follow-up of 199 days, memory responses in different immune compartments were similar for organ transplant recipients and immunocompetent patients. However, responses varied by COVID-19 severity: seroconversion rates for IgG antibodies to spike protein were 97.6% for patients with severe COVID-19, 80.5% for those with mild disease, and 42.1% for those with asymptomatic infection. For nucleoprotein antibodies, seroconversion rates were 92.7%, 75.6%, and 47.4%, respectively.

Similar ranges were found for IgG-producing memory B cells: severe infection, 84.0%; mild infection, 75.0%; and asymptomatic infection, 35.7%; for interferon-γ-producing T cells: 82.5%, 86.9%, and 31.6%, respectively. Regardless of COVID-19 severity, patients with longer times since solid-organ transplantation were more likely to have detectable long-lasting immune memory.

The study provides new data on long-term adaptive immune memory after SARS-CoV-2 infection in solid-organ transplant recipients. The findings show "robust humoral and cellular immune memory" lasting beyond 6 months, similar to that seen in immunocompetent patients.

Responses are driven mainly by the clinical severity of COVID-19, perhaps reflecting the level of viral antigen exposure. The researchers add, "[L]ong-lasting adaptive immunity seems to be challenged to some extent by chronic immunosuppression, especially among those more recently transplanted" [Favà A, et al. A comprehensive assessment of long-term SARS-CoV-2-specific adaptive immune memory in convalescent COVID-19 solid organ transplant recipients. *Kidney Int,* published online ahead of print February 3, 2022. doi: 10.1016/j.kint.2021.12.029; https://www.kidney-international.org/article/S0085-2538(22)00029-1/fulltext]. ■

RAASi Discontinuation for Hyperkalemia May Increase Adverse Outcomes

For patients with chronic kidney disease (CKD), discontinuing renin-angiotensin-aldosterone system inhibitors (RAASi) during episodes of hyperkalemia is associated with increased mortality and cardiovascular events, reports a pre-proof paper in the *American Journal of Kidney Diseases*.

The retrospective study included data on adult CKD patients with new episodes of RAASi-related hyperkalemia with a serum potassium level 5.5 mM or higher. Drawn from Canadian provincial databases, the analysis included 7200 patients in Manitoba and 71,290 patients in Ontario. The mean ages were 72.39 and 79.48 years, respectively. Several types of comorbidity were more frequent in the Manitoba cohort.

In response to hyperkalemia, RAASi therapy was discontinued in 35.08% of patients in the Manitoba cohort versus 14.0% in the Ontario cohort. On Cox proportional hazards analysis, RAASi discontinuation was associated with increased all-cause mortality: hazard ratio (HR) 1.32 in Manitoba and 1.47 in Ontario. Discontinuation was also linked to higher cardiovascular mortality: HR 1.28 in Manitoba and 1.32 in Ontario.

Associations were also noted for fatal and nonfatal cardiovascular events: HR 1.17 in Manitoba and 1.18 in Ontario. An association between RAASi discontinuation and risk of dialysis initiation was significant in the Ontario cohort: HR 1.11. Use of a submaximal RAASi dose was also associated with increased all-cause mortality compared with a maximal dose: HR 1.24 in Manitoba and 1.11 in Ontario.

Although RAASi are recommended as first-line therapy for CKD, they are also associated with increased risk of hyperkalemia. There is no accepted standard of care for chronic hyperkalemia in CKD patients. As shown by these Canadian data, RAASi discontinuation or dose reduction is a common strategy.

The study shows that among CKD patients with hyperkalemia, RAASi discontinuation is associated with increased all-cause mortality and cardiovascular events. "Newer medications for the treatment of hyperkalemia may enable patients to continue their RAASi after an episode of hyperkalemia," the investigators conclude [Leon SJ, et al. Hyperkalemia-related discontinuation of renin-angiotensin-aldosterone system inhibitors and clinical outcomes in CKD: A population-based cohort study. *Am J Kidney Dis*, published online ahead of print January 24, 2022. doi: 10.1053/j.ajkd.2022.01.002; https://www.ajkd.org/article/S0272-6386(22)00034-8/fulltext]. ■

KFRE Is Superior to eGFR Alone for ESKD Risk Prediction

The four-variable kidney failure risk equation (KFRE) is a better predictor of end stage kidney disease (ESKD) risk compared with the estimated glomerular filtration rate (eGFR) alone, with or without adjustment for race, reports a study in the *Annals of Internal Medicine*.

