ASN American Society of Nephrology

KIDNEY WEEK EDITION

Kidney News

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New Race-Free eGFR Equation Welcomed, Focus Turns to Implementation

By Eric Seaborg

Laboratories across the country should quickly implement a "refitted" Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation that does not include a race coefficient for estimating glomerular filtration rate (GFR), but the future of estimated GFR (eGFR) could lie with equations that combine creatinine with cystatin C because they offer greater accuracy. Those are two key takeaways from the recently released report of the National Kidney Foundation (NKF)-American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases.

Because the task force is recommending an adaptation of a widely used equation, experts told *ASN Kidney News* that they see few barriers to its adoption by many laboratories.

The recommendations were published simultaneously in *JASN* (1) and the *American Journal of Kidney Diseases* (2) and were accompanied by a pair of related articles in *The New England Journal of Medicine* (*NEJM*) (3, 4). In one of the *NEJM* articles, the researchers of the CKD-EPI—the source of the eGFR equations currently in wide use—reanalyzed their data sets to evaluate three current and four new equations.

The task force settled on one of the new equations, which it refers to as the CKD-EPI creatinine equation refit without the race variable (CKD-EPIcr_R), to recommend for immediate use. "In addition to not including race in the calculation and reporting, it included diversity in its development, is immediately available to all labs in the U.S., and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals," according to the task force report.

That laboratory availability will obviously be a key. The task force included an influential laboratory representative in the person of Greg Miller, PhD, a former president of the American Association for Clinical Chemistry (AACC).

"I anticipate reasonably rapid uptake to use the new equation," said Miller, who is professor of pathology and co-director of clinical chemistry at Virginia Commonwealth University in Richmond. "The change is to software to use the new equations in place of the existing equations. The mathematical form of the new equations is very similar to the previous CKD-EPI or MDRD [Modification of Diet in Renal Disease] equations."

But he estimated it will take 6 months even in the labs that are "anxiously awaiting" the recommendation, and a timeframe of 1 year or 2 is realistic for other labs: "Implementing the new equations requires labs to schedule the

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Kidney Week Scientific Sessions

THURSDAY

Public Health Lessons Learned and Implications for Future Pandemics
Panel with Anthony Fauci and Sanjay Gupta

Applied Precision Medicine in Glomerular Diseases
Barry M. Brenner, MD, Endowed Lectureship: Matthias Kretzler, MD

FRIDAY

Social Inequities in Health: How Can We Effectively Reduce Them?
State-of-the-Art Lecture: David R. Williams

Genetic Discovery in IgA Nephropathy
American Society of Nephrology-American Heart Association Donald W. Seldin Young Investigator Award: Krzysztof Kiryluk

Elephant in the Room: Sex and Racial Disparities in Kidney Transplantation
Garabed Eknoyan, MD, Endowed Lectureship: L. Ebony Boulware

Oxygen Biology and Metabolism in the Kidneys
Robert W. Schrier, MD, Endowed Lectureship: Masaomi Nangaku

From Morphology to Mechanisms
Michelle P. Winn, MD, Endowed Lectureship: Vivette D'Agati

SATURDAY

The Future of Health and Medicine: Where Can Technology Take Us?
State-of-the-Art Lecture: Daniel Kraft

Make It Plain: The Patient Perspective on CKD Terminology
Celeste Castillo Lee Memorial Lectureship: Glenda V. Roberts

Novel Insight into the Contribution of Phosphate to Mineral and Bone Defects in CKD
Jack W. Coburn, MD, Endowed Lectureship: Hartmut H. Malluche

Evolution of Renal Pathophysiology: Key Observations over Five Decades
Burton D. Rose, MD, Endowed Lectureship: Helmut G. Rennke

SUNDAY

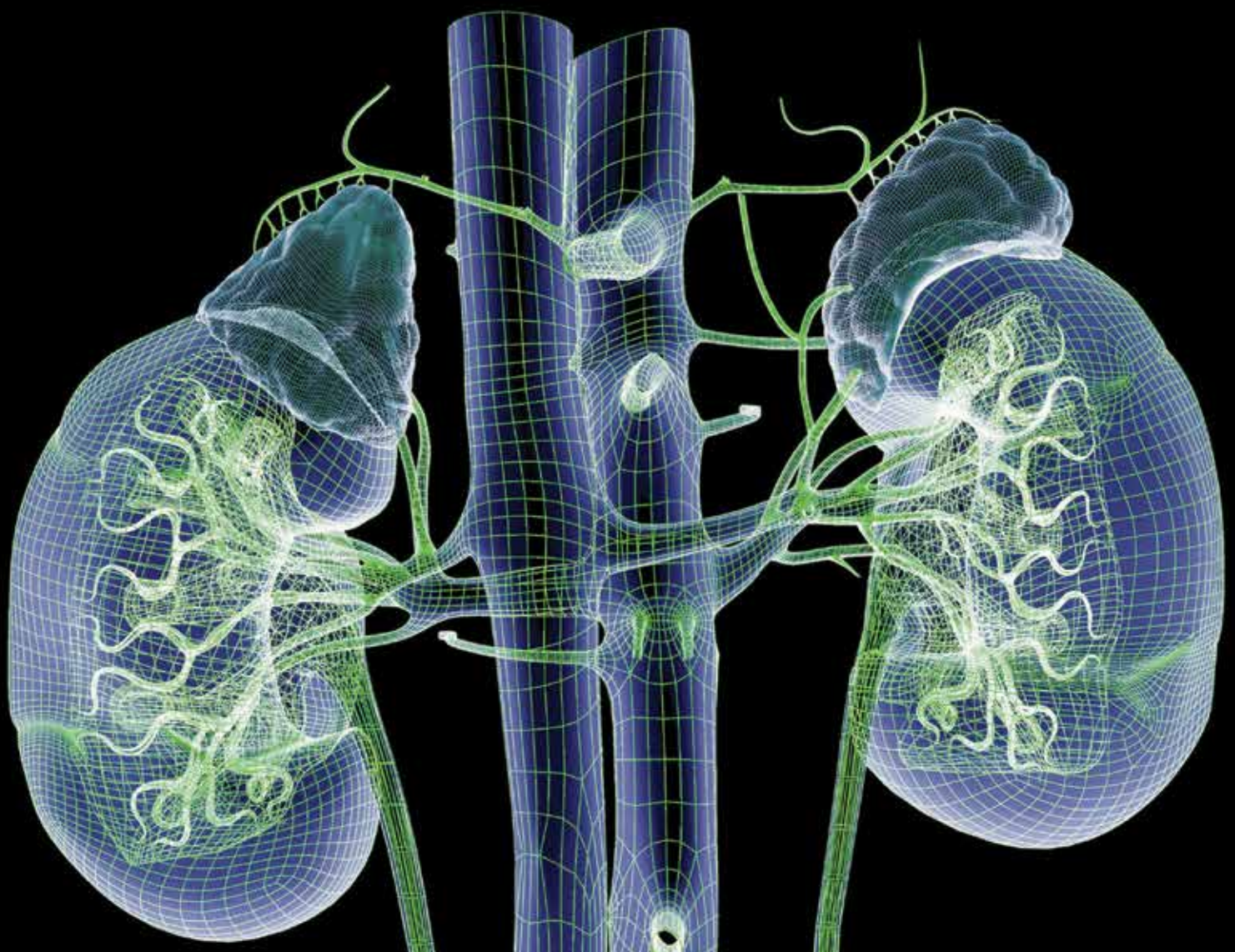
Telomeres and Telomerase in Health and Kidney Disease
State-of-the-Art Lecture: Carol W. Greider

From Understanding Kidney Development to Rebuilding a Kidney: Progress and Challenges
Homer W. Smith Award: Melissa H. Little

Inside the Beltway: Why Everyone is a Stakeholder in Kidney Health Policy
Blagg Endowed Lectureship: Reps. DelBene and Bucshon

Inside

CHINOOK
THERAPEUTICS



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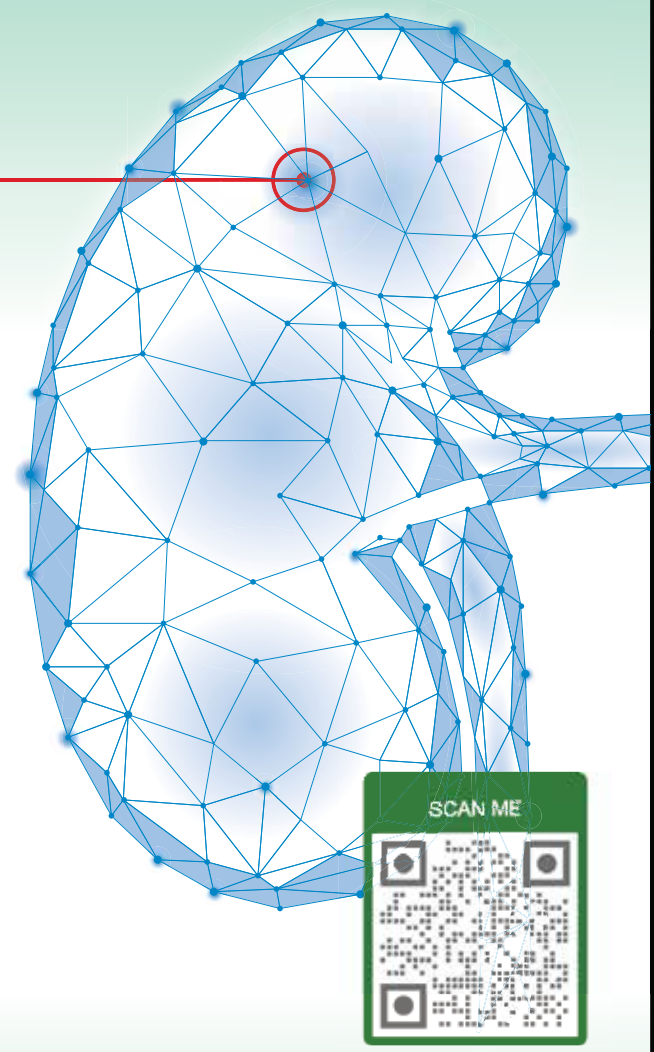
TARGETED THERAPY

for IgA Nephropathy

The ALIGN Study is evaluating an investigational medication* called atrasentan, which has the potential to reduce proteinuria and preserve kidney function in patients with immunoglobulin A nephropathy (IgAN).



ALIGN

Diagnosis of IgAN, FSGS, Alport syndrome or DKD?

The AFFINITY Study is evaluating an investigational medication* called atrasentan, which has the potential to reduce proteinuria and preserve kidney function in patients with IgAN, focal segmental glomerulosclerosis (FSGS), Alport syndrome and diabetic kidney disease (DKD).

AFFINITY

* An investigational drug is a drug that has not yet been approved by regulatory authorities. Efficacy and safety have not been established. There is no guarantee that it will become commercially available for the use(s) under investigation.

ASN American Society of Nephrology

KidneyNews

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ASN Kidney Week—New in 2021

Transition from Hybrid to Fully Virtual

With increasing uncertainties around variants of the COVID-19 virus, ASN canceled plans for the in-person component of ASN Kidney Week 2021 in San Diego, CA. Putting health and safety first, ASN firmly believes this decision is in the best interest of meeting participants, stakeholders, partners, and—most important—the millions of people who have entrusted us with their healthcare.

Please refer to the Kidney Week FAQs for more information.

Meeting Platform

All meeting content will be available to all participants on the Kidney Week platform until Friday, January 7, 2022. In late January 2022, this content will move to the ASN eLearning Center for up to three years and continue to be complimentary to meeting participants who obtain an access code. Access code information will be available in October.

Joint ASN-NAM Opening Plenary on Thursday, November 4

ASN and the National Academy of Medicine have partnered on the opening plenary featuring a COVID-19 panel discussing the most up-to-date information about COVID-19 with a global focus on kidney health:

- Sanjay Gupta, MD, CNN, Emory University (Moderator)
- Anthony S. Fauci, MD, National Institute of Allergy and Infectious Diseases, National Institutes of Health (Keynote)
- Amitava Banerjee, MD, MPH, DPhil, University College London
- Ashish K. Jha, MD, MPH, Brown University
- Jeffrey I. Silberzweig, MD, FASN, The Rogosin Institute
- Susan R. Weiss, PhD, University of Pennsylvania

Inaugural Garabed Eknoyan, MD, Endowed Lectureship

Garabed Eknoyan, MD

ASN is pleased to announce this new lectureship honoring Garabed Eknoyan, MD, the esteemed researcher, educator, and clinician. Dr. Eknoyan is widely recognized as a key architect of evidence-based and expert-generated clinical practice guidelines in nephrology. His commitment to identifying the best demonstrated clinical practices has led to improved outcomes and enhanced care for kidney patients. This lectureship in his honor recognizes innovative advances in clinical care of patients with CKD or ESKD on dialysis.

L. Ebony Boulware, MD, MPH, will deliver the inaugural lecture on "Elephant in the Room: Sex and Racial Disparities in Kidney Transplantation."

ASN gratefully acknowledges Wadi N. Suki, MD, for support of this lectureship.

Advances in Research Conference on Artificial Intelligence and Implementation Science

All Early Programs will be fully virtual with on-demand content available in the meeting platform on Monday, October 25. Co-chaired by Steven G. Coca, DO, MS, and Reem Mustafa, MD, PhD, MPH, FASN, this year's Advances in Research Conference features experts in computational biology, machine learning (ML), and informatics who discuss the latest advances, facilitators, and barriers to wider implementation of AI in medicine and nephrology. Provided a foundation of key principles, terms, and applications related to AI and implementation science, participants explore the opportunities these tools can bring to improving research and clinical care in kidney diseases.

New Race-Free eGFR Equation

Continued from cover

changes with IT departments and obtain a priority for making the change."

Hospital-affiliated and national referral laboratories are likely to be aware of and act on the recommendations first, but there are more than 100,000 labs that measure creatinine registered under the Clinical Laboratory Improvement Amendments (CLIA). It could take time for smaller labs like those in doctors' offices to get the message and make the change to the new equations.

"Persistently repeated communication using a variety of approaches will be needed," Miller said, and the AACC, College of American Pathologists, and American Society for Clinical Pathology have all "indicated support to communicate to members and the public."

The AACC had its own task force on removing race from GFR estimates, chaired by Melanie Hoenig, MD, an associate professor of medicine at Harvard Medical School and a nephrologist at Beth Israel Deaconess Medical Center who spearheaded that institution's effort to move away from the standard equation 4 years ago. After its own evidence-based review, AACC "will endorse the NKF-ASN plan for immediate shift to the CKD-EPI refit" equation, Hoenig said.

Other centers at the forefront in the reconsideration of the race coefficient reported being eager to switch to the new equation.

"Our institution will be implementing the new CKD-EPI Cr equation as soon as possible," said Alp Ikizler, MD, director of the Division of Nephrology at Vanderbilt University. Last year, Vanderbilt dropped African American reporting with "no replacement for race-related or adjusted reporting."

"We are very pleased that the recommendations include implementing a new race-free eGFR Cr equation which can be easily and quickly implemented by all labs in the U.S. This will entail a change in coding and should not be difficult to implement," Ikizler said in a collaborative email to *ASN Kidney News* with Beatrice Concepcion, MD, who has been the lead at Vanderbilt for this initiative. They will also be exploring the possibility of reporting an eGFR using a combined creatinine and cystatin C equation.

"We anticipate implementing it shortly," said Rajnish Mehrotra, MD, MBBS, interim head of the Division of Nephrology at the University of Washington School of Medicine in Seattle. "It provides greater accuracy than the 2009 CKD-EPI equation that we are currently using without the race coefficient . . . and the magnitude of change with the 'refit' is actually not large and implementing it will mean changes to coding to adjust the calculation."

Illustrating the low barrier to introducing the change, the NKF already has a calculator on its website (https://www.kidney.org/professionals/kdoqi/gfr_calculator) for what it is calling the CKD-EPI creatinine equation (2021).

What may feel like a small change in the equation was the result of an exhaustive process by the task force, which included 14 members with broad expertise in healthcare disparities, epidemiology, health services research, genetic ancestry, clinical chemistry, patient safety and performance improvement, pharmacology, and social sciences, as well as two patients.

The task force conducted more than 40 sessions to assemble and review the data and evidence, including hundreds of papers, and heard testimony covering a broad range of related topics from 97 experts presenting a diversity of views, as well as from patients and other stakeholders. The task force considered 26 different potential strategies suggested by a variety of experts.

"The holistic approach incorporated input from the medical community and patients to identify an approach that balanced social justice with scientific rigor," NKF-ASN task force co-chair Cynthia Delgado, MD, said. Delgado is associate professor of medicine at the San Francisco Veterans Affairs Healthcare System and the University of California, San Francisco (UCSF).

The other task force co-chair, Neil Powe, MD, MPH, MBA, cautioned that nephrologists should remember that the equation is only one part of the diagnostic process. Powe is chief of medicine at the Priscilla Chan & Mark Zuckerberg San Francisco General Hospital & Trauma Center and distinguished professor at UCSF.

"The equation cannot be taken in isolation of the whole approach to diagnosing kidney disease," Powe said. "You don't just measure how well the kidney is working by looking at the GFR. You have to look at albumin excretion and protein excretion by the kidney, and take a holistic view" of the individual's entire clinical situation.

"I am really excited that the task force achieved its goal," Powe said. "However, the goal was not just an equation. For someone like myself, who's studied health disparities in kidney disease for a few decades, the goal was to achieve health equity and quality of care for Black Americans and other minorities, and that is bigger than the equation. We need to put our focus on eliminating disparities and differences in care of people by race. So, there is a lot more work to achieve that goal, and I hope everyone congeals around that. Let's go out and do the work that we need to do to really achieve health equity."

The University of Washington's Mehrotra echoed that sentiment: "Removing the race coefficient from eGFR is just the first and very small step in reducing health disparities with kidney disease. There is a lot of urgent work that still needs to be done to bring equity to kidney care delivery."

In another category of long-term goals, both *NEJM* articles (see sidebar) concluded that including cystatin C in GFR estimates improves results, so the NKF-ASN task force included a second recommendation: "We recommend national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in adults who are at risk for or have chronic kidney disease, because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either one marker alone."

Former AACC president Miller said that this greater use is within reach: "The measurement of creatinine and cystatin C [is] well standardized. The new equations offer an opportunity to standardize the calculations to have consistent eGFR values from all laboratories."

The nephrologists contacted by *ASN Kidney News* expressed satisfaction with the work of the task force. "I am impressed with the task force process and product," Hoenig said. "They used a methodical and comprehensive approach. I particularly liked how they explored the evidence, pursued a range of voices, and then made it clear that these voices were heard."

"[We] think the task force should be commended for their outstanding work," said Vanderbilt's Ikizler and Concepcion. "We think this is just a first step in dismantling race-based medicine, and we as a nephrology community should continue to lead in this effort, with the ultimate goal of achieving health equity for all. The next step is to spread the word and educate the community (primary care providers, other specialties, colleagues in laboratory medicine) regarding this change and its implementation. Practicing nephrologists will undoubtedly take the lead and will need to advocate for this change in institutions where they practice. Patient education and resources will also be very important." ■

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New England Journal Publishes New Equations

The task force report was released on the same day as a pair of studies in *The New England Journal of Medicine* (*NEJM*) focused on new methods of estimating kidney function.

One of these studies, by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), identified the new equation endorsed for use by the NKF-ASN task force that the task force refers to as the CKD-EPI creatinine equation refit.

To develop the new equations, the CKD-EPI researchers went back to the data sets previously used to develop the equations in current use for estimating glomerular filtration rate (GFR). These sets included the 10 studies used for the CKD-EPI 2009 estimated GFR (eGFR) creatinine as well as the 13 studies used in development of the CKD-EPI 2012 eGFR cystatin C and eGFR creatinine-cystatin C equations. The researchers used the data sets to compare the accuracy of the estimates of various equations to measured GFR.

For external validation, the researchers used a new data set they dubbed the CKD-EPI 2021, which consisted of the CKD-EPI 2012 external validation data set and 12 additional new studies to compare the performance of current and new equations. The researchers evaluated three current and four new equations. They noted that many institutions have been using the current CKD-EPI equation but dropping the race coefficient, a practice that "could lead to large errors in GFR estimation in some Black persons," and that the new "refit" equation "may be more equitable…because it averages observed differences across all persons and may be more appropriate for the increasingly diverse U.S. population."

Overall, however, the researchers concluded that "new eGFR equations that incorporate creatinine and cystatin C but omit race are more accurate and led to smaller differences between Black participants and non-Black participants than new equations without race with either creatinine or cystatin C alone."

The other *NEJM* article, by Hsu et al., analyzed data from a sample of 1248 participants in the Chronic Renal Insufficiency Cohort study database to test models for estimating GFR. The researchers concluded: "The use of the serum creatinine level to estimate the GFR without race (or genetic ancestry) introduced systematic misclassification that could not be eliminated even when numerous non-GFR determinants of the serum creatinine level were accounted for. The estimation of GFR with the use of cystatin C generated similar results while eliminating the negative consequences of the current race-based approaches."

An editorial published in conjunction with the two papers highlighted the importance of cystatin C: "If the capacity to measure cystatin C routinely were widespread, cystatin C equations would become practical; thus, we suggest that the use of cystatin C measurements should be encouraged and funded." ■

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CKD=chronic kidney disease; CV=cardiovascular; eGFR=estimated glomerular filtration rate; MI=myocardial infarction; T2D=type 2 diabetes.

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%)

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IMPORTANT SAFETY INFORMATION (cont'd)

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

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 see the following page for brief summary of full Prescribing Information.