The researchers used data from the Chronic Renal Insufficiency Cohort to evaluate different eGFR equations for prediction of ESKD, defined as dialysis initiation or transplantation. The analysis included data on 3873 participants with chronic kidney disease (CKD), with a total of 13,902 2-year risk periods.

For each participant, eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation, based on serum creatinine and cystatin C, with or without adjustment for race.

A 2-year risk of ESKD was estimated using the validated KFRE, which includes age, sex, eGFR, and urinary albumin-creatinine ratio. The old and new eGFR equations, alone and as part of the KFRE, were evaluated as predictors of ESKD risk.

At up to 15 years' follow-up, 856 participants developed ESKD. With or without race-adjusted eGFR, the KFRE was superior in predicting ESKD risk: area under the curve ranged from 0.945 to 0.954 compared with 0.900 to 0.927 with eGFR alone. Although the KFRE had a similar predictive performance with different eGFR equations, the creatinine equation without race adjustment had better calibration among participants of Black race.

A KFRE score greater than 20% had 94%–97% specificity in predicting 2-year ESKD risk, similar to the 95%–98% range with eGFR less than 20 mL/min/1.73 m^2. However, KFRE over 20% had higher specificity: 68%–78% compared with 42%–66% with eGFR under 20 mL/min/1.73 m^2. Prediction was consistently better with KFRE, regardless of the eGFR estimating equation used.

Previous eGFR equations included adjustment for race, reflecting evidence that individuals of Black race have higher average serum creatinine. Newer equations have removed adjustment for race, but the impact on ESKD risk prediction remains unclear. Because the KFRE includes more information than eGFR alone, it may improve risk prediction and clinical decision-making.

The new analysis finds that KFRE scores are a better predictor of 2-year ESKD risk compared with eGFR alone. "[A] KFRE score greater than 20% could be used for preparing for kidney replacement therapy," the researchers write [Bundy JD, et al. Prediction of end-stage kidney disease using estimated glomerular filtration rate with and without race: A prospective cohort study. *Ann Intern Med*, published online ahead of print January 11, 2022. doi: 10.7326/M21-2928; https://www.acpjournals.org/doi/10.7326/M21-2928]. ■

National Kidney Month, World Kidney Day Campaigns Launch in March

By Karen Blum

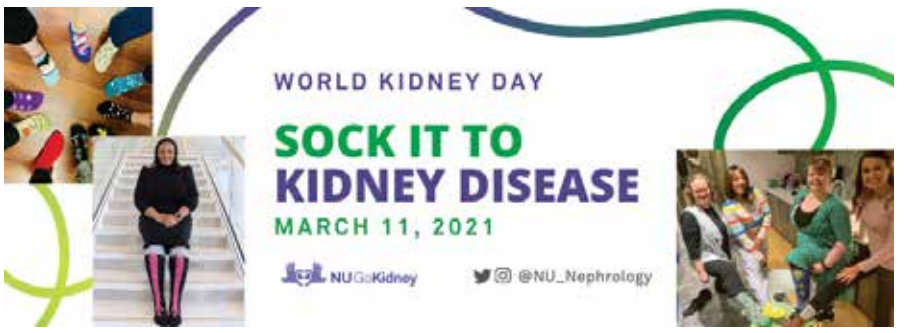
Raising awareness of kidney diseases worldwide and empowering people living with them are the focus of campaigns launching in March.

One in three adults in the United States is at risk for kidney diseases. To shed light on the prevalence of this condition, the National Kidney Foundation (NKF), in honor of National Kidney Month, asks, "Are you the 33%?"

The slogan is part of a strategic digital campaign focused on reaching, educating, and empowering Americans who are Hispanic and of Black race, as well as individuals over age 35 or those who have one or more risk factors for kidney diseases, to take control of their kidney health. Outreach planned by the foundation includes digital advertisements, tailored web content, and a customized email series.

"We want people in the community who are at risk for kidney disease to understand their risks, so that we can empower them to take control of their health and have conversations with their clinicians about testing for kidney disease," said Joseph Vassalotti, MD, chief medical officer of the NKF and an associate clinical professor of medicine at Mount Sinai in New York. Ethnic and racial disparities with regard to kidney diseases unfortunately have worsened with the COVID-19 pandemic, he said. "We have a lot of work to do to improve patient-level awareness of kidney disease."

The Northwestern University George M. O'Brien Kidney Research Core Center (NU GoKidney) celebrates World Kidney Day with its "Sock It to Kidney Disease" campaign to help raise awareness and empower people living with kidney diseases. Working with kidney diseases research advocate and hip-hop artist David Rush, who first suspected his kidney health problems by the tightness of his socks around his ankles, NU GoKidney encourages everyone to show their socks on social media to demonstrate solidarity with Rush and others all over the world.



Susan E. Quaggin, MD, FASN, ASN president and director of NU GoKidney, writes, "I am delighted that ASN will be joining NU GoKidney in this year's #SockItToKidneyDisease campaign. Last year, we reached over 350,000 people, and this year—with the help of the ASN membership—we are hoping to reach even more!"

In related news, World Kidney Day is slated for Thursday, March 10, with the theme "Kidney Health for All." Specifically, it calls on the nephrology community and others to work to bridge the knowledge gaps toward better kidney care. "Improving health literacy largely rests with health care providers communicating and educating effectively in code-signed partnership with those with kidney disease," wrote Robyn G. Langham, MD, PhD, a nephrologist with the University of Melbourne in Australia, along with other World Kidney Day Joint Steering Committee members, in an editorial in *Kidney International* and *Nephrology Dialysis Transplantation* (1, 2). "The growing capability of and access to technology provides new opportunities to enhance education and awareness of kidney disease for all stakeholders," the authors said.

"As we move into a much more technically literate world, health literacy is sort of struggling to keep up," Langham told *Kidney News*. "It's fair to say that most people would know a little bit about their heart, heart disease, cholesterol and blood pressure. But when you ask [average people] on the street about kidneys, they don't know where they are; they don't know what they do. It's a little bit harder when it's a hidden organ that does all of its work silently in the background, and it has very few ways of telling us that it's sick."

Kidney organizations should work toward shifting the patient-deficit health literacy narrative to that of being the responsibility of health care providers and health policymakers, Langham and her coauthors wrote. Low health literacy occurs in all countries regardless of income status; therefore, simple, low-cost strategies are likely to be effective. Good communication can be implemented by all kidney health team members, they said, including nurses, advanced practice providers, dietitians, pharmacists, and other allied health professionals.

"Through this vision, kidney organizations will lead the shift to improved patient-centered care, support for care partners, health outcomes, and the global societal burden of kidney health care," the authors wrote.

This is a call to nephrologists to be better communicators to patients and caregivers, medical students, physician colleagues, and others, Langham and Vassalotti agree. Nephrologists tend to start formulating answers to patient questions as they are talking, Langham added. But for health literacy, she said, it's important to fully understand where the patient's need is and to stop and listen before responding.

For more information on National Kidney Month and the NKF campaign, see https://www.kidney.org/nkmtoolbox. For more information on World Kidney Day, see https://www.worldkidneyday.org/2022-campaign/2022-wkd-theme/. These websites have tools, such as messages to share on social media, Zoom backgrounds, posters, and a sample letter requesting businesses and landmarks to "light up orange."

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A Decade of NephMadness: The 2022 Tournament Explained

It's March, spring is in the air, and periodic bracket fever has caught up with the nephrology community for the 10th year in a row! What is NephMadness, you may ask? NephMadness is a medical education event held in your practice, your division, and on social media to celebrate all things kidney.

NephMadness is a single-elimination tournament consisting of 32 nephrology concepts, divided into 8 regions, representing the most exciting topics in nephrology. The purpose of the game is to discuss and debate each of these concepts during the month of March. Throw a NephMadness party for your group, and learn in a fun and inspired way. We even have a PowerPoint presentation pre-made! Go on social media using the hashtag #NephMadness to engage with the online nephrology community.