Reference: 1. KERENDIA (finerenone) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; July 2021.

PP-FINE-US-0778-1 08/21

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION
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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)]*.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany 6711200BS1A

Beyond Medical Knowledge: A Framework to Improve Clinical Reasoning in Nephrology Training

By Suzanne M. Boyle, Stephen M. Sozio, Andrew S. Parsons, and Karen M. Warburton

Clinical reasoning is the process by which clinicians gather, interpret, and synthesize data to arrive at a diagnosis and make management decisions. Research in this field aims to: 1) understand decision-making under conditions of uncertainty and 2) promote systematic approaches to reasoning that minimize cognitive bias and reduce medical error (1, 2). Although most early-stage clinicians develop reasoning skills through repeated clinical exposure, many benefit from more explicit instruction (Figure 1) (3, 4).

Yet, to our knowledge, clinical reasoning curricula are largely absent from fellowship training programs. For many reasons, nephrology trainees would benefit from dedicated clinical reasoning instruction. Nephrology patients are among the most medically complex—often with compromised immune systems, cardiovascular comorbidities, and complicated electrolyte abnormalities—and are often cared for by multiple providers (5). These characteristics create high-stakes clinical scenarios that are vulnerable to cognitive bias. Clinical reasoning deficits are common and underrecognized in graduate medical learners, including nephrology fellows, and may be mistaken for knowledge or organizational deficiencies (6, 7). Struggling fellows are often advised to focus on knowledge acquisition when the root cause of their struggle is not lack of knowledge but, rather, effective application of knowledge (6, 7). This is illustrated by a recent survey of nephrology training program directors, which revealed that approximately 40% of fellows who required remediation had clinical reasoning deficits (6).

The successful nephrology educator's toolkit requires clinical reasoning assessment and coaching resources. In such, our team is developing Reasoning Evaluation in Nephrology Education (RENE), a web-based resource to assess and coach clinical reasoning skills in nephrology fellows (Figure 2). Through support from the William and Sandra Bennett Clinical Scholars Program, we will validate exercises that assess fellows' clinical reasoning. We will also provide a framework for nephrology educators to provide feedback to fellows and coach those with deficits. Unlike traditional assessment tools, such as board certification examinations, the reasoning assessment tool will measure a fellow's ability to synthesize data to make clinical decisions. We hope to engage the nephrology community in the creation and implementation of this novel educational resource. ■

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The authors report no conflicts of interest.

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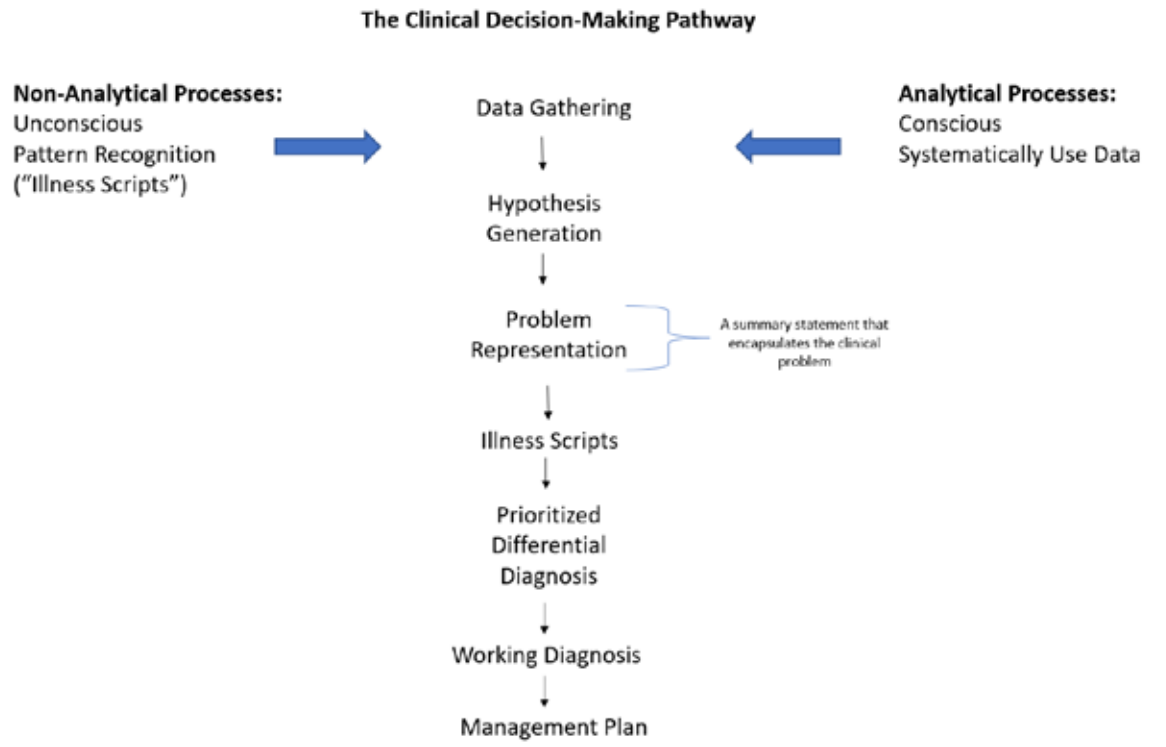
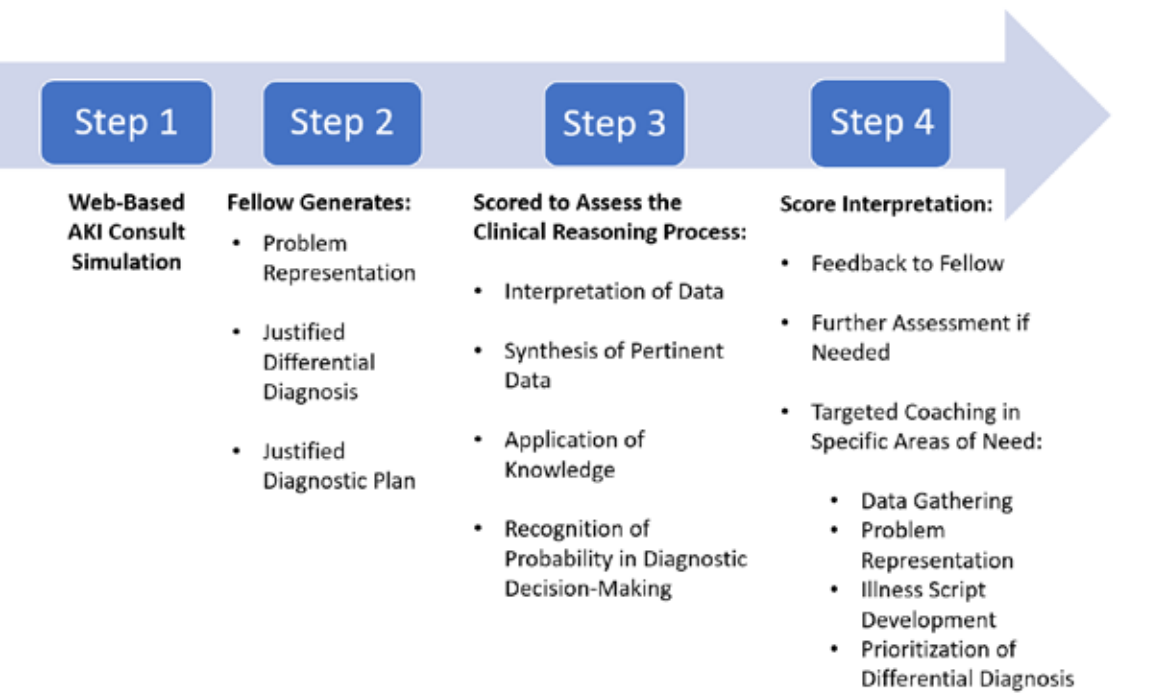
Figure 1. Clinical decision-making pathway

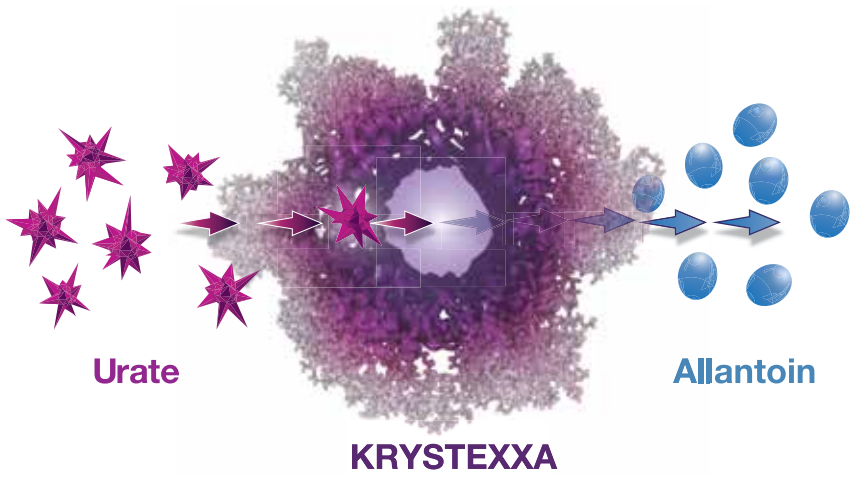


These steps are informed by non-analytical and analytical processes. The non-analytical process is typically fast and unconscious and relies on pattern recognition via illness scripts (stored memories of specific signs/symptoms with associated diagnoses that are refined over time), which makes it prone to cognitive bias. The analytical process is conscious and deliberate and is more often used by novices or by experienced clinicians as a check against cognitive bias.

Figure 2. Components of reasoning evaluation in nephrology education (RENE)



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.

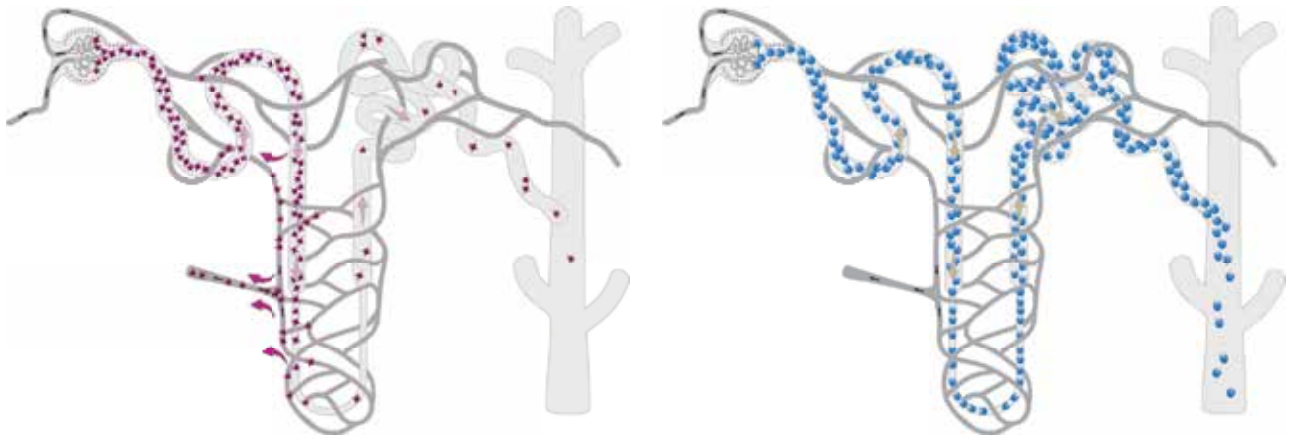
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

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.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland
US License Number 2022

Distributed by:
Horizon Therapeutics
Deerfield, IL 60015

Medicare's Winding Payment Pathway for Innovative Technology

By David L. White

For decades, translational researchers have increased options for treating diseases by bringing together the scientific, medical, and engineering fields to advance the understanding of biology and disease pathogenesis. For example, there are now more than 100 identified genetic causes of cellular dysfunction in patients, work that is further supported by a greater focus on data sharing across academia and industry, opening the doors to new and more individualized treatments that target disease subtypes as a personalized approach. Private investment, through licensing or venture capital, plays an important role in pushing these advances closer to the clinician and patient, with investment opportunities considering both the clinical impact and the receptiveness of the market to implement these innovations into routine practice.

This pathway for translating innovations to the patient has been clearly demonstrated in oncology, which has seen over $14 billion in private investments into the biopharmaceutical sector alone over the past 3 years. Over the same period, investments into a broader set of kidney-related innovation companies that included biopharma as well as healthcare services, diagnostics, and devices only received $2.4 billion.

This imbalance is in part why ASN made its own $25 million commitment to the Kidney Innovation Accelerator (KidneyX)—a public-private partnership between the US Department of Health and Human Services (HHS) and ASN to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases, now the ninth leading cause of death in the United States, resulting in more deaths than breast cancer. Unfortunately, kidney diseases and kidney failure are more common among Black, Hispanic or Latinx, and Native or Indigenous Americans; Asians; Hawaiians and Other Pacific Islanders; people in lower income brackets; and the elderly. These are communities that also have been disproportionately affected by the COVID-19 pandemic, exacerbating existing disparities.

Since its launch in 2018, KidneyX has run five prize competitions and supported innovators in 22 states. By accelerating the development of drugs, devices, biologics, and other therapies across the spectrum of kidney care, KidneyX seeks to improve the lives of the 37 million Americans and 850 million people worldwide currently afflicted with kidney diseases.

ASN believes payment policies within the Medicare End Stage Renal Disease (ESRD) payment bundle have long been a disincentive for innovation in dialysis care delivery, and objectively knowing the magnitude of that impact is difficult. Following the route to payment pathways for innovation in the Medicare system is also challenging. One only need look at the Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES) in the ESRD bundle and the proposed rule on Medicare Coverage of Innovative Technology (MCIT) and definition of "reasonable and necessary."

Over the past several years and again in August 2021, ASN has written to the Centers for Medicare & Medicaid Services (CMS) clarifying that there are multiple challenges to introducing innovative devices, drugs, biologics, and other therapies into the ESRD Prospective Payment System (PPS) even after the US Food and Drug Administration (FDA) has granted certain advance approvals. First, ASN maintains that there are barriers related to the use of items during the first few years after introduction. Second, there are no current policies to adjust the base bundle rate to account for new products. Third, and most notable, is the challenge raised by the definition and interpretation of substantial clinical improvement (SCI) criteria.

ASN expressed its concerns to CMS that SCIs are numerous and expansive in scope and that very few parties will consider investment in improving care of people with kidney failure if requirements continue to result in no devices receiving TPNIES payment status. In addition, the data are required to demonstrate that SCI represents a far greater

outlay of resources than the approved 65% rate of reimbursement over 3 years, ASN argues. Finally, the 65% rate of reimbursement, for only 3 years, arguably abrogates the need to prove SCI to the extent posited by CMS in the discussion of the applicants in the current proposed rule. This fact is because, under TPNIES, a large portion of the financial risk associated with new technologies (35% in the first 3 years and 100% thereafter) will be shared by the dialysis providers that adopt the new technology.

A final rule on the ESRD program for calendar year 2022 and two separate TPNIES applications contained therein is expected around the time of this publication.

ASN and other members of the kidney community have expressed to CMS their concerns that if the administration fails to address these three challenges, innovation will continue to stagnate. Specifically, ASN's President Susan E. Quaggin, MD, FASN, wrote: "There needs to be an opportunity to introduce new technologies into the kidney failure space that results in a willingness for innovators to take the risk of investing in the care of kidney failure patients. ASN fears that the current proposal does not present this opportunity." (1)

The Alliance for Home Dialysis, of which ASN is a Steering Committee member, and ASN maintain that improvements in in-center dialysis care and increases in the use of home dialysis are important for improving overall outcomes and the quality of life for people receiving maintenance dialysis. Both organizations have expressed concern that the current TPNIES criteria may not sufficiently address the issues critical to advancing home dialysis nor do they fully support the second goal of the federal government's Advancing American Kidney Health (AAKH) initiative of improving access to, and the quality of, person-centered treatment options. In addition to ASN's own comment letter to CMS, the society joined the Alliance for Home Dialysis in making several recommendations and statements of support for TPNIES and innovation payment to CMS, including extending TPNIES eligibility to at least 3 years and adjusting for providers that do not have the resources to purchase new devices and may prefer to maintain subscriptions with manufacturers or lease equipment (2).

Bills in the House and Senate would allow new and innovative devices for kidney failure that receive FDA "de novo" status to also receive an automatic 3-year add-on payment through the bundle. The de novo process provides a pathway to classify novel medical devices for which general controls alone or general and special controls provide reasonable assurance of safety and effectiveness for the intended use but for which there is no legally marketed predicate device. ASN

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Innovative Technology

Continued from page 15

has officially endorsed these bills.

"Reasonable and necessary"

The issue of coverage of innovative technology is the confusing story of the short-lived MCIT, or Medicare Coverage of Innovative Technology rule. Shortly before the Biden-Harris administration came into office in January 2021, the Trump administration issued a final rule creating MCIT under CMS—a new, accelerated Medicare coverage pathway for innovative products the FDA deems "breakthrough," which the FDA approves on an expedited basis and could include devices harnessing new technologies, like implants or gene-based tests, to diagnose or treat life-threatening or irreversibly debilitating diseases or conditions like cancer and heart disease. Under the MCIT rule, Medicare could provide national coverage simultaneously with FDA approval, up to a period of 4 years. After the coverage period was over, CMS would reevaluate the device based on clinical and real-world evidence of improvement in health outcomes among Medicare beneficiaries to determine more permanent coverage. This 4-year timeline was designed to incentivize the manufacturers of these breakthrough devices to develop additional evidence regarding the applicability of their products to the Medicare population, so they might continue Medicare coverage beyond the initial 4 years, so thought the outgoing administration (3).

The new administration delayed the implementation of the final rule until December 15, 2021. However, in September 2021, CMS issued a proposed rule that "would repeal the Medicare Coverage of Innovative Technology (MCIT) and Definition of 'Reasonable and Necessary' final rule, which was published on January 14, 2021, and would be effective on December 15, 2021" (4). The Biden administration effectively moved to "kill" a last-minute rule issued by the outgoing administration, a move that is not unusual. What was unusual to many observers was the language used by CMS to address its role in covering innovative technology versus the role of the FDA in approving these technologies. CMS wrote the following:

However, after further consideration of all public comments, we no longer agree that the FDA safety and effectiveness standards alone are sufficient to support open-ended Medicare coverage. FDA and CMS act under different statutes that have different goals and the standard for coverage (that is, a determination that a device is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member) is not synonymous with standards for safety and efficacy standards for marketing authorization for the broader population.

Among other things, FDA conducts premarket review of certain devices to evaluate their safety and effectiveness and determines if they meet the applicable standard to be marketed in the United States. In doing so, FDA relies on scientific and medical evidence that does not necessarily include patients from the Medicare population. In general, under the Medicare statute, CMS is charged with determining whether items and services are reasonable and necessary to diagnose or treat an illness or injury or to improve the functioning of a malformed body member.

One consideration for CMS in making national coverage determinations under the reasonable and necessary statute is whether the item/service improves health outcomes for Medicare beneficiaries. It is important to determine whether Medicare beneficiaries' health outcomes are improved because these individuals are often older, with multiple comorbidities, and are often underrepresented or not represented in many clinical studies (4).

ASN had advocated for keeping and modifying MCIT. This proposed rule leaves little doubt that MCIT will be repealed and leaves many observers wondering just what the future pathway to Medicare payment for innovative technologies will look like. ■

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Alport syndrome is more prevalent than you may think.

In fact, Alport syndrome is the second most common cause of inherited kidney failure, affecting ~30,000 – 60,000 men and women, boys and girls in the United States.[1,2]

Alport syndrome often goes undetected, especially in females and those with non sex-linked inheritance patterns.[3,4] Learn the common signs and genetic markers.

Scan the QR code for a deep dive on Alport syndrome

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REATA PHARMACEUTICALS

ANDROMEDA: Incorporating Daratumumab into Upfront Treatment for AL Amyloidosis Accelerates Therapeutic Progress by Light Years

By Heather Landau

Monoclonal immunoglobulin (Ig)/light chain (AL)-associated systemic amyloidosis is caused by clonal plasma cells producing abnormal Ig light chains that misfold into amyloid fibrils, deposit in vital organs, disrupt organ function, and if left untreated, ultimately result in death. Given its insidious onset and nonspecific symptomatology, delay in AL amyloidosis diagnosis is unfortunately typical (1). The prognosis of patients is primarily driven by an advanced organ, specifically cardiac involvement (2). The kidney is affected in 70% of patients manifesting as proteinuria and progressive kidney dysfunction, which leads to the need for kidney replacement therapy in 15%–30% of patients (3). Rapid and deep hematologic responses to plasma cell-directed therapy are critical to preserve organ function and reverse organ deterioration.

The ANDROMEDA trial represents therapeutic progress at warp speed.

The off-label standard-of-care treatment for newly diagnosed patients in the United States has been a combination of a proteasome inhibitor (bortezomib), an alkylator (cyclophosphamide), and steroids (dexamethasone) (VCD) (4–6). In the largest retrospective series of 230 patients treated with VCD, the hematologic overall response rate (ORR) was 60% (complete response [CR] 23%). Organ responses were suboptimal and often delayed (6). In 2015, the anti-CD38 monoclonal antibody daratumumab was approved by the US Food and Drug Administration (FDA) to treat relapsed/refractory multiple myeloma. Daratumumab, a human IgG1κ monoclonal antibody, binds to CD38-expressing cells and induces tumor cell death through various immune-mediated actions. CD38 is overexpressed on amyloidogenic plasma cells, making it a rational target.