Fill out your brackets (individually or as a team), and see if your picks match the 10th anniversary blue ribbon panel. Winners of each matchup will be determined by a 21-member panel of honorable judges—the blue ribbon panel—who have served in this capacity sometime over the past 10 years. The six rounds of voting will culminate in the crowning of the NephMadness champion. The real winners, however, are the thousands of NephMadness fans who get to read and learn some of the finest nephrology educational content of the year, while networking with colleagues on social media and in their own institutions. You can even get CME/MOC credit! NephMadness bracket submissions are open from March 1 through March 31, 2022.

This year's regions are Lupus Nephritis, Animal House 3 (back by popular demand), Hemodialysis, Inequities (this work is never finished), Parasites, Cardiorenal, Neonatal, and Nephropathology (Figure 1).

NephMadness began in 2013 as a way to harness the passion of March Madness, "one of the biggest, most exciting and fun events of all of sports" (1), and apply it to our beloved field of nephrology. Since then, gamification of medical education has begun in earnest. In the past 10 years, the executive team has grown to include Anna Burgner, Timothy Yau, Samira Farouk, Pascale Khairallah, and Anna Vinnikova, with each person bringing his or her unique expertise to the game.

Don't forget that players with the highest scores, the best NephMadness parties, and much more will win NephMadness swag, awarded by the *American Journal of Kidney Diseases* and the National Kidney Foundation. ■

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Figure 1. 2022 NephMadness Tournament

Intravenous Iron—Moving beyond Anemia

By Nupur N. Uppal and Steven Fishbane

In recent years, cardiologists have taken an approach to intravenous (IV) iron that is very different from that of nephrologists. In kidney disease, the role of IV iron is contemplated solely in relation to anemia, to improve hemoglobin, and as a support for erythropoietin-stimulating agent (ESA) therapy. This is a narrow view that fails to recognize that iron is not just important to manage anemia but that it is a basic health need for humans through its much broader significance for muscular function, energy creation, and storage as adenosine triphosphate.

In cardiology, this approach has led to a series of trials where IV iron has been studied, not to raise hemoglobin but to improve various higher-level health outcomes. This has been most apparent in seminal studies of IV iron in symptomatic patients with chronic heart failure (New York Heart Association class II-III) and iron deficiency (defined as ferritin <100 µg/L or between 100 and 299 µg/L with transferrin saturation <20% (1), ferritin <100 ng/mL, or 100–300 ng/mL with transferrin saturation <20% (2)). In these studies, IV iron has been shown to improve functional capacity and quality of life (QoL), improve heart failure stage, reduce hospitalizations, and ameliorate other critically important measures of health, regardless of the level of hemoglobin (1, 2). Recently, another trial that included patients with iron deficiency (ferritin level <100 µg/L or between 100 and 299 µg/L with transferrin saturation <20%) and a left-ventricular ejection fraction ≤50%, who stabilized after an episode of acute heart failure exacerbation, has also shown beneficial effects of IV iron on health-related QoL as early as 4 weeks after initiation of therapy (3).

In a recent article published in *Cardiovascular Research*, Petrie et al. (4) performed a post hoc analysis of the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial, a study comparing higher-dose IV iron with a more reactive approach among 2141 patients on maintenance hemodialysis who were already being treated with ESAs. The primary outcome of the PIVOTAL trial found a small but significant improvement in a composite endpoint of non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for heart failure, or death (5). Petrie and colleagues (4) focused specifically on MI. They found that the proactive high-dose IV iron group had a reduced rate of non-fatal and fatal MI (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.52–0.93, p = 0.01) and non-fatal MI (HR 0.69, 95% CI 0.51–0.93; p = 0.01) when compared with reactive IV iron. This is an eminent finding that helps to bridge nephrology into a broader view of IV iron in which we look beyond anemia toward an appreciation of iron's beneficial cardiac and other health effects.

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Dr. Uppal reports no conflicts of interest. Dr. Fishbane has been a research consultant with Akebia Therapeutics, GlaxoSmithKline, AstraZeneca, and FibroGen.