In a small series of 25 patients, ORR was 76% with one-third of patients achieving CR (7). Since then, prospective studies of daratumumab in relapsed disease showed rapid (median time to response 1–4 weeks) and deep hematologic responses (8). Given impressive efficacy in the relapse setting, daratumumab was evaluated in a large randomized phase 3 study of almost 400 newly diagnosed patients treated with VCD, with or without daratumumab (ANDROMEDA, ClinicalTrials.gov: NCT03201965). The addition of the monoclonal antibody resulted in significant improvement in ORR (92% vs. 77%; CR 53% vs. 18%), and major organ deterioration progression-free survival favored the quadruplet arm (hazard ratio [HR] for major organ deterioration, hematologic progression, or death: 0.58; 95% confidence interval [CI], 0.36 to 0.93; p = 0.02) (Figure 1). The quadruplet was also associated with doubling of organ responses at 6 months (cardiac response 42% vs. 22%, renal response 53% vs. 24%) (9). Patients achieved responses faster and stayed on therapy longer in the quadruplet arm (10). Based on these data, the FDA endorsed daratumumab in combination with VCD (dara-VCD) in a historic approval as the first and only FDA-approved drug for AL amyloidosis on January 15, 2021.

The ANDROMEDA trial represents therapeutic progress at warp speed. Prior to these data, a CR rate of 53% had only been achieved with high-dose melphalan followed by autologous hematopoietic cell transplant (AHCT) plus bortezomib-based consolidation, which is therapy available to only a very select patient population representing 25% of all patients (11). Even then, organ responses were typically appreciable over months to years. With the use of daratumumab upfront, more rapid organ recovery may increase the pool of AHCT candidates. Alternatively, if the goal is hematologic CR, and that can be achieved with daratumumab-based therapy, perhaps fewer patients will require AHCT and be spared the associated toxicity. Time will tell how durable the responses to dara-VCD will be. ■

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Dr. Landau has received research support for clinical trials from Takeda. She served on the Advisory Boards of Takeda, Celgene, Janssen, Sanofi, and Caelum Biosciences and has been a consultant for Karyopharm and Pfizer.

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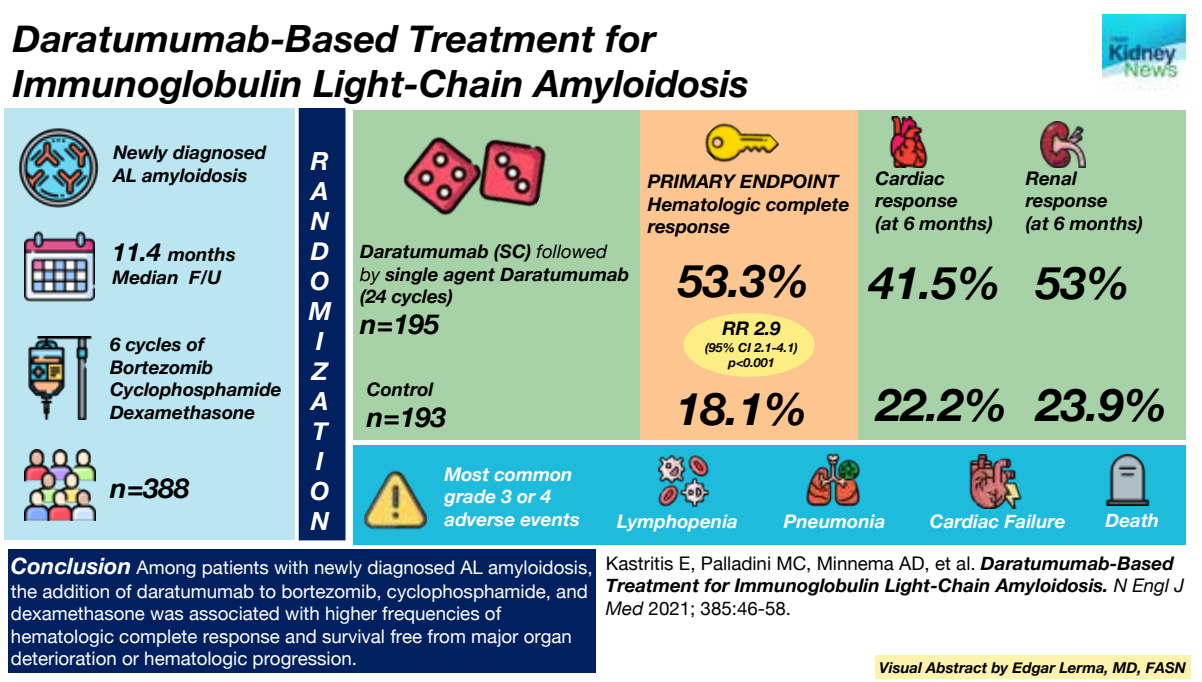
Figure 1.



INVOKANA®: the FIRST SGLT2i proven to slow the progression of DKD in adults with DKD* and T2D and the ONLY SGLT2i indicated to reduce the risk of 3-point MACE (heart attack, stroke , and CV death) in adults with T2D and established CVD[1-5]

*With albuminuria >300 mg/day.

INVOKANA® is the first SGLT2i indicated to reduce the risk of end-stage kidney disease[1,6]

CREDENCE

30% RRR

Relative risk reduction of the primary composite of:

- **End-stage kidney disease†** (dialysis, transplant, or eGFR <15)
- **Doubling of serum creatinine**
- **Renal death‡**
- **CV death**

Patients with DKD* and T2D

HR=0.70 (95% CI: 0.59, 0.82); *P*=0.00001

Placebo + ACEi or ARB therapy (n=2199)
Event rate: 6.1 (per 100 patient-years)

INVOKANA® 100 mg + ACEi or ARB therapy (n=2202)
Event rate: 4.3 (per 100 patient-years)

‡There were not enough events to evaluate the risk of renal death (placebo, n=5; INVOKANA®, n=2). **INVOKANA® is not indicated to reduce the risk of renal death.**

INVOKANA® is the only SGLT2i to demonstrate a reduction in the relative risk of all components of MACE in 2 clinical trials[1,5,6,7‖]

CREDENCE

20% RRR§

Patients with DKD* and T2D

HR=0.80 (95% CI: 0.67, 0.95); *P*=0.01

Placebo + ACEi or ARB therapy (n=2199)
Event rate: 4.9 (per 100 patient-years)

INVOKANA® 100 mg + ACEi or ARB therapy (n=2202)
Event rate: 3.9 (per 100 patient-years)

CANVAS

18% RRR§

Patients with T2D and CVD

HR=0.82 (95% CI: 0.72, 0.95); *P*=0.008

Placebo + standard of care (n=2900)
Event rate: 4.13 (per 100 patient-years)

INVOKANA® 100 mg and 300 mg + standard of care (n=3756)
Event rate: 3.41 (per 100 patient-years)

Relative risk reduction in the composite of 3-point major adverse cardiac events[1,7]:

- **Heart attack**
- **Stroke**
- **CV death**

‖Prespecified secondary endpoint for CREDENCE; prespecified primary endpoint for CANVAS.

In the landmark renal CREDENCE trial, INVOKANA® demonstrated a proven safety profile in patients with an eGFR of 30 to <90[1,6]

- Similar overall AEs with INVOKANA® vs placebo (35.1 vs 37.9 per 100 patient-years). Male GMI incidence was 0.84 vs 0.09 per 100 patient-years, respectively. DKA incidence was 0.22 vs 0.02 per 100 patient-years, respectively.¶ No imbalance in fracture or amputation. Hypotension incidence was 2.8% vs 1.5%, respectively. Hypoglycemia incidence was 4.43 vs 4.89 per 100 patient-years, respectively#

In the CV outcomes CANVAS Program, INVOKANA® demonstrated a proven safety profile in patients with T2D and established CVD[5]

- Similar overall AEs with INVOKANA® vs placebo (10.43 vs 12.00 per 100 patient-years). Male GMI incidence was 3.49 vs 1.08 per 100 patient-years, respectively. DKA incidence was 0.06 vs 0.03 per 100 patient-years, respectively. Hypoglycemia incidence was 5.00 vs 4.64 per 100 patient-years, respectively

AEs=adverse events; CANVAS=Canagliflozin Cardiovascular Assessment Study; CREDENCE=Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV=cardiovascular; CVD=cardiovascular disease; DKA=diabetic ketoacidosis; DKD=diabetic kidney disease; GMI=genital mycotic infection; HR=hazard ratio; MACE=major adverse cardiovascular events; RRR=relative risk reduction; SGLT2i=sodium-glucose co-transporter 2 inhibitor; T2D=type 2 diabetes.

Learn more at INVOKANAhcp.com

Study designs: CREDENCE was a randomized, double-blind, placebo-controlled, parallel group, multicenter, event-driven clinical trial. The trial compared the effects of INVOKANA® 100 mg vs placebo in 4401 men and women with type 2 diabetes and diabetic kidney disease (described as chronic kidney disease with eGFR 30 to <90 mL/min/1.73 m^2 and albuminuria [ratio of albumin to creatinine >300 to 5000 mg/g]) who were already taking a stable, maximum-tolerated, or labeled dose (for ≥4 weeks prior to randomization) of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The mean eGFR of patients was 56.2 mL/min/1.73 m^2 and the median urinary albumin-to-creatinine ratio was 927 mg/g. The primary efficacy outcome was the composite of end-stage kidney disease (dialysis, transplant, or eGFR <15 mL/min/1.73 m^2), doubling of serum creatinine, or renal or cardiovascular (CV) death. Prespecified secondary outcomes included a composite of CV death or hospitalization for heart failure; a composite of heart attack, stroke, or CV death; hospitalization for heart failure; and a composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death.[6]

The CANVAS Program was an integrated analysis of 2 trials (the CANVAS trial and the CANVAS-R trial) with a total of 10,142 men and women with type 2 diabetes. Of the participants, 96.0% completed the trial and vital status was confirmed for 99.6%. The mean follow-up for the CANVAS Program was 188.2 weeks, while the length of follow-up was 295.9 weeks and 108.0 weeks in the CANVAS and CANVAS-R trials, respectively. Participants were either ≥30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or ≥50 years of age with ≥2 risk factors** for cardiovascular disease. The primary efficacy outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[5]

**≥2 of the following risk factors for CVD: duration of diabetes ≥10 years, systolic blood pressure >140 mm Hg while they were receiving ≥1 antihypertensive agents, currently smoking, microalbuminuria or macroalbuminuria, or HDL cholesterol level <1 mmol/L (38.7 mg/dL).

INDICATIONS

INVOKANA® is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD)
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day

Limitations of Use

INVOKANA® is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

INVOKANA® is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA® is likely to be ineffective in this setting based upon its mechanism of action.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Patients on dialysis

Please read additional Important Safety Information and Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

eGFR is measured in mL/min/1.73 m^2.
*With albuminuria >300 mg/day.
†End-stage kidney disease was defined as dialysis for ≥30 days, kidney transplantation, or an eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days.
§RRR was calculated using the following formula: 100 x (1−HR).
¶All potential ketone-related events were adjudicated for diabetic ketoacidosis by an independent adjudication committee on the basis of clinical presentation and predefined biochemical measures.
#In all glycemic control trials of INVOKANA®, hypoglycemia was defined as any event, regardless of symptoms, in which biochemical hypoglycemia was documented (any glucose value ≤70 mg/dL) or any hypoglycemic episode was considered severe. Severe hypoglycemia was defined as an event consistent with hypoglycemia in which the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained).[1]

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Invokana®
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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Patients on dialysis

WARNINGS AND PRECAUTIONS

- **Lower-Limb Amputation:** An increased risk of lower-limb amputations associated with INVOKANA® use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower-limb amputations was observed at both the 100-mg and 300-mg once-daily dosage regimens.

  Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA® in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA® in the two trials). Some patients had multiple amputations, some involving both lower limbs.

  Lower-limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy. Before initiating INVOKANA®, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.
- **Volume Depletion:** INVOKANA® can cause intravascular volume contraction, which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been postmarketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA® in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.
- **Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA® for at least 3 days prior to surgery. Monitor for ketoacidosis and temporarily discontinue in other clinical situations known to predispose to ketoacidosis. Ensure risk factors for ketoacidosis are resolved prior to restarting therapy. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA® and seek medical attention immediately if signs and symptoms occur.
- **Urosepsis and Pyelonephritis:** Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA® may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA®.

Please read Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

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(canagliflozin) tablets

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Necrotizing fasciitis of the perineum, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, has been identified in postmarketing surveillance in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections, especially in uncircumcised males or patients with prior infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Prior to initiation, consider factors that contribute to fracture risk.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Co-administration with rifampin lowered INVOKANA® exposure, which may reduce the efficacy of INVOKANA®. For patients with eGFR ≥60 mL/min/1.73 m^2, if an inducer of UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA® 200 mg and who require additional glycemic control.

  For patients with eGFR <60 mL/min/1.73 m^2, if an inducer of UGTs is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** INVOKANA® is not recommended in pregnant women, especially during the second and third trimesters.
- **Lactation:** INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume, particularly with the 300-mg dose; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years.
- **Renal Impairment:** The efficacy and safety of INVOKANA® for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of the study. Patients with renal impairment using INVOKANA® for glycemic control may be more likely to experience hypotension and may be at a higher risk for acute kidney injury. INVOKANA® is contraindicated in patients with ESKD on dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

cp-68813v5

Please read Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

References: 1. INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Jardiance® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Farxiga® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **4.** Steglatro™ [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. **5.** Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. **6.** Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. Supplementary appendix available at: doi:10.1056/NEJMoa1811744. **7.** Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation*. 2018;137(4):323-334.

INVOKANA®

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

Limitations of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions]*.

INVOKANA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is likely to be ineffective in this setting based upon its mechanism of action.

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions and Adverse Reactions]*.
- Patients on dialysis *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 3 and 4, respectively *[see Adverse Reactions]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

Volume Depletion: INVOKANA can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions]*. There have been post-marketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*.

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting INVOKANA.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA and seek medical attention immediately if signs and symptoms occur.

Urosepsis and Pyelonephritis: There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with INVOKANA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Bone Fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lower Limb Amputation *[see Warnings and Precautions]*
- Volume Depletion *[see Warnings and Precautions]*
- Ketoacidosis *[see Warnings and Precautions]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Bone Fracture *[see Warnings and Precautions]*

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

Pool of Placebo-Controlled Trials for Glycemic Control: The data in Table 1 is derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions from Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

\# Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Placebo-Controlled Trial in Diabetic Nephropathy: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in CREDENCE, a study in patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.3) in Full Prescribing Information]*. These data reflect exposure of 2,201 patients to INVOKANA and a mean duration of exposure to INVOKANA of 137 weeks.

- The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively, with 2.6 years mean duration of follow-up.
- Incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with INVOKANA 100 mg and placebo, respectively.
- The incidence of hypotension was 2.8% and 1.5% on INVOKANA 100 mg and placebo, respectively.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 patients to INVOKANA) were consistent with those listed in Table 1.

Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.2) in Full Prescribing Information]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively.

Table 2: CANVAS Amputations

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma: In the CANVAS trial (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and INVOKANA, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions in these trials were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 4) *[see Use in Specific Populations]*.

Table 4: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls: In a pool of nine clinical trials with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections

INVOKANA® (canagliflozin) tablets

(22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 randomized trials evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis.

Hypoglycemia: In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials of glycemic control *[see Clinical Studies (14.1) in Full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 5).

Table 5: Incidence of Hypoglycemia* in Randomized Clinical Studies of Glycemic Control

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture: In the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities.

Laboratory and Imaging Tests*: Increases in Serum Creatinine and Decreases in eGFR*: Initiation of INVOKANA causes an increase in serum creatinine and decrease in estimated GFR. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

Increases in Serum Potassium: In a pooled population of patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Use in Specific Populations]*.

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with INVOKANA 100 mg relative to placebo.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four glycemic control placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials of glycemic control, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density: Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1) in Full Prescribing Information]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

Postmarketing Experience: Additional adverse reactions have been identified during post-approval use of INVOKANA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ketoacidosis

Acute Kidney Injury

Anaphylaxis, Angioedema

Urosepsis and Pyelonephritis

Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

DRUG INTERACTIONS

UGT Enzyme Inducers: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy.

For patients with eGFR 60 mL/min/1.73 m^2 or greater, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA 200 mg and who require additional glycemic control.

For patients with eGFR less than 60 mL/min/1.73 m^2, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >10. The estimated background risk of 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.

Clinical Considerations*: Disease-associated maternal and/or embryo/fetal risk*: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data: Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Lactation: Risk Summary: There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA is not recommended while breastfeeding.

Data: *Animal Data*: Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

INVOKANA® (canagliflozin) tablets

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in Full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.1) in Full Prescribing Information]*. These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of study. Patients with renal impairment using INVOKANA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury *[see Warnings and Precautions]*.

Efficacy and safety studies with INVOKANA did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is contraindicated in patients with ESKD on dialysis *[see Contraindications and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Lower Limb Amputation: Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions]*.

Volume Depletion: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of INVOKANA, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical attention immediately *[see Warnings and Precautions]*.

Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKANA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions]*.

Bone Fracture: Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions]*.

Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations]*.

Laboratory Tests: Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions]*.

Missed Dose: If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Active ingredient made in Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

cp-22015v4

janssen

PLENARY SESSION

Kidney Week to Open with Groundbreaking COVID-19 Panel

Anthony Fauci, MD

Sanjay Gupta, MD

ASN is partnering with the National Academy of Medicine to kick off Kidney Week with a first-of-its-kind opening plenary presenting a COVID-19 update, with a global focus on kidney health.

Anthony Fauci, MD, will present the keynote address on "Public Health Lessons Learned and Implications for Future Pandemics."

The moderator will be the well-known CNN chief medical correspondent Sanjay Gupta, MD.

The plenary speakers will highlight the viral pathogenesis and importance of the COVID-19 variants in the development of next-generation therapies and vaccines and provide expert opinions on public health policy and the potential long-term impact on cardiovascular and kidney health.

Perhaps the highest profile career official in the federal response to COVID-19, Dr. Fauci has been director of the National Institute of Allergy and Infectious Diseases since 1984, where he oversees an extensive research portfolio focused on infectious and immune-mediated diseases. As the long-time chief of the institute's laboratory of immunoregulation, he has made many seminal contributions in basic and clinical research and is one of the world's most-cited biomedical scientists.

Dr. Gupta is a practicing neurosurgeon who has won multiple Emmy awards for his work reporting on health and medical news for all of CNN's programs domestically and internationally. He has covered some of the most important health stories in the United States and around the world since 2001.

Amitava Banerjee, MD, MPH, DPhil

Ashish K. Jha, MD, MPH

Jeffrey I. Silberzweig, MD

Susan R. Weiss, PhD

They will be joined on the panel by the following four other experts:

- Amitava Banerjee, MD, MPH, DPhil, is professor of clinical data science at University College London and honorary consultant cardiologist at University College London Hospitals and Barts Health National Health Service Trusts. He is a researcher, educator, and practicing clinician whose interests span health informatics, learning health systems, cardiovascular epidemiology, global health, and evidence-based healthcare. His expertise in epidemiology, biostatistics, public health, and cardiovascular medicine has led to collaborations across traditional disciplines.
- Ashish K. Jha, MD, MPH, is the dean of the school of public health at Brown University. He is recognized globally as an expert on pandemic preparedness and response. He has led groundbreaking research around the Ebola virus and has worked on the frontlines of the COVID-19 response, leading national and international analyses of key issues and advising state and federal policymakers.
- Jeffrey I. Silberzweig, MD, is the medical director of the dialysis units at New York-Presbyterian's Weill Cornell and Lower Manhattan Hospitals and the chief medical officer of The Rogosin Institute. He is associate professor of clinical medicine at Weill Cornell Medical College, where he is associate director of the internal medicine residency and nephrology fellowship programs. He has co-chaired the ASN Emergency Partnership Initiative since 2019. When ASN formed its COVID-19 Response Team in the early days of the pandemic, Dr. Silberzweig took on the challenge of serving as co-chair and as chair of its outpatient dialysis subcommittee.
- Susan R. Weiss, PhD, is professor and vice chair of the Department of Microbiology at the University of Pennsylvania Perelman School of Medicine. She is also co-director of the Penn Center for Research on Coronaviruses and Other Emerging Pathogens. During her long career, she has worked on many aspects of coronavirus replication and pathogenesis, making contributions to understanding the basic biology as well as organ tropism and virulence. For the past 10 years, her work has focused on coronavirus interaction with the host immune response and viral antagonists of double-stranded RNA-induced antiviral pathways.

Scientist to Address the Use of Precision Medicine to Treat Kidney Disease

Matthias Kretzler, MD

A leading researcher in bioinformatics will deliver the Barry M. Brenner, MD, Endowed Lectureship on "Applied Precision Medicine in Glomerular Diseases" on Thursday, November 4.

The speaker will be Matthias Kretzler, MD, who is the Warner-Lambert/Parke-Davis professor of internal medicine, nephrology, and computational bioinformatics at the University of Michigan Medical School in Ann Arbor.

Dr. Kretzler's research is aimed at defining chronic kidney disease in mechanistic terms and using this knowledge for targeted therapeutic interventions. In pursuit of this goal, his research team has developed a translational research pipeline centered on integrated systems-biology analysis of kidney disease. For over 25 years, the team has built a track record of interdisciplinary integration of large-scale data sets in international research networks in the United States, Europe, China, and sub-Saharan Africa. These studies enable precision medicine across the genotype–phenotype continuum using carefully monitored environmental exposures, genetic predispositions, epigenetic markers, transcriptional networks, proteomic profiles, metabolic fingerprints, digital histological biopsy archives, and prospective clinical disease characterization.

This work has resulted in more than 350 publications describing new disease predictors, de novo drug development, and clinical trials of novel therapeutics in chronic kidney disease.

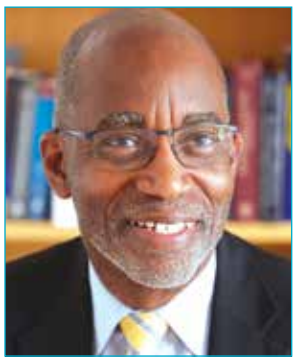
Dr. Kretzler leads the U54 Nephrotic Syndrome Research Network in the Rare Disease Clinical Research Network II. He is a principal investigator of the coordinating center of the Cure Glomerulonephropathy (CureGN) research network, the National Institutes of Health (NIH) acceleration of medicine in lupus program, and the NIH-funded integrated systems biology approach to diabetic microvascular complications program.

Among his many honors, he has received the Janssen-Cilag Award and the Carl Ludwig Young Investigator Award from the German Nephrology Association, the Mary Jane Kugel Award from the Juvenile Diabetes Research Foundation, and the Young Investigator Award from ASN.

Dr. Kretzler received his MD/PhD equivalent from the University of Heidelberg, Germany. He completed his internal medicine residency and nephrology fellowship at the University of Munich. He completed a research fellowship in physiology and nephrology at the University of Michigan.

STATE-OF-THE-ART LECTURE

National Leader on Reducing Social Inequities in Healthcare to Speak



David R. Williams, PhD, MPH

David R. Williams, PhD, MPH, will present a state-of-the-art lecture on "Social Inequities in Health: How Can We Effectively Reduce Them?" on Friday, November 5.

Dr. Williams is the Florence and Laura Norman Professor of Public Health and Chair of the Department of Social and Behavioral Sciences at the Harvard T.H. Chan School of Public Health. He is also a professor of African and African American Studies at Harvard University.

Dr. Williams has played a national leadership role in raising awareness of the problem of health inequities and identifying interventions to address them. His work on the issue includes serving as the staff director of the Robert Wood Johnson Foundation Commission to Build a Healthier America. This nonpartisan health commission is focused on identifying evidence-based nonmedical strategies that can improve the health of all Americans and reduce racial and socioeconomic gaps in health. He was a scientific advisor to the award-winning PBS film series, *Unnatural Causes: Is Inequality Making Us Sick?*

Dr. Williams has served on 10 committees for the National Academy of Sciences, including the committee that prepared the 2003 report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare*. His research has been featured in the national print and television media and in his TED talk.

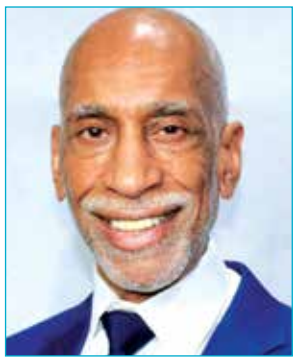
An internationally recognized social scientist, he has been invited to deliver keynote addresses to scientific conferences in Europe, Africa, Australia, the Middle East, and South America. His research has enhanced the understanding of the complex ways in which socioeconomic status, race, stress, racism, health behavior, and religious involvement can affect health. The author of more than 500 scientific papers, he has served on the editorial boards of 12 scientific journals and as a reviewer for more than 75 others. He developed the Everyday Discrimination Scale, which is the most widely used measure of discrimination in health studies.

Dr. Williams has received numerous honors and awards. He was elected to the National Academy of Medicine in 2001, the American Academy of Arts and Sciences in 2007, and the National Academy of Sciences in 2019. He has also received distinguished contribution awards from the American Sociological Association, the American Psychological Association, and the New York Academy of Medicine.

Dr. Williams was ranked as one of the "Top 10 Most Cited Social Scientists in the World" in 2005 by the Institute for Scientific Information (ISI) Essential Science Indicators and as the "Most Cited Black Scholar in the Social Sciences" in 2008 by the *Journal of Black Issues in Higher Education*. In 2014, Thomson Reuters ranked him as one of the "World's Most Influential Scientific Minds."

His prior academic appointments include 6 years on the faculty of Yale University and 14 years at the University of Michigan. He holds an MPH from Loma Linda University in California and a PhD in sociology from the University of Michigan.

John P. Peters Award to Honor Donald E. Wesson



Donald E. Wesson, MD, MBA, FASN

ASN will recognize the wide-ranging contributions of Donald E. Wesson, MD, MBA, FASN, with the presentation of the John P. Peters Award on Friday, November 5. The John P. Peters Award is given for outstanding contributions to improving the lives of patients and furthering the understanding of the kidney in health and disease.

Dr. Wesson is professor of medicine at Texas A&M University in Dallas and president of Donald E. Wesson Consulting. His pioneering research and many leadership roles in academic medicine and clinical care have advanced nephrology, medicine, and public policy.

He is a long-time advocate for improving the health of communities through focused, data-driven population health initiatives and an internationally recognized researcher in kidney acidifying mechanisms. He has translated his basic science studies to clinical studies examining the role of nutrition in population health and the kidney-protective benefits of nutrition.

Dr. Wesson's research has centered on the role of the kidney in maintaining acid-base and electrolyte homeostasis and is a remarkable example of bench-to-bedside translation. He published a series of seminal papers on the bidirectional transport of bicarbonate along the proximal and distal nephron. His pioneering studies established the role of endogenous endothelins as mediators of distal tubular acidification. The studies connected renal endothelin generation with dietary acid consumption, which significantly advanced understanding of chronic kidney disease progression.

Dr. Wesson has used his leadership roles in large health systems to propel system-wide improvements in care delivery, particularly for underserved and under-resourced communities. He served as president of the Baylor Scott & White Health and Wellness Center, senior vice president of Baylor Scott & White Weight Management Services, and chief academic officer of Baylor Scott & White Health. He was vice dean of the Texas A&M University College of Medicine. At Texas Tech University Health Sciences Center, he was the S.C. Arnett professor of medicine and chair of the Department of Internal Medicine.

In these roles, he led strategies that reduced rising rates of emergency department use and hospitalization. He helped create a level-three primary care clinic in a city recreational center that integrated wellness and prevention programs.

Dr. Wesson has also been active in service to the profession of nephrology. He has been ASN secretary-treasurer and served on many ASN committees. He was an inaugural member of the ASN Public Policy Advisory Board, where his vision and leadership were central to improving ASN's focus on diversity and inclusion. He helped establish ASN's partnership with the Robert Wood Johnson Foundation to address the shortage of minority scholars filling academic and research appointments in nephrology.

Dr. Wesson also chaired the Board of Directors of the American Board of Internal Medicine. He has served the National Kidney Foundation in many capacities, including on the Board of Directors and as president of the National Kidney Foundation of West Texas.

He completed his medical degree and residency at Baylor College of Medicine and his nephrology fellowship at the University of Illinois College of Medicine. He received an MBA from the University of Texas, Austin.

New Trailblazer Award Will Honor Barbara T. Murphy

Barbara T. Murphy, MB BAO BCh

ASN will introduce a new lifetime achievement award, the ASN Trailblazer Award, on Friday, November 5. The inaugural recipient will be Barbara T. Murphy, MB BAO BCh, who lost her battle with glioblastoma on June 30, 2021. At the time of her death, Dr. Murphy was ASN president-elect.

The new award honors leaders who strengthen the foundation of nephrology while advancing the field through innovation, creativity, inspiration, and tenacity.

"ASN will present the award to Barbara T. Murphy [posthumously] in recognition of her extraordinary contributions to patient care, research, and education as well as her advocacy, creativity, entrepreneurship, leadership, and community service," said ASN President Susan E. Quaggin, MD.

Dr. Murphy was the Murray M. Rosenberg professor of medicine and chair of the Department of Medicine at the Mount Sinai Health System in New York City. She was also dean of clinical integration and population health for the Icahn School of Medicine.

Dr. Murphy's research focused on the use of high-throughput genomic technologies to elucidate the immune mechanisms that lead to graft injury and loss, with the aim of identifying gene expression profiles and genetic variants to predict post-transplantation outcomes. Her work involved finding ways to directly impact patient access to healthcare, specifically regarding long-term coverage for immunosuppression.

Dr. Murphy advocated nationally and globally for patients suffering from kidney diseases and for increased funding for kidney research. She played a leadership role in a number of professional societies, symposiums, advisory groups, committees, and task forces. A longtime member, she served ASN in many capacities. She also served as president of the American Society of Transplantation and co-chaired its Public Policy Committee.

Dr. Murphy worked on several journals, including *CJASN, American Journal of Kidney Diseases, American Journal of Transplantation*, and *Graft*. She was one of the editors of *Therapy in Nephrology & Hypertension: A Companion to Brenner & Rector's The Kidney, Third Edition*.

Among Dr. Murphy's many honors, *Irish America* magazine named her one of its Top 50 Power Women, the American Kidney Fund named her Nephrologist of the Year, and the Kidney & Urology Foundation of America gave her its Lester Hoenig Award.

Dr. Murphy earned her medical degree from the Royal College of Surgeons in Dublin, Ireland. She completed an internship, residency, and clinical nephrology fellowship at Beaumont Hospital in Dublin. She pursued postdoctoral training with a fellowship in nephrology and additional training in transplant immunology at Harvard Medical School's Brigham and Women's Hospital.

Young Investigator Recognized for Contributions in Genetic Studies of Kidney Disease

Krzysztof Kiryluk, MD

The American Society of Nephrology-American Heart Association Donald W. Seldin Young Investigator Award will be presented to Krzysztof Kiryluk, MD, MS, who will speak on "Genetic Discovery in IgA Nephropathy" on Friday, November 5.

Dr. Kiryluk is associate professor of medicine in the Division of Nephrology at Columbia University in New York City.

His research aims to define genetic factors that contribute to the risk of kidney disease. He leads several large collaborative national and international genetic studies of glomerular disorders, including IgA nephropathy and membranous nephropathy. He is investigating genetic regulators of IgA production and O-glycosylation and their relationship to human health and disease.

Dr. Kiryluk uses functional genomics and systems genetics approaches to elucidate molecular mechanisms underlying inherited kidney disorders. He is also developing novel approaches to identifying genetic predictors of kidney allograft rejection using genome-wide donor-recipient compatibility studies.

Some of Dr. Kiryluk's interests fall at the interface of research and clinical care. He is developing new informatics methods to harness the power of clinical and molecular big data to enhance genetic discovery and improve clinical care of kidney patients. On this front, he is leading several local and national precision medicine efforts, including molecular studies of acute kidney injury in the precision medicine project of the National Institute of Diabetes and Digestive and Kidney Diseases and the Electronic Medical Records and Genomics (eMERGE) consortium of the National Human Genome Research Initiative.

Dr. Kiryluk is also involved in education. He directs the renal physiology and pathophysiology course for medical students at the Columbia College of Physicians & Surgeons, co-directs the Columbia TL1 training program in precision medicine for graduate and postdoctoral students, and co-leads the Columbia Clinical and Translational Science program's precision medicine resource.

He is a member of the editorial boards of *JASN* and *Kidney International*. He is currently guest editor for cases in precision medicine for the *Annals of Internal Medicine*.

He received an Innovations in Kidney Education Award and a Carl W. Gottschalk Research Scholar Award from ASN and a Young Investigator Award from the American Society of Hypertension.

Dr. Kiryluk received his medical degree from the Columbia College of Physicians & Surgeons and then completed an internal medicine residency at Massachusetts General Hospital and a nephrology fellowship at New York-Presbyterian Hospital, Columbia University. He received a master's in biostatistics from the Columbia University Mailman School of Public Health.

Disparities in Healthcare to be Focus of Eknoyan Lecture

L. Ebony Boulware, MD, MPH

A Duke University physician will present the Garabed Eknoyan, MD, Endowed Lectureship on Friday, November 5, on "Elephant in the Room: Sex and Racial Disparities in Kidney Transplantation."

The speaker will be L. Ebony Boulware, MD, MPH, who is the Eleanor Easley distinguished professor of medicine, director of the Duke Clinical and Translational Science Institute, vice dean for translational science, and associate vice chancellor for translational research in the School of Medicine at Duke University. She also serves as chief of the Division of General Internal Medicine.

Dr. Boulware is a general internist and clinical epidemiologist focused on improving health and health equity for individuals and communities affected by chronic conditions such as kidney disease and hypertension. A national thought leader in health equity, she has identified patient, clinician, system, and community-level barriers that result in disparate outcomes for Black people and other underserved groups. She investigates the influence of attitudinal, social, and environmental contexts as well as healthcare provider and health-system practices that contribute to inequities in health outcomes.

Using pragmatic trials, Dr. Boulware has developed successful interventions, shaped guidelines, raised physician awareness, and changed clinical practice. Throughout her work, she has sought to improve transparency and trustworthiness in science and medicine.

Dr. Boulware frequently engages community members, patients, family members, and other stakeholders in her research to develop sustainable interventions to improve health. Her research has been continuously funded by the National Institutes of Health, Patient-Centered Outcomes Research Institute, Health Resources and Services Administration, Agency for Healthcare Research and Quality, and several foundations.

She has published more than 180 manuscripts, editorials, and book chapters.

Dr. Boulware received an MD from Duke University and an MPH from the Johns Hopkins Bloomberg School of Public Health. She completed her medical training as a resident and chief resident at the University of Maryland, followed by a general internal medicine research fellowship at Johns Hopkins.

She became a faculty member in the Johns Hopkins School of Medicine and Bloomberg School of Public Health in 2002. In 2013, she joined Duke University as chief of the Division of General Internal Medicine. Dr. Boulware is an elected member of the American Society for Clinical Investigation, National Academy of Medicine, and American Academy of Arts and Sciences.

Schrier Lectureship to Focus on Oxygen Biology and Metabolism

Masaomi Nangaku, MD, PhD

The Robert W. Schrier, MD, Endowed Lectureship will focus on "Oxygen Biology and Metabolism in the Kidneys" on Friday, November 5.

The speaker will be Masaomi Nangaku, MD, PhD, who is vice dean, professor, and head of the Division of Nephrology and Endocrinology at The University of Tokyo Graduate School of Medicine.

Dr. Nangaku's scientific achievements extend to both basic studies of oxygen biology and clinical trials in anemia in chronic kidney disease and diabetic kidney disease. His research efforts include chronic hypoxia and oxidative stress as a common pathway to kidney failure, diabetic kidney disease, acute kidney injury, and anemia in kidney disease patients. His goal is to apply knowledge gained from the bench to the bedside in order to advance clinical medicine and patient care.

His research has led to the publication of more than 360 original articles and 90 review articles in international journals. He has given 110 invited talks at international academic meetings.

Dr. Nangaku is president of the Asian Pacific Society of Nephrology. He is also deputy chair of the research workgroup of the International Society of Nephrology, executive advisor to the Japanese Society of Nephrology, vice president of the Japanese Society of Internal Medicine, and a member of the continuous professional development committee of ASN.

He has served as a member of the scientific program committee for ASN meetings, chair of the scientific program committee of the 2016 Asian Pacific Congress of Nephrology, and chair of the program committee of the 2019 World Congress of Nephrology. He was also a co-organizer of the first Keystone Symposia on Molecular and Cellular Biology focusing on kidney disease.

Dr. Nangaku is a member of the editorial board of several journals and is currently serving his second term as an associate editor of *Kidney International*. He was a member of the emergency medical rescue team at Japan's great earthquake in 2011.

Among many awards, he received a young investigator award from the Japanese Society of Nephrology.

Dr. Nangaku is a graduate of The University of Tokyo School of Medicine. He completed a research fellowship in nephrology at the University of Washington in Seattle.

Glomerular Conditions Expert to Speak on Mechanisms of Disease

Vivette D'Agati, MD

A researcher who has spent more than 20 years investigating glomerular diseases will speak on "From Morphology to Mechanisms," in the Michelle P. Winn, MD, Endowed Lectureship.

Vivette D'Agati, MD, is the Delafield professor of pathology and cell biology at Columbia University Medical Center in New York City, where she has served as director of the Renal Pathology Division since 1984. She will speak on Friday, November 5.

Dr. D'Agati directs one of the largest renal pathology laboratories in the country, which processes approximately 4800 renal biopsies annually. This large biopsy practice has facilitated her research into characterization of emerging glomerular diseases.

Her major research interests are mechanisms of glomerular and tubulointerstitial injury in podocytopathies, immune-mediated glomerulonephritis, and toxic tubulopathies. Her research team has explored how pathologic forms of injury manifest clinically, how disease biomarkers can inform treatment, and the pathogenetic mechanisms governing distinct morphologic patterns of injury.

Her basic research has focused primarily on mechanisms of podocyte dysregulation, injury and depletion in primary and secondary forms of focal segmental glomerulosclerosis (FSGS), and how such dysregulation promotes progressive chronic kidney disease. Her work in animal models has led to characterization of molecular mechanisms of podocyte injury in HIV-associated nephropathy, primary FSGS, and diabetic nephropathy.

Her research team's access to large-scale biopsy results has facilitated the discovery and characterization of new glomerulopathies and emerging forms of drug toxicity, such as immunoglobulin (Ig)A-dominant post-staphylococcal glomerulonephritis, proliferative glomerulonephritis with monoclonal IgG deposits, smoking-related glomerulopathy, phosphate nephropathy, and the nephrotoxicity of bisphosphonates and anabolic steroids.

Dr. D'Agati has published more than 500 peer-reviewed papers and 80 book chapters. She has co-edited six textbooks on renal pathology, including the latest edition of Heptinstall's Pathology of the Kidney.

For the past three decades, she has organized an annual postgraduate course on renal biopsy in kidney diseases that some 200 international registrants attend. She lectures regularly at symposia and courses at national and international meetings.

She served as president of the Renal Pathology Society and on the editorial boards of five journals.

She has received many awards, including the Jacob Churg Award for lifetime achievement from the Renal Pathology Society, a distinguished alumnus award from New York Presbyterian Hospital, and the Edward N. Gibbs Award in Nephrology from the New York Academy of Medicine.

Dr. D'Agati received her MD from New York University School of Medicine. She completed a residency in anatomic pathology and a National Kidney Foundation-sponsored fellowship in renal pathology at Columbia University Medical Center.

STATE-OF-THE-ART LECTURE

Lecture Will Focus on Future Medical Technology

Daniel Kraft, MD

A physician-scientist, inventor, and entrepreneur will deliver a state-of-the-art lecture titled "The Future of Health and Medicine: Where Can Technology Take Us?" on Saturday, November 6.

Daniel Kraft, MD, has served as the Chair for Medicine and Neuroscience at Singularity University since its inception in 2008. Singularity University describes itself as a global community using exponential technologies to tackle the world's biggest challenges. In 2011, Dr. Kraft founded the Exponential Medicine Program there, which explores convergent, rapidly developing technologies and their potential in biomedicine and healthcare.

Dr. Kraft currently chairs the XPRIZE Pandemic Alliance Task Force, a group of more than 60 leading universities, nongovernment organizations, and corporations focused on catalyzing medical solutions.

With more than 25 years of experience in clinical practice, biomedical research, and healthcare innovation, he is often called upon to speak on the future of health, medicine, and technology and has given five TED and TEDMED talks. He has many scientific publications and medical device, immunology, and stem cell-related patents through faculty positions with the Stanford University School of Medicine and as clinical faculty for the Pediatric Bone Marrow Transplantation Service at the University of California San Francisco.

Dr. Kraft's academic research has focused on stem cell biology and regenerative medicine, stem cell-derived immunotherapies for cancer, bioengineering human T cell differentiation, and humanized animal models. His research has been published in journals that include *Nature* and *Science*.

His clinical work focuses on bone marrow and hematopoietic stem cell transplantation for malignant and non-malignant diseases in adults and children, as well as medical devices to enable stem cell-based regenerative medicine, including marrow-derived stem cell harvesting, processing, and delivery. He invented the MarrowMiner, a US Food and Drug Administration-approved device for the minimally invasive harvesting of bone marrow, and founded RegenMed Systems, a company developing regenerative therapies based on adult stem cell technologies.

Dr. Kraft implemented the first text-paging system at Stanford Hospital and advises several digital health-related startups. He recently founded IntelliMedicine, a startup focused on personalized, data-driven, precision medicine.

He is an avid pilot and has served in the Massachusetts and California Air National Guards as a flight surgeon with F-15 and F-16 fighter squadrons. He has conducted research on aerospace medicine that was published with NASA, with which he was a finalist for astronaut selection.

Following medical school at Stanford, Dr. Kraft was board certified in internal medicine and pediatrics after completing a residency at Massachusetts General Hospital and Boston Children's Hospital. He then completed fellowships in hematology, oncology, and bone marrow transplantation at Stanford. He is a member of the inaugural class of the Aspen Institute Health Innovators Fellowship.

ASN to Bestow Scribner Award on Jonathan Himmelfarb

Jonathan Himmelfarb, MD, FASN

The Belding H. Scribner Award will be tendered on Saturday, November 6, to Jonathan Himmelfarb, MD, FASN, for his career-long contributions to the practice of nephrology. Dr. Himmelfarb is professor of medicine, adjunct professor of bioengineering, director of the Kidney Research Institute, and co-director of the Center for Dialysis Innovation at the University of Washington in Seattle. He also holds the Joseph W. Eschbach, MD, Endowed Chair in Kidney Research.

Established in 1995, the Belding H. Scribner Award is presented to individuals who have made outstanding contributions to the care of patients with kidney disorders or have substantially influenced the clinical practice of nephrology. Dr. Himmelfarb's research and clinical achievements are internationally recognized, and he has been a forceful advocate for patient well-being and improving kidney care.