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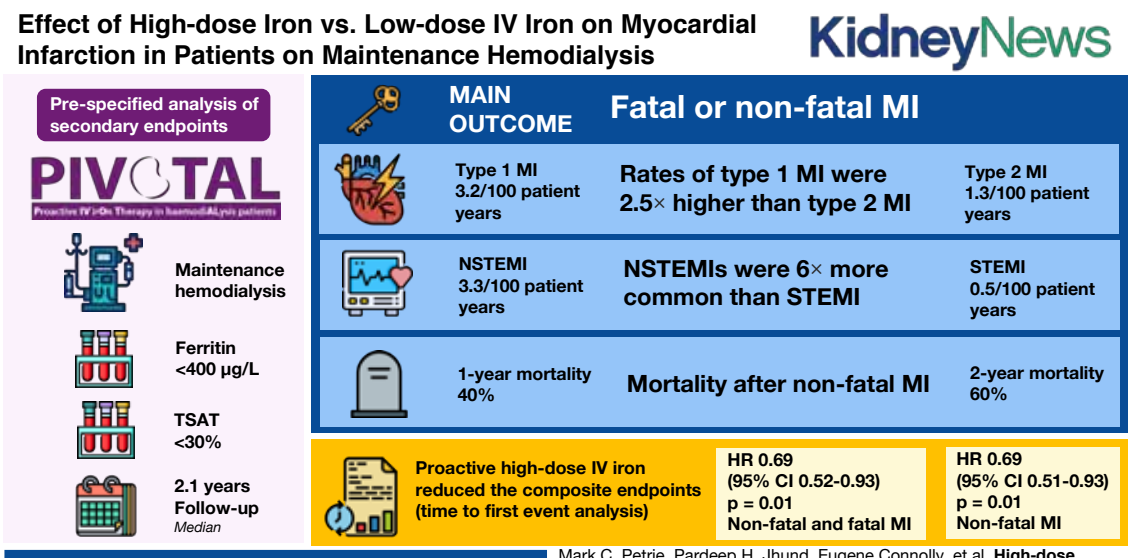

NSTEMI, non-ST-segment elevation myocardial infarction; TSAT, transferrin saturation.

Are you a fellow and have a tip or idea you'd like to share with your fellow peers and the broader kidney community?

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

117th Congress: Short on Time but Not on Kidney Policy Opportunities

Congress is staring down a significant number of legislative backlogs as it begins the 2022 calendar year. Congress must still finalize fiscal year (FY) 2022 appropriations before FY 2023 appropriations negotiations can commence, confirm the heads of both the US Food and Drug Administration and National Institutes of Health amid the global COVID-19 pandemic, and confirm a Supreme Court justice to replace retiring Justice Breyer, all with mid-term elections fast approaching this fall. But, there is cause for genuine optimism among the kidney community, as improving kidney health through transformative regulatory and legislative action continues to receive robust bipartisan support from the Biden administration and both chambers of Congress.

ASN is hoping to capitalize on the momentum of recent kidney policy wins, including working with federal stakeholders to implement new value-based care models, prioritizing COVID-19 vaccination for people with kidney failure in dialysis facilities and for patients who are immunosuppressed, passing legislation to provide immunosuppressive drug coverage to kidney transplant patients, increasing transparency and accountability in organ donation, securing $15 million in funding for Kidney Innovation Accelerator (KidneyX) to increase innovation in kidney health, and promoting improved methods of diagnosing kidney diseases that increase equity.

In an effort to create a world without kidney diseases, ASN engages kidney health professionals, the kidney health community, and stakeholders across the federal government to embrace the four priorities of the "We're United 4 Kidney Health" campaign:

- INTERVENE EARLIER to prevent, diagnose, coordinate care, and educate
- TRANSFORM TRANSPLANT and increase access to donor kidneys
- ACCELERATE INNOVATION and expand patient choice
- ACHIEVE EQUITY and eliminate disparities

The ASN Policy and Advocacy Committee and the ASN Quality Committee used the campaign's four priorities as guiding principles when identifying the following kidney policy priorities for 2022 and beyond:

1. Bolstering federal support for appropriate screening of people at risk for kidney diseases, including revising the outdated US Preventive Services Task Force screening recommendations
2. Increasing equity in access to transplant care and the availability of donated organs, including but not limited to increasing transparency and accountability in donation, reducing organ discards, and ensuring metrics used to evaluate transplant centers and transplant candidates are patient centered and promote organ access
3. Urging Congressional investment in increased funding for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to fund research on estimated glomerular filtration rate (eGFR) with new endogenous filtration markers and on interventions to eliminate racial and ethnic disparities
4. Ensuring patient access to new drugs and devices by improving and clarifying the processes by which Medicare adds new products to the dialysis bundled payment
5. Championing the We're United 4 Kidney Health campaign by galvanizing the nephrology community around four principles for the future of kidney care
6. Investing in making home dialysis an option for more patients, including implementing the recommendations of the ASN Home Dialysis Task Force, advocating for home assistance and remote patient-monitoring opportunities, as well as addressing the nursing shortage
7. Raising awareness about the promise of new classes of preventive kidney medications and addressing patient access issues
8. Advocating for $25 million for KidneyX to support the Artificial Kidney Prize and other prize competitions to continue to drive innovation in kidney health
9. Calling on the Department of Health and Human Services to improve upon the Strategic National Stockpile to ensure it meets the needs of people with kidney diseases in future emergency situations
10. Upholding government agencies to greater data transparency

To achieve these kidney policy goals, ASN will concentrate on educating and building support for new concepts that improve the diagnosis of kidney diseases, building a growing coalition of kidney champions in Congress and the Biden administration, and collaborating with the broader kidney community, including individual patient and professional organizations.

Nephrologists in the Driver's Seat for New Value-Based Partnerships

By Mary Jane Gore

Strive Health (Strive) has launched contracted partnership models under the Medicare program, Comprehensive Kidney Care Contracting (CKCC). Strive has partnered with 260 nephrology providers in five states in federally defined Kidney Contracting Entities (KCEs) to serve 8200 patients. Goals include delaying the progression of chronic kidney disease (CKD) to end stage kidney disease (ESKD) and supporting patients transitioning to dialysis and those going through the transplant process. Such efforts should reduce Medicare costs; a percentage of savings will return to the KCE partners.

Strive also announced that, to date, the company is managing 44,000 complex CKD and ESKD patients through its various nephrology partnerships/direct-care arrangements, and a media release recapped several positive results. For example, the company's approach led to a 36% reduction in 30-day hospital readmissions, compared with a 3-year historical benchmark, for patients who enrolled in a Strive system accountable-care organization program.

With a history since 2018 of using specific analytics and last year's announcement of the Strive Care Partners models to improve kidney patient care, Strive Medical also impressed Nephrology Associates of Northern Illinois and Indiana (NANI) and became a strategic partner with its large multigroup practice. (NANI made an equity investment in Strive, joining New Enterprise Associates, Alphabet's CapitalG, and other venture capital investors.)

NANI nephrologist George Naratadam, DO, who is based in Chicago, said NANI was involved in earlier iterations with ESKD patients, but now the practice has a KCE partner and can retain help, for example, leveraging analytical data, ensuring smoother transitions when a patient leaves the hospital, and doing more work in the office setting with advanced CKD patients as opposed to on dialysis units. Likewise, Naratadam explains, "Depression screening also should be done, and we thought our patients would be best served if we partnered with another organization that specializes in population health."

Strive is embedding complete-care resources within NANI practices, such as preventive care, specialized clinical programs, data integration and analytics, and management of risk contracts. After 6 months of examining its systems and 6 months of working with Strive, the KCE has been operating for 1 month at the time of reporting. NANI is still learning about how best to use the analytic data, but Naratadam said the program already has helped NANI focus on patients with high utilization rates that drive up costs (e.g., patients at higher risk for readmissions or unscreened for existing depression).

The Strive KCEs are founded on the idea of value-based medicine. Strive Senior Vice President of Provider Solutions Ben Kuhn defines value-based care as contracts that "compensate providers for good outcomes rather than the volume of services they deliver." All Strive-partnered KCEs are taking responsibility for the total cost and quality of care for their patients (known as the "Global Option"), taking risk away from Medicare; savings await for effective care. KCEs can contract with a choice of three options, including a safer, graduated risk option, Kuhn said.