As the inaugural director of the Kidney Research Institute, Dr. Himmelfarb built a successful clinical and translational research program. He led efforts to engage patients as participants in the design of research and mentored physician-scientists conducting groundbreaking clinical and basic research.

Dr. Himmelfarb's research, which has led to 320 highly cited scientific publications, has propelled major advances in care. He was one of the first to investigate adverse effects from the use of bioincompatible cellulosic hemodialysis membranes. In a series of seminal publications, he improved the understanding of how the loss of kidney function directly contributes to increased oxidative stress, inflammation, insulin resistance, endothelial dysfunction, and cardiovascular risk. His landmark studies of the epidemiology of acute kidney injury helped change its treatment.

Dr. Himmelfarb helped develop microphysiological systems for kidney disease modeling, drug efficacy testing, and toxicity testing. He co-founded the Center for Dialysis Innovation, which has brought together dialysis innovators from around the world to create substantial technical progress. He is currently the principal investigator of the Kidney Precision Medicine Project, which is using deep molecular phenotypes of kidney biopsies along with longitudinally collected clinical phenotypic data to develop new disease ontologies, disease classification systems, and treatments for acute kidney injury and chronic kidney disease.

Dr. Himmelfarb has held a number of significant positions nationally, serving ASN in many capacities, including as president. His advocacy efforts for the care of patients with kidney disease include chairing the Dialysis Advisory Group, chairing the ASN Public Policy Board, and co-chairing the ASN Diversity and Inclusion Committee.

He is a former associate editor of *JASN* and has served on the editorial boards of *JASN*, *CJASN*, *Kidney International*, *Nature Reviews Nephrology*, and *BMC Medicine*. He has served on expert panels for the US Food and Drug Administration, Veterans Health Administration, and other organizations and has held leadership roles on National Institutes of Health steering committees.

Dr. Himmelfarb received his medical degree from the George Washington University School of Medicine & Health Sciences, followed by a residency at Maine Medical Center and a nephrology fellowship at Brigham and Women's Hospital.

Joanne M. Bargman to Be Given Robert G. Narins Award for Contributions in Education

Joanne M. Bargman, MD

Joanne M. Bargman, MD, will receive the Robert G. Narins Award on Saturday, November 6, for her many efforts in education and training of the next generation of nephrologists. Dr. Bargman is a staff nephrologist at the University Health Network and professor of medicine at the University of Toronto, from which she received her MD followed by a clinical fellowship in nephrology at Stanford University..

Since arriving at the University of Toronto in 1986, she has led nephrology education for undergraduate medical students, core internal medicine, and the postgraduate training program. She previously chaired the departmental educational committee at Toronto General Hospital.

In the past 27 years under her leadership, the Division of Nephrology has trained more than 400 nephrologists from over 40 countries. She built her university's nephrology training program into one of the largest in the world and has influenced future leaders in nephrology across several continents.

Dr. Bargman has provided training in peritoneal dialysis to more than 50 nephrologists from leading programs across Canada. Her worldwide impact has been substantial and continues through her connections with her former trainees. She is on the editorial boards of *CJASN* and *Peritoneal Dialysis International* and is an associate editor of *JASN*. Dr. Bargman is co-author of the chapter on chronic kidney disease in recent editions of *Harrison's Principles of Internal Medicine.*

She has delivered more than 800 invited lectures internationally on subjects as diverse as peritoneal dialysis, glomerulonephritis, and management of lupus. She is also director of peritoneal dialysis for the University Health Network in Toronto, past president of the International Society for Peritoneal Dialysis, and co-director of the renal-rheumatology lupus clinic for the University Health Network.

In recognition of her teaching, Dr. Bargman won the "Silver Shovel," given by the graduating medical class of the University of Toronto to the best undergraduate lecturer. The University of Toronto faculty of medicine presented her with its award for the best teacher in the postgraduate program, and the Canadian Society of Nephrology gave her its award for teaching excellence.

Lecture Will Focus on Patient View of Terminology

Glenda V. Roberts

The terms used in the patient-facing side of nephrology are changing, in sometimes controversial ways. A clinical practice session on this topic will feature the Celeste Castillo Lee Memorial Lectureship, "Make It Plain: The Patient Perspective on CKD Terminology," on Saturday, November 6.

The speaker will be Glenda V. Roberts, a long-term kidney patient who is director of external relations and patient engagement at the Center for Dialysis Innovation and the Kidney Research Institute at the University of Washington. Prior to joining the university, Ms. Roberts spent 35 years as an information technology executive.

Based on her personal experience with kidney disease, Ms. Roberts is a passionate activist for kidney research and patients living with kidney disease. She managed the progression of her disease via diet and exercise for more than 40 years before going on dialysis. Since receiving a kidney transplant in 2010, she has completed eight half-marathons.

Refusing to accept limitations, she enjoyed a fulfilling career, evolving from a software developer to a senior business executive managing multi-million dollar business units for large corporations, including General Electric, Microsoft, and Johnson & Johnson.

For 10 years, she was CEO of OUI Works, a nonprofit providing education, advocacy, and resources to increase organ donation, kidney disease awareness, and assistance for recipients and donors burdened by out-of-pocket transplant-related expenses. For two years, she was executive director of Transplant House, a nonprofit that provides a home away from home for transplant patients and their families who need affordable, extended-stay housing close to hospitals in Seattle.

Ms. Roberts has been involved in myriad patient-centered national and international initiatives focused on addressing patient preferences and improving outcomes. She was recently named to the Kidney Health Initiative (KHI) Patient and Family Partnership Council. KHI is a public-private partnership between ASN and the US Food and Drug Administration to foster the development of new products to improve the lives of people living with kidney diseases.

She was the second patient appointed to serve on the international research advisory committee of the Canadian Can-SOLVE CKD Network.

In addition to serving on advisory boards of the Center for Dialysis Innovation, Kidney Research Institute, and Home Dialyzors United, Ms. Robert brings the patient voice to a number of National Institutes of Health and industry research efforts. She is also involved with the Center for Dialysis Innovation as a member of the leadership team, the port research and development project, and the human factors working group.

Phosphate in CKD Bone Defects to Be Lecture Topic

Hartmut H. Malluche, MD

A long-term researcher in the subject will provide "Novel Insight into the Contribution of Phosphate to Mineral and Bone Defects in CKD" in the Jack W. Coburn, MD, Endowed Lectureship on Saturday, November 6.

The speaker will be Hartmut H. Malluche, MD, who is the Robert G. Luke chair in nephrology and chief of the Division of Nephrology, Bone & Mineral Metabolism at the University of Kentucky in Lexington. Prior to his current role, he was associate professor of medicine in the Division of Nephrology at the University of Southern California Medical Center in Los Angeles.

His research interest is in the field of metabolic bone diseases with a focus on renal osteodystrophy and osteoporosis. This research has led to the publication of more than 400 articles in various scientific journals. He is the editor of the international journal *Clinical Nephrology* and the textbook *Clinical Nephrology, Dialysis and Transplantation*.

Dr. Malluche is the founder and past president of the International Society of Bone Morphometry and was president of the Kentucky Nephrology Research Trust. He has served as a member of numerous scientific advisory councils and clinical research committees, including for the National Institutes of Health and the American Heart Association. He has served on guidelines committees for Kidney Disease: Improving Global Outcomes (KDIGO).

Dr. Malluche has been an invited speaker at many national and international meetings and served on the editorial boards of seven journals.

Among many awards, he has received a distinguished lecturer award from the Chinese Society of Nephrology and an award for excellence in research from the University of Kentucky. He is an honorary member of the Australian and New Zealand Society of Nephrology.

Dr. Malluche received his medical degree from J.W. Goethe University in Frankfurt am Main, Germany, and completed a residency and fellowship at the J.W. Goethe University hospitals.

Renal Pathologist to Share Lessons from a Lifetime's Work

Helmut G. Rennke, MD

The title of the Burton D. Rose, MD, Endowed Lectureship will be "Evolution of Renal Pathophysiology: Key Observations over Five Decades."

The speaker will be Helmut G. Rennke, MD, who is professor of pathology at Harvard Medical School and director of the renal pathology and electron microscopy laboratory at Brigham and Women's Hospital in Boston. The lecture is scheduled for Saturday, November 6.

Dr. Rennke's research in renal pathology is aided by his laboratory's workload of some 1500 cases per year. Most renal biopsies and many of the nephrectomy specimens examined require immunofluorescence and electron microscopy evaluation, in addition to the routine light microscopy examination, to establish a final clinico-pathological correlation and assess the patient's disease.

His most recent research examines poorly understood clinico-pathological correlations in disease, in particular analyzing key clinical and morphological aspects of fibrillary glomerulopathy and collapsing glomerulopathy. He has also focused on vascular diseases in the kidney, examining the hypothesis that thrombophilia is the underlying mechanism responsible for arterial and arteriolar sclerosis and renal scarring.

Dr. Rennke's early experimental work was designed to elucidate various pathophysiological aspects of glomerular function and structure. His studies of the molecular determinants of the permeability of macromolecular transport across the glomerular capillary wall revealed that the molecular charge and configuration, in addition to size, are key factors in the glomerular permeability to proteins. Those molecular factors also proved to be important for the localization of antigens within the glomerular capillary wall and the clinical and structural expression of immune complex-mediated glomerular diseases.

In a large series of studies on renal ablation, his team showed that the progression of kidney disease is in part due to compensatory hemodynamic adaptations and glomerular epithelial cell hypertrophy in a positive-feedback loop that results in obsolescence of filtering capillaries and irreversible glomerulosclerosis.

Dr. Rennke's research has resulted in the publication of 153 research papers, 59 clinical papers, and 29 reviews or book chapters. He is a longtime member of the ASN scientific program committee and four journal editorial boards.

Among many honors, he received the Jacob Churg Award from the Renal Pathology Society and the Premio Víctor R. Miatello Award of the Latin American Society of Nephrology and Hypertension.

Dr. Rennke obtained his MD from the University of Chile Medical School followed by an internship and residency in pathology at Hospital del Salvador in Santiago. He then completed a fellowship in pathology at the University of Kiel in Germany, residencies at the Mallory Institute of Pathology in Boston and what is now Brigham and Women's Hospital, and a research fellowship in pathology at Brigham and Women's Hospital.

STATE-OF-THE-ART LECTURE

Nobel Prize Winner to Describe How Work Relates to Kidney Disease

Carol W. Greider, PhD

A scientist who shared a Nobel Prize for her key discoveries in chromosome replication will discuss the implications for kidney health in a state-of-the-art lecture on Sunday, November 7.

Carol W. Greider, PhD, will speak on "Telomeres and Telomerase in Health and Kidney Disease." Dr. Greider is a distinguished professor of Molecular, Cell, and Developmental Biology at the University of California Santa Cruz, as well as a university professor at Johns Hopkins University.

Dr. Greider shared the 2009 Nobel Prize in Physiology or Medicine with Dr. Elizabeth Blackburn and Dr. Jack Szostak for their work on telomeres and telomerase. After Dr. Blackburn and Dr. Szostak discovered that telomeres—the caps at the ends of chromosomes—have a particular DNA that protects them from being broken down during replication, Dr. Greider extended this research while working on her PhD under Dr. Blackburn. In 1984, Dr. Greider discovered telomerase, an enzyme that maintains the telomeres.

In the absence of telomerase, telomeres shorten progressively as cells divide, and telomere function is lost. For this reason, telomerase is required for cells that undergo many rounds of divisions, especially tumor cells and some stem cells. The discovery catalyzed an explosion of scientific studies that probe connections of telomerase and telomeres with cancer, lung conditions, bone marrow conditions, and diseases of aging.

Dr. Greider has continued to pursue the implications of her discovery. After receiving her PhD in 1987 from the University of California Berkeley, she joined Cold Spring Harbor Laboratory as an independent fellow. While there, she cloned and characterized the RNA component of telomerase.

In 1990, Dr. Greider was appointed an assistant investigator at Cold Spring Harbor Laboratory and then investigator in 1994. She expanded the focus of her telomere research to include the role of telomere length in cellular senescence, cell death, and cancer.

In 1997, Dr. Greider moved her laboratory to the Department of Molecular Biology and Genetics at Johns Hopkins University School of Medicine. In 2003, she was appointed the Daniel Nathans Professor and Director of the Department of Molecular Biology and Genetics. Her group continued to study telomerase and determined the secondary structure of the human telomerase RNA. In addition, they characterized the loss of telomere function in mice, which allowed an understanding of short telomere syndromes in humans such as bone marrow failure, pulmonary fibrosis, and other diseases.

In 2020, Dr. Greider established her laboratory at the University of California Santa Cruz, where her research group studies fundamental mechanisms of telomere length regulation.

She has served on the Editorial Boards of seven journals as well as many National Institutes of Health Advisory Committees. In addition to the Nobel Prize, she has received the Lila Gruber Cancer Research Award, Wiley Prize in Biomedical Sciences, Albert Lasker Award for Basic Medical Research, Dickson Prize in Medicine, Louisa Gross Horwitz Prize, Katharine Berkan Judd Award, and more.

Pioneering Researcher Melissa Little to Receive Smith Award

Melissa H. Little, PhD

Prominent investigator Melissa H. Little, PhD, will be presented the Homer W. Smith Award on Sunday, November 7. This award recognizes outstanding contributions to understanding how kidneys function in normal and diseased states.

Dr. Little will speak on "From Understanding Kidney Development to Rebuilding a Kidney: Progress and Challenges."

She is the theme director of cell biology and senior principal research fellow at the Murdoch Children's Research Institute as well as professor of medicine, dentistry, and health sciences at the University of Melbourne in Australia. She is also program leader of Stem Cells Australia.

Dr. Little's research contributions in experimental nephrology, stem cells, and developmental biology span the last 30 years. She is internationally recognized for her work on the systems biology of kidney development and pioneering studies into potential regenerative therapies. Her team has developed approaches for the re-creation of human kidney tissue from human pluripotent stem cells, including methods for directing the differentiation of stem cells to human kidney organoids. Her group is applying this knowledge to disease modeling, drug screening, cell therapy, and tissue engineering.

Early in her career, Dr. Little helped define the genetic basis of the pediatric renal neoplasm and Wilms' tumor and then began to focus more broadly on kidney development. She has been instrumental in defining the transcriptional networks active during metanephric development by identifying novel genes involved in this process and defining the outcome of mutations in patterning and function.

She has developed quantitative high-resolution imaging techniques that have improved the accuracy with which a subtle developmental defect can be analyzed, resulting in mathematical models of normal development. Dr. Little's work has revealed the highly motile and migratory nature of cells during organogenesis. She performed some of the earliest studies examining whether renal stem cells are present in the postnatal kidney as well as identifying and characterizing potential stem cells in the adult kidney.

Her work has led to more than 260 publications. Dr. Little has collaborated with researchers across the globe. Her approach to research dissemination, including extensive gene expression data, protocols, and research tools, has promoted an open science culture that has led to advances throughout the international community.

Dr. Little is vice president of the International Society for Stem Cell Research and past president of the Australasian Society for Stem Cell Research. An active member of ASN, she served as a speaker on many occasions.

Her work has been recognized by many awards, including the GlaxoSmithKline Award for Research Excellence, Australian Academy of Science Gottschalk Medal in Medical Sciences, Australia and New Zealand Society for Cell and Developmental Biology President's Medal, and International Society of Nephrology Alfred Newton Richards Award.

Dr. Little received her doctorate in biochemistry from the University of Queensland.

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ASN Announces Midcareer Award Winners

ASN's Midcareer Awards recognize individuals who have made substantial and significant contributions in a variety of areas early in their professional lives.

The awards recognize up to three winners in each of five categories: clinical service, education, leadership, mentorship, and research.

Distinguished Clinical Service Award

Award Criteria

- Recognizes individuals who combine the art of medicine with the skills demanded by the scientific body of knowledge in service to patients
- Exemplifies leadership and excellence in the practice of nephrology and whose time is spent primarily in the delivery of patient care
- Has initiated or been involved in volunteer programs or has provided volunteer service post-training

Maureen E. Brogan, MD

Dr. Brogan is the clinical director of the Division of Nephrology at Montefiore Medical Center in New York City, associate professor of medicine at Albert Einstein College of Medicine, and medical director of the DaVita Allerton Dialysis Unit.

In her work at Montefiore Medical Center, she has developed new protocols for continuous kidney replacement therapy, improved the medical documentation process, and established new workflows to improve the care of inpatients receiving peritoneal dialysis.

She worked tirelessly in response to the COVID-19 surge in New York to modify services and workflows to address unexpected care and staffing needs. She worked across departments to re-route and train staff, including working with ICU staff to develop alternate ways to provide dialysis such that all patients who needed it received it.

Dr. Brogan has worked to improve the training of nephrology fellows in dialysis catheter placement and has improved their training in a quality improvement initiative.

She served as the director of the nephrology clinic at Westchester Medical Center in Valhalla, NY, from 2003 through 2018, where she also served as director of the nephrology fellowship program for 11 years. She received teaching awards from New York Medical College, where she helped to revise the medical school renal pathophysiology curriculum.

Dr. Brogan received her medical degree from the SUNY Health Science Center in Brooklyn and completed her residency and nephrology fellowship at the Albert Einstein College of Medicine.

Michelle A. Hladunewich, MD, MS, FASN

Dr. Hladunewich is professor of medicine at the University of Toronto, physician-in-chief at Sunnybrook Health Sciences Centre, and medical lead for Ontario Renal Network glomerulonephritis and specialty clinics.

A recognized expert in the diagnosis and management of kidney disease in pregnancy as well as glomerulonephritis, Dr. Hladunewich built the largest pregnancy and kidney disease clinic in Canada. In conjunction with a maternal fetal medicine clinic, she manages over 100 high-risk pregnancies annually and consults across the globe.

She has also applied this multidisciplinary care model to patients with severe forms of glomerulonephritis. One of the six specialty clinics of excellence recognized by the Ontario Renal Network, Sunnybrook manages more than 500 complex patients annually referred from other renal programs.

Her clinical and research program in women's health and rare glomerular diseases has led to an extensive peer-reviewed publication record and an international reputation.

She has taught extensively locally, nationally, and internationally, giving over 100 lectures across the globe invited by international societies, including keynote addresses and visiting professorships.

She received the Human Touch Award by Cancer Care Ontario and the College of Physicians and Surgeons of Ontario Council Award.

Dr. Hladunewich completed her medical degree at the University of Alberta, her internal medicine training at the University of Toronto, and her critical care and nephrology fellowships at Stanford University Medical Center. She also received a Master of Science in clinical investigation at Stanford University.

Distinguished Educator Award

Award Criteria

- Honors individuals who have made substantial and meritorious contributions in clinical or research education as it relates to nephrology on both the local and national levels
- Has made significant contributions to the education and training of trainees and/or junior faculty
- Has acquired special knowledge and keeps abreast of the latest advances in clinical care or research through participation in lifelong learning

Ursula C. Brewster, MD

Dr. Brewster is associate professor of medicine and director of the nephrology training program at Yale University School of Medicine.

As a clinician-educator, Dr. Brewster's focus is on the care of patients with kidney disease and on the education of fellows and hospital staff.

In her fellowship program, Dr. Brewster developed a curriculum for teaching complex renal physiology that has resulted in a greater understanding of patient care by fellows, as measured by improved in-training scores.

She created and directs the Peters Medical Firm, a nephrology teaching service for residents. This firm has been repeatedly recognized for its excellence in patient-centered care and is a popular rotation for residents.

Dr. Brewster is on the ASN workforce and training committee. Since 2014, she has served on the planning committee for the annual fellowship program directors retreat, where participants share ideas about innovations in education. She developed an annual session using case-based teaching sessions to help orient new program directors.

In 2019, she traveled to Uganda to launch an educational collaborative with nephrologists at Makerere University and Mulago Hospital. She received approval from the Accreditation Council for Graduate Medical Education (ACGME) for a fellowship rotation there. In 2020, Dr. Brewster collaborated with colleagues from two other universities on an application to the ACGME to establish a new two-year training program that combines nephrology and palliative care.

Dr. Brewster received her medical degree from Dartmouth University School of Medicine. She completed her residency and nephrology fellowship at Yale University School of Medicine.

Distinguished Leader Award

Award Criteria

- Has sustained achievements in leadership and advanced ASN's mission to "lead the fight against kidney disease by educating health professionals, sharing new knowledge, advancing research, and advocating the highest quality of care for patients"
- Recognizes leadership in any number of areas of medicine, including clinical, educational, research, or administrative efforts

Sylvia E. Rosas, MD, MS

Dr. Rosas is a nephrologist and epidemiologist at the Joslin Diabetes Center in Boston, director of the Latino Kidney Clinic, associate professor of medicine at Harvard Medical School, and a nephrologist at the Beth Israel Deaconess Medical Center.

Her research focuses on the epidemiology of metabolic and cardiovascular disease complications in patients with chronic kidney disease (CKD), particularly diabetic kidney disease. She has also examined health disparities in CKD among individuals of Hispanic/Latino background.

Dr. Rosas is her center's principal investigator (PI) in a multicenter study funded by the National Institute of Diabetes and Digestive and Kidney Diseases to evaluate the role of the *APOL1* gene in kidney transplant outcomes. She is also the PI for a precision medicine program at Joslin Diabetes Center aimed at evaluating kidney biopsies to create a kidney tissue atlas; define disease subgroups; and identify critical cells, pathways, and targets for potential therapies.

Dr. Rosas is the president-elect of the National Kidney Foundation. She is a member of the editorial board of *CJASN* and *Advances in Chronic Kidney Disease*. She chaired the minority affairs committee of the Organ Procurement and Transplantation Network/United Network for Organ Sharing.