Naratadam explained that NANI is currently focusing on finding more opportunities for patient education, including a video for patients, and discussions with a practice or Strive nurse practitioner. He anecdotally recounts how the KCE also is embracing care coordination. After patients on dialysis experienced problems on weekends, he noted, "We got a very nice report on my region and our bigger groups' access data, and we saw based on the claims data exactly where people had gone, what the cost was, and how they were admitted…. I think it was an eye opener."

The KCE care coordinator, provided by Strive, can arrange rides "to get a patient 10 miles more than [he or she] would have gotten on [his or her] own, to a dialysis center for assistance, get de-clotted before the weekend, and not get admitted," Naratadam says. He also explained that with the new partnership, already one patient has been able to quickly obtain secondary health insurance, the issue that was holding up a kidney transplant. The practice relied on a Strive social worker for insurance assistance and a care coordinator to work with the transplant center.

Kuhn said the common theme across Strive's KCEs is prevention—of progression to kidney failure, of hospitalization, or of unplanned or unexpected crash onto dialysis.

Failing Kidney Transplants Require a Multidisciplinary Approach, including Palliative Care

By Christina Mejia

Despite improvements in long-term allograft survival in the United States, at least one-quarter of deceased donor kidney transplant recipients will experience allograft failure in their lifetime (1). Studies have shown that the period of transition back to dialysis is marked by increased morbidity and mortality, and recipients with failing allografts receive suboptimal care (2, 3). Transplant communities are starting to recognize the challenges that these recipients face.

The British Transplantation Society and more recently, the American Society of Transplantation released recommendations providing guidance on issues such as immunosuppression withdrawal and preparation for dialysis or re-transplantation (4, 5). Close communication between transplant and general nephrologists is encouraged, and use of a multidisciplinary team, including a nutritionist, pharmacist, nurse, and social worker, has been proposed to address the complications of advanced chronic kidney disease and complications attributable to transplant and chronic immunosuppression (Figure 1). What remains underappreciated, however, is the role of palliative care in the management of recipients with failing allografts. This is despite the increasing number of older transplant candidates and knowledge that the majority of kidney transplant recipients succumb to the burden of their comorbid conditions, such as cardiovascular disease and malignancy (6). One study found that compared with patients who were never waitlisted or transplanted, patients exposed to the kidney transplant process were more likely to receive intensive care or invasive procedures in the last month of their life and were less likely to be considered for hospice (7).

In a recent research letter to *Kidney Medicine,* Murakami et al. (8) reported the impact of implementing an inpatient kidney palliative care service on end-of-life care decisions among kidney transplant recipients with failing allografts and those who experienced death with a functioning allograft. Dubbed KidneyPal, the service was composed of a social worker, a nurse practitioner, and a palliative care specialist who "aligned" themselves with nephrology. The authors performed a cross-sectional study comparing the period 2 years before and after the implementation of KidneyPal. The program had minimal impact on end-of-life decisions among recipients who experienced death with a functioning allograft. However, for recipients with failing allografts, inpatient palliative consultation and death in hospice increased after KidneyPal implementation. Among recipients with failing allografts, discussions about treatment options for allograft failure and symptom management and consideration for a time-limited trial of dialysis also increased.

The role of palliative care in solid organ transplant recipients is better realized in liver, heart, and lung transplant recipients than in kidney recipients (9). This is not surprising because dialysis remains an option after kidney allograft failure, whereas life-prolonging interventions are more limited after non-kidney allografts fail. Non-kidney allograft recipients are also more likely to have been exposed to palliative consultation before transplant due to their poorer health status compared with kidney failure patients.

In the past decade, however, interest in palliative care nephrology has been increasing. More studies have been published exploring conservative kidney management, shared decision-making, and outcomes such as quality of life and symptom management (10). Most studies involve incident kidney failure patients, whereas the study by Murakami et al. (8) is one of the few that focused on kidney transplant recipients. Their study highlighted the value of a specialized palliative care service, capable of offering discussions about issues unique to kidney patients, such as goals of dialysis (e.g., trial, bridging, or destination therapy).