She has received numerous awards, including the National Kidney Foundation New England Physician of the Year.

Dr. Rosas completed medical school at the University of Rosario in Bogota, Colombia, and internal medicine training at Michael Reese Hospital/University of Illinois at Chicago. She completed clinical nephrology training, a master's in clinical epidemiology, and the Wharton Management Program at the University of Pennsylvania.

Michael J. Ross, MD

Dr. Ross is professor of medicine, professor of developmental and molecular biology, and chief of the Division of Nephrology at Montefiore Medical Center and Albert Einstein College of Medicine in New York City.

He is a national leader in research related to HIV-associated kidney diseases, with a focus on the mechanisms underlying HIV-associated nephropathy. He has contributed more than 50 original publications.

Under his guidance, the nephrology division at Albert Einstein College of Medicine and Montefiore Medical Center has expanded its National Institutes of Health funding and clinical services. During the COVID-19 surge in the spring of 2020, Dr. Ross led the division's response, assisting overwhelmed ICU staff and coordinating with a variety of organizations to address supply and staffing shortages.

Dr. Ross has served in several national and international leadership roles. He chaired the ASN fellowship match task force and was deputy editor of *Kidney International* for five years. He is currently editor of the nephrology section of the American College of Physicians Medical Knowledge Self-Assessment Program.

When he was chief of nephrology at the James J. Peters VA Medical Center, he helped establish the only VA kidney transplant program in the northeastern United States.

Dr. Ross has also been a leader in nephrology education. He directed the nephrology fellowship training program at the Icahn School of Medicine at Mount Sinai for more than 10 years.

Dr. Ross received his MD from New York University. He did his internal medicine training at Duke University and his nephrology fellowship at Mount Sinai.

Cynthia Delgado, MD

Dr. Delgado is associate professor of medicine at the University of California, San Francisco, as well as associate chief of nephrology for clinical operations and director of the dialysis program at the San Francisco VA Health System.

Her research focuses on functional status, frailty, body composition, quality of life, and related outcomes among individuals with chronic kidney disease.

Dr. Delgado chairs the ASN Diversity, Equity, and Inclusion Committee and co-chairs the ASN-National Kidney Foundation Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease.

She has led efforts to improve mentoring and support of trainees from racial and ethnic minority groups. She has also served as a volunteer preceptor with medical students caring for the uninsured.

During the COVID-19 pandemic, she has led the Veterans Integrated Service Network nephrology response, creating contingency plans for dialysis units across northern California and Hawaii. Her leadership in implementing remote delivery of care and meeting staffing and supply-chain challenges helped ensure that patients continued to receive essential kidney care.

Dr. Delgado received her medical degree from the Rutgers Robert Wood Johnson Medical School in New Jersey. She completed a residency in internal medicine at the Mt. Sinai School of Medicine in New York City and a nephrology fellowship at UC San Francisco.

Distinguished Mentor Award

Award Criteria

- Recognizes individuals who have made contributions to the kidney community through the mentorship and development of other clinicians or researchers
- Inspires trainees to pursue nephrology and become leaders in the transformation of healthcare through innovations in research, education, and practice

Kerri L. Cavanaugh, MD, MHS

Dr. Cavanaugh is associate professor of medicine in the Division of Nephrology and Hypertension at Vanderbilt University Medical Center. She is also a nephrologist with the Tennessee Valley Healthcare System Veterans Affairs Medical Center.

Her research centers on identifying the factors that influence how patients learn about complex chronic disease and how to translate health information into effective self-care. She has demonstrated the risk related to limited health literacy among patients with moderate-to-advanced kidney disease and developed multi-level interventions to improve care.

She has an extensive publications record, is a highly sought speaker at national and international levels, has served on multiple editorial boards, and has led key research collaborations.

Dr. Cavanaugh has mentored almost 30 undergraduate students, graduate students, residents, and fellows who now hold academic faculty positions and has published more than 30 manuscripts with these mentees as first authors. Dr. Cavanaugh's mentorship work includes providing a research environment that supports rigorous investigation of healthcare practices in order to deliver equitable care and eliminate system-level barriers.

She served as associate director for a summer training research program, mentoring more than a dozen students, a number of whom have published in scientific journals. She has served as co-director of the primary core curriculum clinical conference, renal grand rounds, and visiting lectureship programs and developed new processes to ensure diverse representation in program content and speakers.

Dr. Cavanaugh received her medical degree from Yale University School of Medicine and completed her residency, nephrology fellowship, and Master of Health Science in clinical epidemiology at Johns Hopkins University School of Medicine.

Michelle Denburg, MD

Dr. Denburg is associate professor of pediatrics and epidemiology at the University of Pennsylvania Perelman School of Medicine, director of research and attending physician in the Division of Nephrology at the Children's Hospital of Philadelphia, and senior scholar in the Center for Clinical Epidemiology & Biostatistics at the University of Pennsylvania.

Dr. Denburg's research centers on complications of childhood kidney diseases, including chronic kidney disease, glomerular disease, and kidney stone disease, with a focus on bone health and mineral metabolism. She is the principal investigator of multiple NIH-funded pediatric studies in these populations that have provided a rich array of resources and support for her mentees. She is co-principal investigator in the Chronic Kidney Disease Biomarkers Consortium and leads a multi-institutional learning network focused on improving health and well-being in children with glomerular disorders.

In her many leadership and research roles, Dr. Denburg has devoted considerable time, expertise, and resources to mentoring clinical fellows and junior faculty members from many subspecialties, including nephrology, endocrinology, urology, and gastroenterology. She has also worked with undergraduate students, medical students, pediatric residents, and biostatistics graduate students.

Her mentoring has also been recognized by the Children's Hospital of Philadelphia with its Carole Marcus Mid-Career Award to Promote Career Development and Mentoring in Pediatric Research.

Dr. Denburg received her medical degree from the Weill Medical College of Cornell University and her Master of Science in clinical epidemiology from the University of Pennsylvania. She completed her residency at Columbia University School of Medicine and her pediatric nephrology fellowship at the Children's Hospital of Philadelphia.

Distinguished Researcher Award

Award Criteria

- Recognizes individuals who have made substantial research contributions to the discipline of nephrology
- Displays innovation and excellence in research to advance the science and/or practice of nephrology

Jodie L. Babitt, MD

Dr. Babitt is associate professor of medicine at Harvard Medical School and director of translational research in the nephrology division of Massachusetts General Hospital.

An active clinician, educator, and mentor, Dr. Babitt is also the principal investigator of an NIH-funded laboratory conducting fundamental and translational research into the molecular basis and treatment of iron disorders.

Dr. Babitt made the seminal discovery that the bone morphogenetic protein signaling pathway has a central role in controlling expression of the iron regulatory hormone hepcidin to govern systemic iron homeostasis. Her work has shed important mechanistic insight into the pathophysiology of anemia of chronic kidney disease (CKD), hereditary hemochromatosis, beta-thalassemia, and other iron disorders.

She has built on these fundamental discoveries to pioneer the use of novel biologic and small molecule agents to treat the anemia of CKD and other iron disorders.

Dr. Babitt currently serves on the board of directors of the International BioIron Society and as co-chair of the committee updating the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on anemia management in CKD.

She has received numerous honors for her work, including the International BioIron Society Marcel Simon Award for excellence in hemochromatosis research.

Dr. Babitt graduated from Harvard Medical School and the Massachusetts Institute of Technology Health Sciences and Technology Program. She completed her residency at Beth Israel Deaconess Medical Center and a nephrology fellowship at Massachusetts General Hospital and Brigham and Women's Hospital.

Steven G. Coca, DO, MS

Dr. Coca is associate professor of medicine at the Icahn School of Medicine at Mount Sinai in New York City, where he is also associate chair for clinical and translational research in the Department of Internal Medicine and director of clinical research in the Division of Nephrology.

His research focuses on the epidemiology of acute kidney injury and chronic kidney disease (CKD), with particular emphasis on the role of blood and urine biomarkers for risk stratification. Dr. Coca has been at the forefront of efforts to implement bioprognostic tests in diabetic kidney disease, testing the clinical utility of prognostic, predictive, and efficacy biomarkers in several large cohort studies.

He has also investigated machine-learning techniques and multi-dimensional data acquisition to create risk-stratification tools related to CKD and studied the impact of exercise on longitudinal changes in the kidney.

Since 2005, Dr. Coca has published 193 peer-reviewed research articles, reviews, and editorials and given numerous talks at national and international conferences and academic medical centers. He has served as a research mentor for 14 nephrology fellows as well as many postdoctoral fellows, internal medicine residents, and junior faculty members.

He serves on the editorial boards of *JASN*, *CJASN*, and *Kidney International* and as an associate editor of *Kidney360*.

Dr. Coca received his medical degree from the University of New England College of Osteopathic Medicine. He completed his residency, nephrology fellowship, and Master of Science in epidemiology and public health at the Yale University School of Medicine.

Congressional Kidney Caucus Co-Chairs to Discuss Kidney Health Policy

Rep. Suzan DelBene

Rep. Larry Bucshon

Representatives Suzan DelBene (WA-01) and Larry Bucshon, MD (IN-08), leading voices in Congress for improving the health of the 37 million Americans living with kidney diseases, will deliver the Christopher R. Blagg, MD, Endowed Lectureship on "Inside the Beltway: Why Everyone is a Stakeholder in Kidney Health Policy."

As co-chairs of the Congressional Kidney Caucus, the representatives have shaped the development of kidney health policy, including emphasizing earlier detection, prevention, and patient choice in treatment. Longstanding advocates for innovation, Reps. DelBene and Bucshon are staunch proponents of KidneyX. Their leadership has resulted in multiple years of federal funding and widespread recognition for the program and its mission to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases.

Reps. DelBene and Bucshon will discuss the role of the Congressional Kidney Caucus in establishing health policy, why increasing innovation and improving the US transplant system are essential for improving care, and how kidney health professionals can help systemic problems in kidney health and build a future that centers on patient experience, choice, and outcomes.

Before election to Congress in 2012, Rep. DelBene worked in the biotechnology industry as an executive and entrepreneur. She helped start drugstore.com as its vice president of marketing and store development, served as CEO and president of business software company Nimble Technology, and spent 12 years at Microsoft, most recently as corporate vice president of the company's mobile communications business. Rep. Bucshon is a board-certified cardiothoracic surgeon who practiced surgery for 15 years before being elected to Congress, serving as chief of cardiothoracic surgery and medical director of the open heart recovery intensive care unit at St. Mary's Hospital and as president of Ohio Valley HeartCare.

Rep. DelBene received a BA from Reed College and a masters in business administration from the University of Washington Foster School of Business. Rep. Bucshon received a BS from the University of Illinois at Urbana-Champaign and a Doctor of Medicine from the University of Illinois at Chicago.

Detective Nephron

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

Nephron 2022 is almost here. What do you have for us today, my dear apprentice?

Mac I have a 76-year-old man with AKI….

Nephron (*excited*): AKI…we haven't done that in a while. What is the serum creatinine?

Mac Trust me, you are going to love this one! Serum creatinine is 6 mg/dL, up from his baseline of 1.0 mg/dL just a few weeks ago.

Nephron Come on, spill the *details*….

Mac Hmm...hold your horses. He has a history of benign prostate hypertrophy and small bowel resection many years ago and presented with gradual onset of decreased urinary output, fatigue, anorexia, and confusion that had gradually progressed over the preceding 3 weeks.

Nephron Stop…nice! What an amazing topic…. Nephrologists love AKI, but I am tired of COVID-19-related AKI.

Mac Yes, it's AKI….

Nephron Why? This is obstruction…stop right there….

Mac (*laughing out loud*): Serum c-ANCA, p-ANCA, ANA, and complement C3 and C4 levels were within normal values. There was no serologic evidence of hepatitis B or C infection. SARS-CoV-2 PCR ×2 negative. No proteinuria.

Nephron (*angry*): Normal renal function...or some folks want "kidney function"...a few weeks ago and now such rapid AKI. Only three things come to mind: obstruction, obstruction, obstruction….

Mac (*surprised*): Shhh….Well, acute interstitial nephritis or severe acute tubular injury can also lead to rapid AKI…but yes, obstruction.… Let me tell you a bit more before you lose interest. We did a bedside sonogram, and no signs of distal or proximal obstruction. A radiologist also confirmed that.

Nephron (*bored, rolling his eyes*): Oh yes, the Hocus POCUS—seems like nephrology is doing all crazy things now.... I am sure the potassium is high, and sodium is low. You know we can still have obstruction despite your POCUS and official sonogram showing non-obstructive findings.

Mac Yes, potassium is 5.5 mg/dL, and sodium is at 134 mM. There is obviously some metabolic acidosis, and BUN is 80 mg/dL. Urinalysis showed 24 WBCs/hpf, 1264 RBCs/hpf, and muddy brown casts.

Nephron (*winking*): Did you spin it?

Mac No, he is not on dialysis.

Nephron (*laughing*): No, I meant spin the urine, not starting dialysis. I thought only surgeons called getting dialysis spinning.

Mac The urine sediment had muddy brown casts, no WBC casts, no RBC casts…but…

Nephron But what? You saw some crazy crystals?

Mac (*trying to remember*): None really.

Nephron (*jumps in*): And I assume you ruled out myeloma, NSAID use, PPI use…all that….

Mac (*surprised*): Obviously! I even have a biopsy finding….

Silence

Mac Hmm. Do you want to know it?

Nephron (*shocked*): Not used to such a drastic turn of events. Usually, L.O. Henle wouldn't tell me things after a kidney biopsy. He would wait for me to tell him. You have surprised me…. Interesting….

Mac (*jumps in*): The kidney biopsy showed tubular and interstitial damage with large calcium oxalate crystals in tubular lumens, epithelial cells, and interstitium. There is moderate interstitial fibrosis and tubular atrophy. IF and EM didn't add much to the diagnosis.

Nephron So why are you here? You have a diagnosis…oxalate nephropathy.

Mac (*sure*): Yes, but why? Why does this patient have oxalate nephropathy? We always make a diagnosis like this and forget to find out why.

Nephron Perfect! This is fascinating and often missed. Oxalate nephropathy can be as high as 4% in all kidney biopsies. Rarely studied, but most cases have nonspecific nephrosclerosis and diabetic nephropathy with the diagnosis as well. Causes, as you are aware, can be vast. Pathologists make the diagnosis, but many times as nephrologists, we are not thinking of oxalate nephropathy in our differential diagnosis.

Mac (*confused*): Well, he can't have primary hyperoxaluria. That is an autosomal recessive disease with more of a pediatric age group and too late for this presentation. That is due to overproduction of oxalate and oxalate precursor glyoxylate leading to systemwide deposition of calcium oxalate.

Nephron (*interrupting*): Excellent, but never say never! Rarely, primary hyperoxaluria can present in adulthood too. But more importantly, remember surgeries…. As internists, we often forget surgical interventions. Normally, calcium binds oxalate in the bowel to form insoluble calcium oxalate that is excreted in the feces. In a state of fat malabsorption, calcium is bound by free fatty acids and becomes unavailable for oxalate binding. There is then increased soluble oxalate available to be absorbed by the bowel. An intact colon appears likely important for oxalate absorption, and hyperoxaluria in enteric hyperoxaluria has generally not been observed in patients where the colon is not utilized such as in patients with ileostomies after colectomy. The risk of calcium oxalate precipitation is likely worsened by volume

depletion from diarrhea as well as bicarbonate loss, which can lead to metabolic acidosis and hypocitraturia. Both nephrolithiasis and oxalate nephropathy were frequent complications of one of the first surgical treatments for obesity—jejunoileal bypass. Even the more recent Roux-en-Y gastric bypass, which replaced jejunoileal bypass as the procedure of choice for malabsorptive bariatric surgery, has been recognized as a cause of oxalate nephropathy. Orlistat, a weight-loss agent that also causes fat malabsorption, has similarly been recognized to cause hyperoxaluria and oxalate nephropathy. For those onconephrologists out there, keep in mind, oxalate nephropathy after pancreatic exocrine insufficiency is described, and there are emerging data for risk after pancreatectomy for pancreas adenocarcinoma as well from single-center studies. Clearly, the pancreas has some role here but not clear data.

Mac Although our patient had not undergone such a surgery, he had undergone small bowel resection for intestinal obstruction many years ago. It can be speculated that his impaired fat absorption increased fat in the intestine, which decreased free Ca^{2+} due to binding of Ca^{2+} to the intestinal fat. This may have caused calcium oxalate to decrease and free oxalate to increase, which increased absorption of oxalate in blood, leading to deposition of oxalate in renal tissue. I also read that patients who get even cholecystectomy can cause aggravation of enteric malabsorption of fat, thereby causing the deposition of oxalate. To me, it seems like any history of a potential GI surgery should raise some red flags to us as nephrologists.

Nephron Good work, Mac! I think that we often ignore that "surgical history" component and think, "Why would that affect the kidney?" But as you know, all things affect the kidney…but can that abrupt rise be explained by his prior surgery?

Mac (*nodding*): No recent infections either. It has been suggested that antibiotic use, especially antibiotics that deplete intestinal *Oxalobacter formigenes*, which metabolizes oxalate, could lead to hyperoxaluria. Depletion of gut Oxalobacter was associated with increased urinary oxalate, especially in kidney stone-forming patients. He didn't have any history of kidney stones.

Nephron (*puzzled*): Who comes up with these names of organisms in infectious diseases? Between the new chemotherapy names and organism names, medicine has become challenging to pronounce these names…ugh! I can give an entire talk on that….

Mac So that is out. He has been very careful regarding SARS-CoV-2 and has received both his mRNA vaccine shots. Yes, we have heard of podocytopathies and ANCA disease from it. Now don't tell me you think his oxalate nephropathy is from the vaccine?

Nephron Hahaha…no way…but let's go ask him about a few other things he may be taking to prevent getting the virus. I have a hunch on what he might be taking.

Mac and Nephron exit to visit the patient at the bedside. They have a long conversation and return back to the office with an answer.

Nephron Mac! Bedside rounds are the best! Brilliant!

Mac (*confused*): Going back to the patient and getting more history of present illness are so key in several cases.

Nephron Fascinating information. Who takes such massive doses of vitamin C?

Mac People will do anything to prevent themselves from getting COVID-19…despite lack of evidence.

Nephron (*jumps in*): Oxalate nephropathy can be seen with excessive intake of high oxalate foods or mega doses of vitamin C, although some cases have been reported involving more moderate amounts, especially with chronic intake. *NEJM* even published a case called "Iced-Tea Nephropathy." Juicing of vegetables can also cause it. It has been speculated that juiced oxalate foods may be more effectively absorbed in the intestine via the paracellular pathway via solvent drag and because of dilution of calcium by water. Vitamin C is likely a more bioavailable source of oxalate than food. Oral intake of 2–7 g of vitamin C and obviously IV vitamin C, which was given during inpatient COVID-19 treatments, can lead to oxalate nephropathy. Our patient was taking 4 g of vitamin C daily for the last year to prevent infection from the virus. That coupled with the chronic resected small bowel likely caused the oxalate nephropathy.

Mac (*surprised*): I have heard that even star fruit, *Averrhoa bilimbi* (a fruit in parts of Southeast Asia), high intake of peanuts and cashews, rhubarb, and black iced tea can cause it. Interestingly, spinach and purslane have the highest oxalate (milligram) content per 100 g.

Nephron Fantastic! Those causes are mainly case reports and case series. I think surgeries are the bigger culprit coupled with ingestions in most cases of oxalate nephropathy.

Mac For your information, he told me something else. He said that in the last month, he has been worried about his health, and he started eating more purslane, as it is "full of antioxidants."

Nephron Well done, apprentice. Keep an open mind. Again, never assume. Make sure you have gone over all aspects of your differential diagnosis. A detailed history led to the cause of the oxalate nephropathy.

Mac (*with a wink*): For treatment, I assume stopping these agents will help. I assume agents like pyridoxine, vitamin C intake, and citrate intake may not help much here. Glad that drugs like lumasiran are approved for primary hyperoxaluria...but here, not so helpful. Hydration and stopping of agents likely will do it.

Nephron Yes. Treatments for secondary oxalate nephropathy are tough. Data are limited to basically nothing….

A few weeks later…

Mac (*with excitement*): With hydration and time, his serum creatinine is 1.8 mg/dL and stable. Not back to normal completely, but we can live with that. Too much of anything is not good for you—even your vitamins!

Nephron (*laughing*): Don't even get me started on that one…. Let's leave that for a discussion over my favorite New York-style coffee…. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, Professor of Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. Thanks are extended to Dr. Rimda Wanchoo, Professor of Medicine, and Dr. Purva Sharma, Assistant Professor of Medicine, both at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, for their editorial assistance. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.

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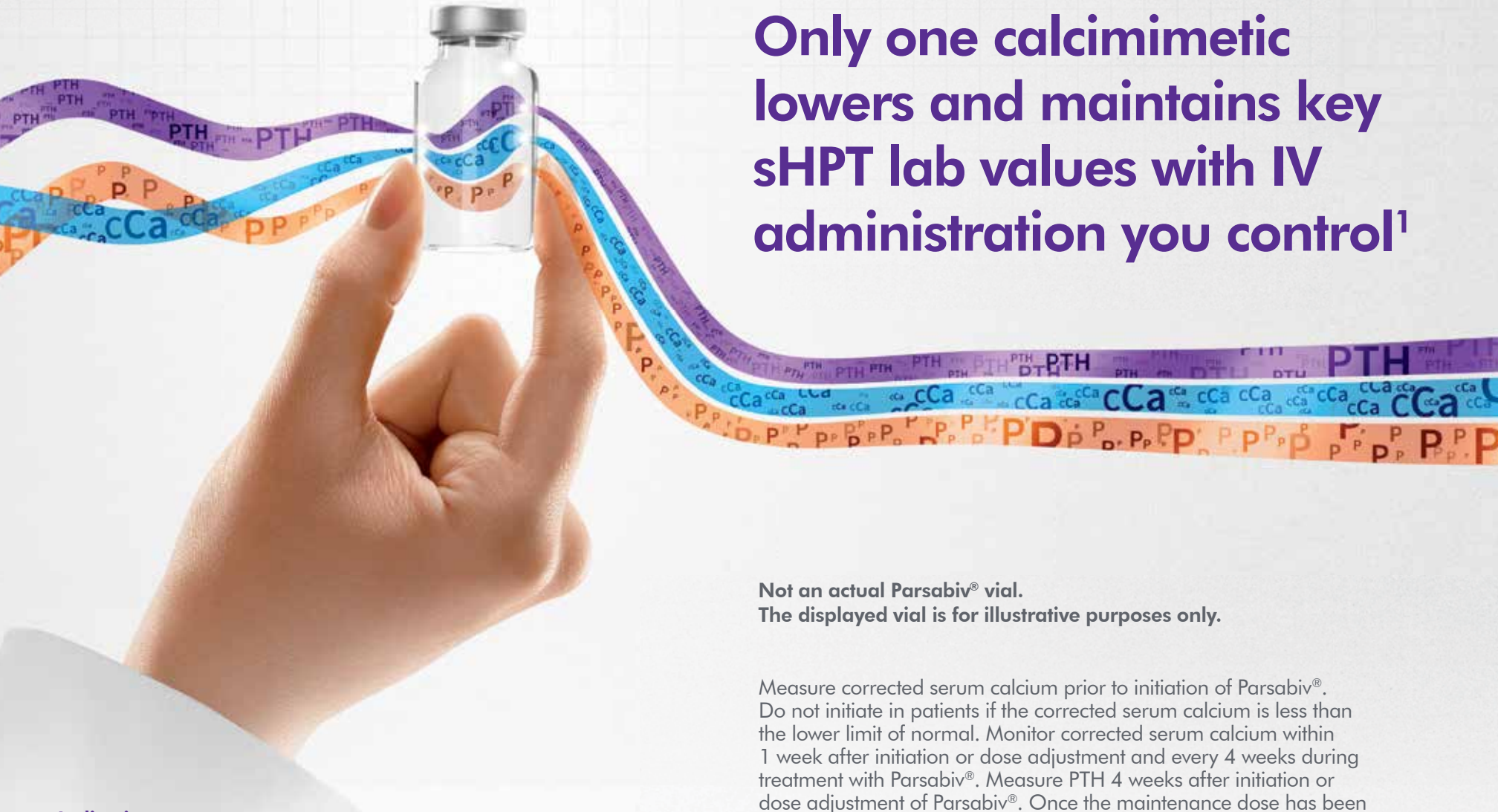

Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv® vial.
The displayed vial is for illustrative purposes only.

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.

Indication

Parsabiv® (etelcalcetide) 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 CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: 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.

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.

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.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv® in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding 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 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%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv® (etelcalcetide) prescribing information, Amgen.

Parsabiv® (etelcalcetide) Injection for intravenous use

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

Visit **ParsabivHCP.com** for more information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
(etelcalcetide) Injection for intravenous use
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®

PARSABIV® (etelcalcetide)

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

Interventions in Nephrology: India

The Nephrologist's Forte or the Radiologist's Prerogative?

By Zaheer Virani

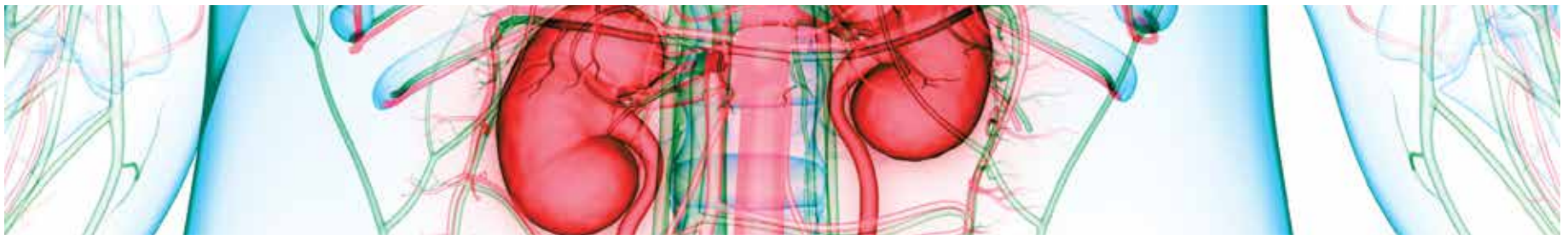
India is a developing country with a large patient population suffering from end stage kidney disease (ESKD) (1). The need for kidney replacement therapy in the form of dialysis ranges from being a planned procedure to an emergency requiring immediate initiation. Optimal dialysis access planning should ideally begin in the pre-dialysis stage. The planning depends upon the co-morbidities, patient preferences, local anatomy, demographics (age and sex), and availability of an interventional nephrologist or radiologist. The goal of dialysis access planning is to obtain successful immediate and long-term dialysis access with the least number of complications. Indeed, where there is a vein, there is a way. The question that remains is: Who will pave this way: the nephrologist or the interventional radiologist?

ESKD patients tend to stay with their treating nephrologist for a long period of time. Patients develop a level of comfort and faith through their doctors, and thus, the nephrologist is in the best situation to know the special needs of each patient. In a setting with low financial resources, the nephrologist who can diagnose, treat, and rectify vascular access issues without delay or cost escalation will need to assume the role of the interventional nephrologist! Apart from financial limitations, there is a massive dearth of nephrologists in India, especially in the rural setting. This scarcity is second only to that of interventional radiologists, making the training of the nephrologist in interventions a much more prudent plan (1).

An interventional nephrologist is trained to do kidney ultrasounds and biopsies, which with a clinical history and laboratory values help inform a quick diagnosis and initiation of treatment. Even when it comes to modality and timing of access placement for peritoneal or hemodialysis, the nephrologist is the best judge of the patient's immediate and long-term needs. The percutaneous peritoneal dialysis catheter insertion success rates by nephrologists are on a par with surgical procedures, albeit with reduced need for general anesthesia and faster healing (2). Interventional nephrologists place both tunneled-cuffed and non-tunneled catheters with good success rates (3). The ownership of the results and further dialysis prescription and complications are easier to monitor, as all services have been provided by a single individual.

Commonly, definite diagnosis and treatment in nephrology warrant tissue diagnosis in the form of a kidney biopsy. This procedure has come a long way from being done as a surgical open-wedge biopsy to a blind percutaneous procedure using surface anatomy landmarks. Success of the procedure remains inconsistent and largely operator dependent. Refinement in the technique and appropriate training in ultrasound-guided real-time biopsy remain urgent needs. The introduction of ultrasonography-guided renal biopsies likely hearlded the paradigm of incorporating technology into nephrology.

Primary arteriovenous fistula (AVF) failure rates have been described at approximately 40%, with the majority of these due to juxta anastomotic stenosis (4). The nephrologist and the dialysis team can do a simple AVF examination before every dialysis and diagnose this condition early, thereby abetting the need for a fistuloplasty. This will reduce the dependence on temporary hemodialysis catheters and reduce healthcare costs and complications. Results of these procedures have an extremely favorable complication profile when done by a nephrologist (5). A nephrologist is likely to be the first responder in the case of an acute fistula thrombosis and can quickly make a diagnosis using examination and ultrasound. This will hasten the time for a thrombectomy and not allow the clot to organize, which could be



challenging for an interventional radiologist who might be busy with other procedures. With time, the thrombi get organized and adhere to the vessel wall and may be refractory to removal by percutaneous methods.

Interventional nephrology has its own set of difficulties. A hurdle unique to India is the Pre-Conception and Pre-Natal Diagnostic Techniques Act of 1994, which was passed with the original intent to prevent female feticide after determination of prenatal sex. This act makes it difficult for nephrologists to have access to an ultrasound machine, as they are not trained as radiologists, thus necessitating assistance from their institutions to get a machine. The ultrasound machine must also be registered with the chief medical officer of the district (6).

Interventional radiologists are trained exclusively for intervention and spend most of their time performing interventions, whereas nephrologists are expected to balance a busy outpatient and inpatient service as well. The interventions that are most commonly performed by nephrologists are dialysis access placements (vascular access and peritoneal dialysis catheters), percutaneous renal biopsies, and fistulograms. Most training cen-ters in India now incorporate interventional nephrology in their curricula for nephrology fellowships. These procedures are commonly taught by the nephrology mentors. Trainees are made to observe the procedures performed by the seniors and gradually are allowed to perform the procedures under supervision until the mentor is confident the trainee can perform them independently. Usually, there is no formal examination to ensure their competence. There are very few formal interventional nephrology fellowships in India, and board-certified courses are needed. Thus, many nephrologists across the country prefer to leave the interventions in the hands of the formally trained interventional radiologists.

There is no doubt that certain complex clinical procedures demand the presence of an interventional radiologist. Interventional nephrology is probably more of a necessity, especially in a limited resource setting, than a luxury. It would be prudent and may be ideal for both to work as a team rather than engaging in a battle of wills until the procedures are more widely available. ■

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The author reports no conflicts of interest.

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WHEN TREATING HYPERKALEMIA

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LOKELMA®
(sodium zirconium cyclosilicate)
5 g | 10 g for oral suspension

INDICATION AND LIMITATION OF USE
LOKELMA is indicated for the treatment of hyperkalemia in adults.
LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

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*In Study 1, LOKELMA 10 g tid demonstrated a greater reduction in serum K^+ levels vs placebo at 48 hours (P<0.001) and started to work as early as 1 hour in patients with hyperkalemia not on dialysis.[1,2]

†In Study 2, patients with hyperkalemia who achieved normokalemia with LOKELMA in the 48-hour initial phase entered into the 28-day maintenance phase, where those who continued LOKELMA maintained lower mean serum K^+ levels vs those who switched to placebo, with a greater proportion of patients having mean serum K^+ in the normal range with LOKELMA vs placebo. Patients in Study 2 who continued into the open-label, 11-month extension phase sustained normokalemia with continued LOKELMA dosing.[1]

‡In a retrospective analysis of data from Study 3, 483 patients were receiving RAAS inhibitor at baseline. Of those patients, 74% maintained dose, 13% increased dose, 14% decreased dose, and 11% discontinued RAAS inhibitor use during the 12-month open-label trial. Patients were counted more than once if they required more than 1 RAAS inhibitor adjustment, so the total percentage across all 4 categories may exceed 100%.[3]

References: 1. LOKELMA® (sodium zirconium cyclosilicate) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia [article and supplementary material]. *N Engl J Med*. 2015;372(3):222-231. **3.** Spinowitz BS, Fishbane S, Pergola PE, et al; ZS-005 Study Investigators. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol*. 2019;14(6):798-809. **4.** Data on file, US-53732, AZPLP.

IMPORTANT SAFETY INFORMATION FOR LOKELMA® (sodium zirconium cyclosilicate)

WARNINGS AND PRECAUTIONS:

- **Gastrointestinal Adverse Events in Patients with Motility Disorders:** Avoid LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders. LOKELMA has not been studied in patients with these conditions and it may be ineffective and may worsen gastrointestinal conditions.
- **Edema:** Each 5-g dose of LOKELMA contains approximately 400 mg of sodium, but the extent of absorption by the patient is unknown. In clinical trials of LOKELMA in patients who were not on dialysis, edema was observed and was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (eg, heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed.

  In a clinical trial of LOKELMA in patients on chronic hemodialysis in which most patients were treated with doses of 5 g to 10 g once daily on non-dialysis days, there was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between the LOKELMA and placebo groups.
- **Hypokalemia in Patients on Hemodialysis:** Patients on hemodialysis may be prone to acute illness that can increase the risk of hypokalemia on LOKELMA (eg, illnesses associated with decreased oral intake, diarrhea). Consider adjusting LOKELMA dose based on potassium levels in these settings.

ADVERSE REACTIONS:

The most common adverse reaction in non-dialysis patients with LOKELMA was mild to moderate edema. In placebo-controlled trials up to 28 days, edema was reported in 4.4%, 5.9%, 16.1% of non-dialysis patients treated with 5 g, 10 g, and 15 g of LOKELMA once daily, respectively vs 2.4% of non-dialysis patients receiving placebo.

DRUG INTERACTIONS:

LOKELMA can transiently increase gastric pH. In general, oral medications with pH-dependent solubility should be administered at least 2 hours before or 2 hours after LOKELMA. Spacing is not needed if it has been determined the concomitant medication does not exhibit pH-dependent solubility.

DOSING:

- **Non-hemodialysis Patients:** For initial treatment of hyperkalemia, the recommended starting dose is 10 g administered three times a day up to 48 hours. For maintenance treatment, the recommended starting dose is 10 g once daily. Monitor serum potassium and adjust dose of LOKELMA at 1-week intervals or longer in increments of 5 g based on serum potassium and desired target range. The recommended maintenance dose range is from 5 g every other day to 15 g daily. Discontinue or decrease the dose of LOKELMA if serum potassium is below the desired target range.
- **Hemodialysis Patients:** For patients on chronic hemodialysis, administer LOKELMA only on non-dialysis days. The recommended starting dose is 5 g once daily on non-dialysis days. Consider a starting dose of 10 g once daily on non-dialysis days in patients with serum potassium greater than 6.5 mEq/L. Monitor serum potassium and adjust the dose of LOKELMA based on the pre-dialysis serum potassium value after the long interdialytic interval and desired target range. During initiation and after dose adjustment, assess serum potassium after one week. Discontinue or decrease the dose of LOKELMA if serum potassium falls below the desired target range based on pre-dialysis value after the long interdialytic interval or the patient develops clinically significant hypokalemia. The recommended maintenance dose range is from 5 g to 15 g once daily, on non-dialysis days.

Please read Brief Summary of Prescribing Information on adjacent page.

LOKELMA® (sodium zirconium cyclosilicate) for oral suspension

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

LOKELMA is indicated for the treatment of hyperkalemia in adults.

Limitation of Use

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action *[see Clinical Pharmacology (12.2) and Clinical Studies (14) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Recommended Dosage

For initial treatment of hyperkalemia, the recommended dose of LOKELMA is 10 g administered three times a day for up to 48 hours. Administer LOKELMA orally as a suspension in water *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

For continued treatment, the recommended dose is 10 g once daily. Monitor serum potassium and adjust the dose of LOKELMA based on the serum potassium level and desired target range. During maintenance treatment, up-titrate based on the serum potassium level at intervals of 1-week or longer and in increments of 5 g. Decrease the dose of LOKELMA or discontinue if the serum potassium is below the desired target range. The recommended maintenance dose range is from 5 g every other day to 15 g daily.

Dosage Adjustment for Patients on Chronic Hemodialysis

For patients on chronic hemodialysis, administer LOKELMA only on non-dialysis days.

The recommended starting dose is 5 g once daily on non-dialysis days. Consider a starting dose of 10 g once daily on non-dialysis days in patients with serum potassium greater than 6.5 mEq/L. Monitor serum potassium and adjust the dose of LOKELMA based on the pre-dialysis serum potassium value after the long inter-dialytic interval and desired target range.

During initiation and after a dose adjustment, assess serum potassium after one week. The recommended maintenance dose range is from 5 g to 15 g once daily, on non-dialysis days.

Discontinue or decrease the dose of LOKELMA if:

- serum potassium falls below the desired target range based on the pre-dialysis value after the long interdialytic interval, or;
- the patient develops clinically significant hypokalemia

Reconstitution and Administration

In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA *[see Drug Interactions (7) in the full Prescribing Information]*.

Instruct patients to empty the entire contents of the packet(s) into a drinking glass containing approximately 3 tablespoons of water or more if desired. Stir well and drink immediately. If powder remains in the drinking glass, add water, stir and drink immediately. Repeat until no powder remains to ensure the entire dose is taken.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Gastrointestinal Adverse Events in Patients with Motility Disorders

Avoid use of LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because LOKELMA has not been studied in patients with these conditions and may be ineffective and may worsen gastrointestinal conditions.

Edema

Each 5 g dose of LOKELMA contains approximately 400 mg of sodium, but the extent of absorption by the patient is unknown. In clinical trials of LOKELMA in patients who were not on dialysis, edema was observed and was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (e.g., heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed *[see Adverse Reactions (6) in the full Prescribing Information]*.

In a clinical trial of LOKELMA in patients on chronic hemodialysis in which most patients were treated with doses of 5 to 10 g once daily on non-dialysis days, there was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between the LOKELMA and placebo groups.

Hypokalemia in Patients on Hemodialysis

Patients on hemodialysis may be prone to acute illness that can increase the risk of hypokalemia on LOKELMA (e.g., illnesses associated with decreased oral intake, diarrhea). Consider adjusting Lokelma dose based on potassium levels in these settings.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the label:

- Edema *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Clinical Studies Experience

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

The total exposure to LOKELMA in the safety and efficacy clinical trials of patients not on dialysis with hyperkalemia was 1,760 patients with 652 patients exposed to LOKELMA for at least 6 months and 507 patients exposed for at least one year.

The population (n=1,009) in the placebo-controlled trials included patients aged 22 to 96 years, females (n=454), Caucasians (n=859) and Blacks (n=130). Patients had hyperkalemia in association with comorbid diseases such as chronic kidney disease, heart failure, and diabetes mellitus.

In placebo-controlled trials in which patients who were not on dialysis were treated with once daily doses of LOKELMA for up to 28 days, edema was reported in 4.4% of patients receiving 5 g, 5.9% of patients receiving 10 g and 16.1% of patients receiving 15 g LOKELMA compared to 2.4% of patients receiving placebo. In longer-term uncontrolled trials in which most patients were maintained on doses <15 g once daily, adverse reactions of edema (edema, generalized edema and peripheral edema) were reported in 8% to 11% of patients.

Laboratory Abnormalities

In clinical trials in patients who were not on dialysis, 4.1% of LOKELMA-treated patients developed hypokalemia with a serum potassium value less than 3.5 mEq/L, which resolved with dosage reduction or discontinuation of LOKELMA. In a clinical trial of LOKELMA in patients on chronic hemodialysis, 5% of patients developed pre-dialysis hypokalemia (serum potassium <3.5 mEq/L) in both the LOKELMA and placebo groups; 3% and 1% of patients developed a serum potassium < 3.0 mEq/L in the LOKELMA and placebo groups, respectively.

DRUG INTERACTIONS

LOKELMA can transiently increase gastric pH. As a result, LOKELMA can change the absorption of co-administered drugs that exhibit pH-dependent solubility, potentially leading to altered efficacy or safety of these drugs when taken close to the time LOKELMA is administered. In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in the full Prescribing Information]*. LOKELMA is not expected to impact systemic exposure of drugs that do not exhibit pH-dependent solubility and so spacing is not needed if it has been determined that the concomitant medication does not exhibit pH-dependent solubility.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

LOKELMA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure to the drug.

Lactation

Risk Summary

LOKELMA is not absorbed systemically following oral administration, and breastfeeding is not expected to result in exposure of the child to LOKELMA.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of LOKELMA, 58% were age 65 and over, while 25% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

PATIENT COUNSELING INFORMATION

Dosing

Instruct the patient how to reconstitute LOKELMA for administration. Inform the patient that it is necessary to drink the full dose *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

Instruct dialysis patients who experience acute illness (e.g., decreased oral intake of food or fluids, diarrhea) to contact the health care provider. The dose of Lokelma may need to be adjusted. *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Drug Interactions

Advise patients who are taking other oral medications to separate dosing of LOKELMA by at least 2 hours (before or after) *[see Drug Interactions (7) in the full Prescribing Information]*.

Diet

Advise patients to adjust dietary sodium, if appropriate *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

U.S. Patent No: 6332985, 8808750, 8877255, 8802152, 9592253

Manufactured by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
4/20 US-45478 9/20

The ASN COVID-19 Response Team: Finding the Silver Lining

By Jeffrey Silberzweig, Alan S. Kliger, and Susan Stark

The COVID-19 pandemic has been devastating for kidney patients and challenging for nephrologists, nurses, and other caregivers. However, in the kidney community, it has led to collaborations that reduced the impact of COVID-19—collaborations that promise to serve kidney patients and professionals long into the future.

In March 2020, ASN formed the COVID-19 Response Team as a forum to gather accurate, unbiased information from reliable sources and to share it broadly with the kidney community, nationally, and regionally. The pandemic's ever-changing realities required continuous refinement, underscored the need to learn from one another's experience, and offered the opportunity to build on existing relationships among dialysis providers. The COVID-19 Response Team brought together knowledge and experience from the Centers for Disease Control and Prevention (CDC), dialysis providers, industry, patients, and government to deliver the best care possible to kidney disease patients. These efforts were spearheaded by four subcommittees: Outpatient Hemodialysis, Home Dialysis, Transplantation, and Acute Kidney Care. The Response Team's work was supported at every turn by the dedicated staff of ASN's Excellence in Patient Care Team, Policy and Government Affairs Team, and society leadership.

To keep the kidney community informed, Response Team nephrologists, infectious disease specialists, transplant physicians, nurses, social workers, and psychologists hosted more than 20 webinars yielding more than 50,000 views. ASN's COVID-19 resource portal has had more than 100,000 downloads. Response Team leaders were quoted in leading publications including *The New York Times*, *The Washington Post*, and *The Philadelphia Inquirer*; hosted appearances on the PBS NewsHour as well as several other television outlets; and authored more than 20 manuscripts published in national and international journals including *JASN*, *CJASN*, *Kidney International*, and *AJKD*.