The role of palliative care in recipients with failing allograft can further be expanded to address unique psychosocial issues that these patients experience. In addition to depression and denial, even compliant patients resort to self-blame, thinking they could have done something to prevent allograft failure. Some recipients express intense fear of returning to dialysis because of previous experience, whereas others are simply unfamiliar with the recent advancements in dialysis such as home hemodialysis. Because improved quality of life is one of the major advantages of kidney transplant over remaining on dialysis, helping recipients come to terms with the expected changes in quality of life may help alleviate the emotional trauma from transitioning back to dialysis.

Finally, with guidance from transplant nephrologists, palliative care specialists can assist in managing patient expectations regarding re-transplant candidacy, especially for those who have become frailer since their first transplant surgery. Although Murakami et al. (8) explored KidneyPal in hospitalized patients, future directions should include expanding access to palliative care in the outpatient setting where discussions can occur early, and patients and their families are not pressed for time.

Kidney recipients with failing allografts are medically and psychosocially complex, and there is still a lot to be learned to provide them with better care. Initiatives such as KidneyPal remind us of the importance of a multidisciplinary and patient-centered approach to managing recipients with failing allografts. ■

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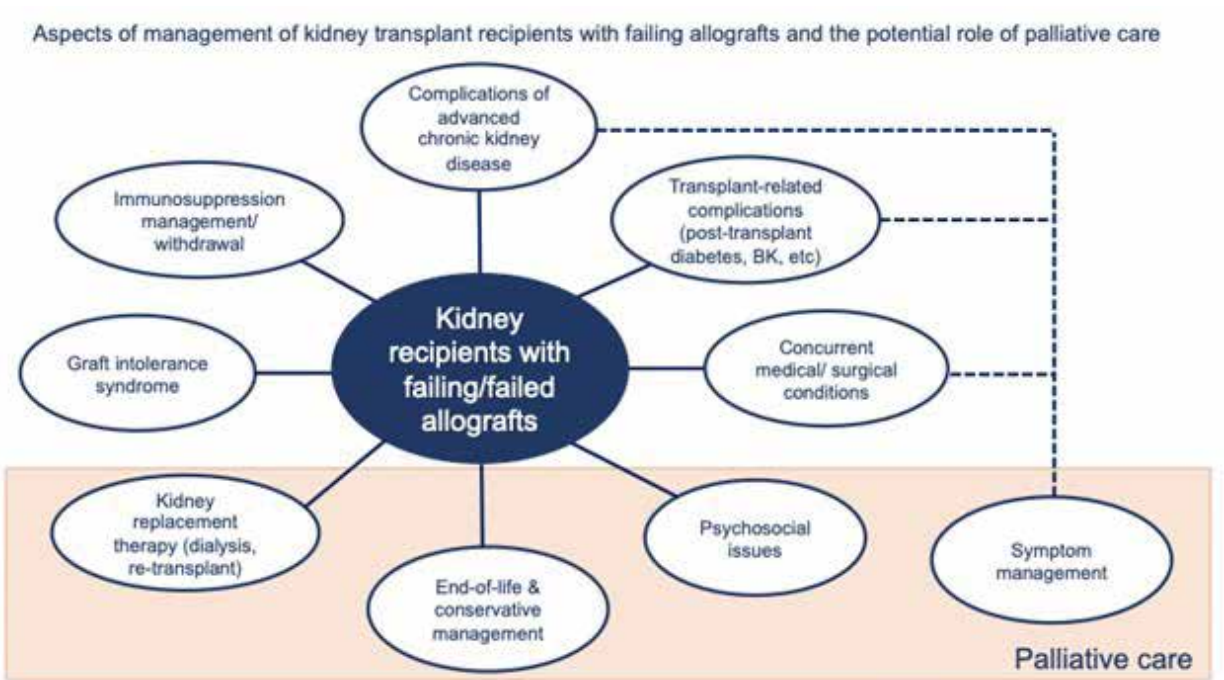
Figure 1.



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