On March 11, 2020, ASN began hosting national meetings of chief medical officers (CMOs) of US dialysis companies to share guidance about caring for kidney patients infected with COVID-19. Experts from the CDC participated with CMOs to share US and international experience about the evolution of the pandemic. Weekly meetings with the CMOs have continued and serve as a forum for open sharing of critical information. Discussions allow these leaders to learn from one another, collaborate, and develop strategies to improve patient outcomes while managing all aspects of the pandemic. These meetings also provide a support network for the leaders of these dialysis companies.

In April 2020, ASN focused on a regional crisis after receiving reports of shortages of acute dialysis supplies in New York City hospitals. Response Team leaders immediately convened a meeting of clinical leaders from nine area hospital organizations to determine the extent of the shortages. Meetings were held with manufacturers of dialysis solutions, the Assistant Secretary for Preparedness and Response (ASPR), and representatives of the Department of Defense. Hospital leaders contributed data to ASN documenting rates of utilization of dialysis solutions and equipment. Response Team leaders shared the data with manufacturers and government officials and provided a clear picture of the precise shortages and critical needs. Manufacturers were able to quickly adjust supply deliveries to all hospital organizations that week. Together with local hospital creativity and ingenuity, these efforts allowed all patients requiring kidney replacement therapy to receive this life-saving treatment.

ASN and the Response Team recognized early on that the key to reducing the impact of COVID-19 on kidney patients is to prevent or ameliorate the effects of SARS-CoV-2 infection with vaccines. The initial recommendation by the Advisory Committee on Immunization Practices (ACIP) released in December 2020 placed kidney patients in category 1C, meaning that many would not have priority access to receive vaccination. ASN, understanding that dialysis and transplant patients were at particularly high risk for complications and death from COVID-19, joined dialysis providers to advocate for kidney patients to receive higher priority. On March 25, 2021, following many meetings with dialysis organizations, ASN, the Department of Health and Human Services, and the CDC, the White House announced a priority vaccine delivery plan for dialysis patients, the Network Administrator Model. Larger dialysis providers served as a hub for delivery of vaccine to patients receiving care at all dialysis facilities in the United States. At the time, only 25% of dialysis patients had been vaccinated. After successful deployment of this Network Administrator Model, almost 80% of patients have been vaccinated.

The COVID-19 pandemic has changed many of the ways we work to keep dialysis and transplant patients safe. Perhaps the silver linings are the lessons we learned: 1) collaboration among competing dialysis companies improves outcomes for all, and 2) information sharing among professionals, industry, and government facilitates emergency planning, product delivery, and patient care. Throughout the pandemic ASN has served as a convening body to facilitate the best care for people with kidney disease. ■

ASN thanks the members of the COVID-19 Response Team for their leadership and guidance throughout the COVID-19 pandemic: Alan S. Kliger, MD (Co-Chair); Jeffrey Silberzweig, MD (Co-Chair and Chair, Outpatient Dialysis Subcommittee); Nicole Lurie, MD; Alp Ikizler, MD; Kristina Bryant, MD; Vineeta Kumar, MD (Chair, Transplant Subcommittee); Jeffrey Perl, MD (Chair, Home Dialysis Subcommittee); Anitha Vijayan, MD (Chair, Acute Kidney Care Subcommittee); Debbie Cote, RN; Elizabeth McNamara, RN; Matthew Sinclair, MD; and Glenda Roberts.

The authors report no conflicts of interest.

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Is the Kidney the Culprit? Nephrology Perspectives on Hyperuricemia, Gout, and CKD

The Burden of Systemic Urate Deposition and a Treatment Option for Uncontrolled Gout

THE SYSTEMIC NATURE OF GOUT

"You don't learn much about gout during nephrology training—it's not a big part of what we do. But yet, when you get into practice, you see a lot of gout and learn to treat the symptoms on the fly. You don't really learn about the disease itself."

– **Dr. William Paxton**

Gout is typically thought of as an arthropathy characterized by tophi in the extremities. In textbooks and guidelines, it is portrayed as an inflammatory arthritis resulting from monosodium urate (MSU) crystals depositing around the tissues surrounding joints, mostly in the extremities.[1,2] However, extra-articular MSU buildup, especially in uncontrolled gout, causes more than just joint pain and damage. MSU deposition has been documented in almost all organ systems, notably, in the spine, heart, and kidney.[3]

Uncontrolled gout occurs when a patient's symptoms persist and serum uric acid (sUA) levels remain high despite the use of oral urate-lowering therapies.[1,2] In a claims database analysis examining patients with controlled versus uncontrolled gout, patients with uncontrolled gout were more likely to have chronic kidney disease (CKD; 49.4% vs 32.4%, odds ratio [OR] 2.04) and diabetes with renal manifestations (23.6% vs 15.4%; OR, 1.70). Patients with uncontrolled gout generally have a higher comorbidity burden and seek medical care more often than those with controlled gout.[4] In fact, medical care for comorbid conditions is suspected to be an important contributor to the overall economic burden of gout.[5]

Several studies have explored the prevalence of gout in patients with CKD. Krishnan and colleagues found an almost 8-fold increase in gout among patients with moderate to severe renal impairment versus no renal impairment (24% vs 2.9%).[6] Jing and colleagues found that the overall prevalence of gout increases based on the stage of CKD: stages 1/2: 16%; stage 3a: 23.2%; stage 3b: 27.6%; and stages 4/5: 35.6%.[7]

"When you start to think about it mechanistically, patients with CKD are clearly not very good at eliminating urate. When you look at the incidence of gout or hyperuricemia in patients with CKD, you see an increase in the rate of gout as you progress from CKD stage 1-2 and 3-4. **This is why it is important for us as nephrologists to manage gout.** It is one of those conditions for which we have to change our thinking."

A lower sUA target may be preferable for patients with more severe gout. Maintaining lower sUA levels has been shown to increase the speed of tophi resolution and to reduce the frequency of flares.[1] **Monitoring sUA levels is a**

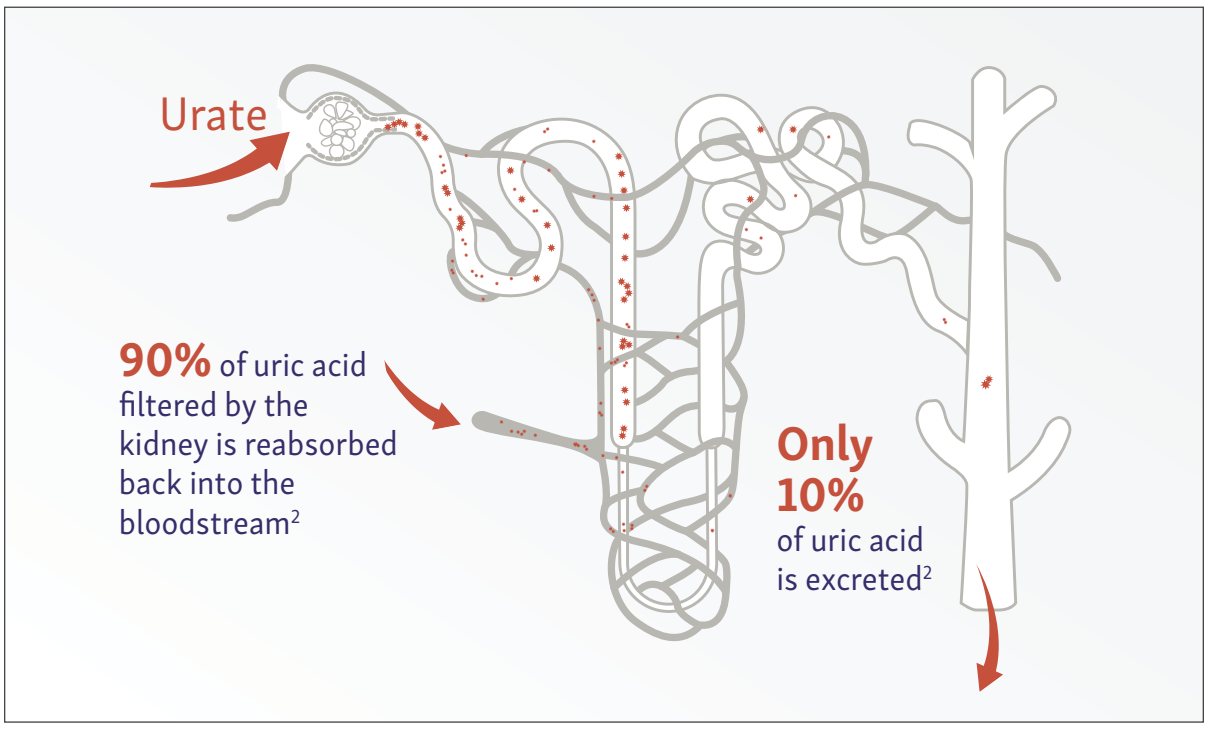

FIGURE 1: Uric Acid Excretion Is Inefficient in Healthy Kidneys; This Inefficiency Is Amplified in Impaired Kidneys[8]

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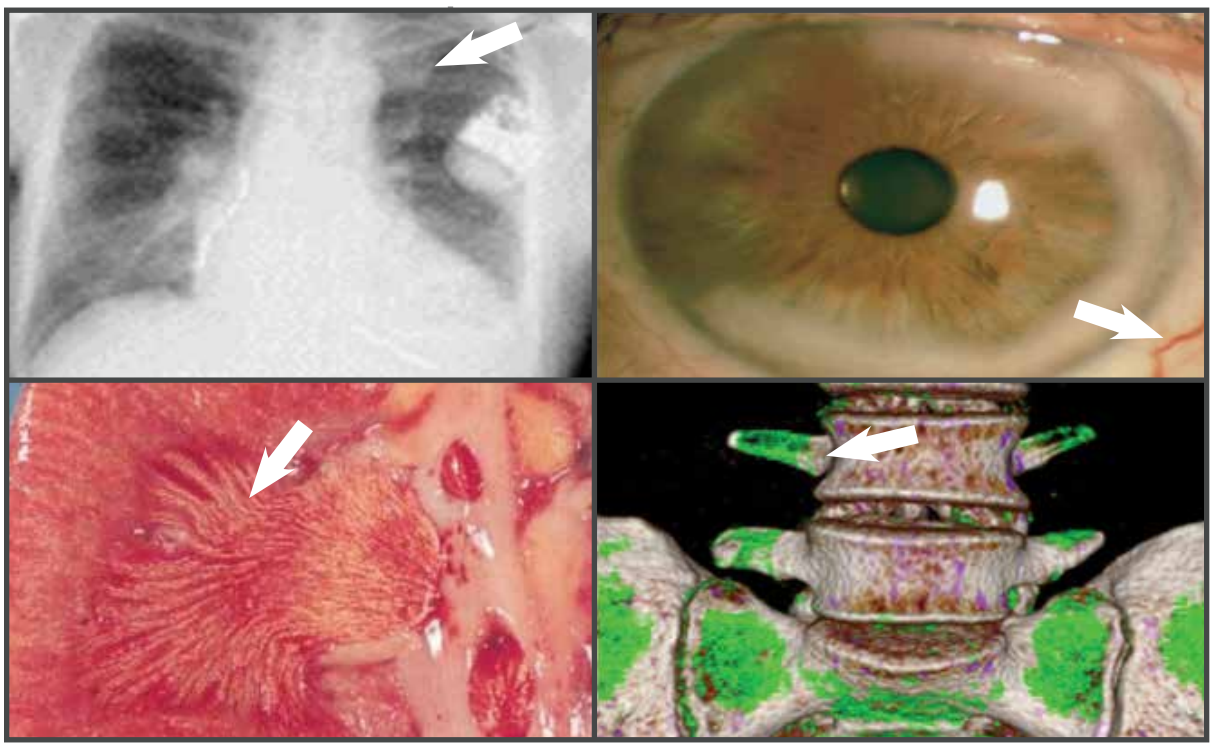

FIGURE 2: Uncontrolled Gout Is a Systemic Disease With Negative Consequences[14-17]
Urate deposition found in the lungs (top left), eye (top right), kidney (bottom left), and spine (bottom right). Images used with permission from Springer Nature, John Wiley and Sons, and Oxford University Press.

vital part of understanding a patient's urate burden; American College of Rheumatology guidelines recommend lowering a patient's sUA level to a minimum of <6 mg/dL. Health care providers, however, may need to lower sUA levels to <5 mg/dL to rapidly dissolve crystals and reduce flare frequency, according to the European League Against Rheumatism and British Society for Rheumatology.[1,9,10]

Many patients receiving oral urate-lowering therapy may not reach an sUA level of <6 mg/dL. When patients are unable to sufficiently achieve stable sUA levels, they are at risk of experiencing negative consequences, including bone erosion and poor quality of life.[11-13] In a phase 3, randomized clinical trial, 762 patients were randomly assigned to receive either febuxostat or allopurinol once daily for 52 weeks. For patients who received febuxostat 80 mg, 53% reached an sUA level of <6 mg/dL at each of the last 3 monthly measurements. In patients receiving allopurinol 300 mg, 21% reached an sUA level of <6 mg/dL at the last 3 measurements (P<0.001 for the comparison of each febuxostat group with the allopurinol group).[11]

The prevalence of specific comorbidities increases with an increase in sUA levels. With sUA levels between 8.0 and 8.9 mg/dL, there is a 20.2% prevalence of stage ≥3 CKD; a 20.6% prevalence of diabetes; a 50% prevalence of hypertension; a 52.9% prevalence of obesity; and a 7.8% and 4.6% prevalence of myocardial infarction and stroke, respectively.[18] Interestingly, gout prevalence is elevated in patients with solid organ transplants, with the highest rates observed in patients with kidney transplant (13.1%).[19]

SURPRISED TO KNOW HOW MANY OF MY PATIENTS HAD GOUT

"As clinicians we recognize that CKD makes gout worse, though in our training as nephrologists, gout is not discussed as a problem that should be urgently addressed. However, when you look at the data—that 1 in 4 moderate-to-severe CKD patients has gout—it is clear we need to shift how we view and manage gout. The research implores us to recognize and address disease progression risks associated with gout in the CKD patients we see every day. When I learned that there was an almost 10-fold increase in gout prevalence compared with normal patients, I could not believe it. I had to review the numbers for myself. In my own chart audit, I found that around 1 in 3 of my CKD patients have gout. Now that I look at it, it just makes sense, uric acid is very hard to eliminate. When the kidney is impaired, the ability to remove uric acid can be further impaired so your rate of deposition increases. *So gout is really a disease of the kidneys.*"
– Dr. Payam Shakouri

What Comes First? The Relationship Between Hyperuricemia/Gout and CKD

"The clinical question remains, is this a circle? I think of gout like having moles in your yard. The moles have tunnels in the ground, and you see them pop up every once in a while. Similarly, hyperuricemia may exist in your patients, and most providers treat when they see flares every once in a while—but really, that is the outcome, not the underlying process that needs to be treated. The decline in renal function leads to accumulation of urate which leads to clinical gout; this cycle may then self-perpetuate. You see evidence of this when you look at patients with CKD. The rate of gout is far less in those who are CKD stage 1 or 2."
– Dr. William Paxton

KRYSTEXXA® (pegloticase), PART OF THE SOLUTION

Lowering uric acid is essential to helping patients manage their uncontrolled gout; oral urate-lowering therapies may not be sufficient for all patients.[1] KRYSTEXXA is a recombinant uricase enzyme that converts uric acid into allantoin, a soluble substance that the kidneys are able to excrete more completely and easily than uric acid. KRYSTEXXA is indicated for the treatment of chronic gout in adult patients who have failed to normalize sUA 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. KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia. It is an infusion dosed every 2 weeks intravenously.[20]

KRYSTEXXA should be administered in healthcare settings where providers are prepared to manage reactions after administration of KRYSTEXXA. Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Reaction may occur with any infusion, including a first infusion, and generally manifests within 2 hours. The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.[20]

KRYSTEXXA is contraindicated in patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency. Screen patients for G6PD deficiency prior to starting treatment with KRYSTEXXA.[20]

A pooled analysis was conducted using intent-to-treat populations in 2 multicenter, randomized, double-blind, placebo-controlled trials of adult patients with uncontrolled gout receiving intravenous infusions of KRYSTEXXA 8 mg every 2 weeks. Primary endpoint response was defined as achieving an sUA level <6 mg/dL for ≥80% of the time during Months 3 and 6; a total of 42% of patients treated with KRYSTEXXA were full responders versus 0% of patients who received placebo (P<0.001). At baseline, mean sUA levels in patients in the study were approximately 10 mg/dL. Approximately 24 hours after the first dose, mean sUA levels in patients in the KRYSTEXXA group was <1 mg/dL. Incomplete responders treated with KRYSTEXXA biweekly achieved mean sUA levels <6 mg/dL through Week 10, allowing some clearance of their urate burden. Because the responses were not durable and sUA levels increased over time, these patients were considered to be incomplete responders. The sUA increase seen in these patients was due to the development of antidrug antibodies, which bind to KRYSTEXXA, thereby increasing clearance of the uricase enzyme and resulting in a rise in sUA levels.[20-22]

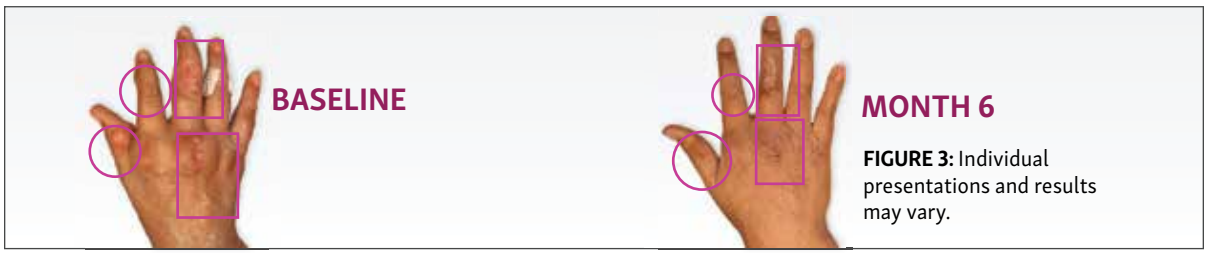

FIGURE 3: Individual presentations and results may vary.

Circles indicate tophi; rectangles indicate surgical incisions. A total of 45% of patients treated with KRYSTEXXA achieved the secondary endpoint of a complete response (defined as 100% resolution of at least one target tophus with no new tophi appearing and no worsening of tophi) versus 8% of patients receiving placebo (P=0.002); 26% of incomplete responders achieved complete tophi resolution.[20,23]

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.
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.

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KRYSTEXXA® pegloticase

As with any urate-lowering therapy, uric acid crystals begin to dissolve as sUA levels decrease while on KRYSTEXXA, and the uric acid buildup moves back into the bloodstream. This can cause mobilization flares, which may be prevented or alleviated with the use of anti-inflammatory medications.[20]

The most common serious adverse effects noted within the pivotal clinical trials include gout flares (77% in patients who received KRYSTEXXA vs 81% in placebo), infusion reactions (26% vs 5%, respectively), and severe infusion reactions (anaphylaxis; 5% vs 0%, respectively). Four cases of severe infusion reactions were retrospectively reclassified as anaphylaxis by the FDA. The majority of infusion reactions in the pivotal clinical trials were resolved by slowing or interrupting the infusion and restarting at the same or slower rate.[20,21,24]

The preinfusion level of sUA is a powerful biomarker for identifying risk of infusion reactions. In a post hoc analysis, investigators noted that 95% of infusion reactions occurred when sUA levels were >6 mg/dL. If a preinfusion sUA level is ≤6 mg/dL, treatment can be continued. If levels are >6 mg/dL, especially 2 consecutive levels, consider discontinuing treatment to avoid risk of infusion reaction.[20,24]

There are no dose adjustments 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. A subgroup analysis of KRYSTEXXA phase 3 trials was conducted using data from patients with stages 3 and 4 CKD and found that patients with CKD experienced similar reductions in sUA levels compared with patients without CKD. There was no difference in the safety or efficacy of KRYSTEXXA across stages 1-4 CKD, and kidney function remained consistent.[20,25]

ANTIDRUG ANTIBODIES AND IMMUNOMODULATION

It is not uncommon to see biologic therapies elicit an immune response as a result of antidrug antibody development. In the case of pegloticase, antidrug antibodies may accelerate the clearance of pegloticase from the circulation, resulting in a potential return to pretherapy sUA levels. Although it may be difficult to predict the development of antidrug antibodies, immunomodulation

Publication[28-38]*	n	Immunomodulator	Dose and Route of Administration	Timing†	Type of Study
Khanna PP, et al	22	MMF	2 g/day PO‡	-2 weeks	Randomized, double-blind, controlled trial
Botson JK, et al	14	MTX	15 mg/week PO	-4 weeks	Open-label clinical trial
Albert JA, et al	1 9	MTX MTX	12.5 mg/week PO 25 mg/week SubQ	+2 weeks -5 to -2 weeks	Retrospective chart review
Masri K, et al	6	LEF	10 mg/day for 7 days PO then 20 mg/day PO	-7 to +6 months	Retrospective chart review
Rainey H, et al	10	AZA	1.25 mg/kg/day for 7 days PO then 2.5 mg/kg/day PO	-2 weeks	Open-label trial
Bessen MY, et al	5 1 1	MTX MTX then AZA Cyclosporine	15 mg/week PO 15 mg/week PO, 100 mg/day PO 100 mg/day PO‡	Day 0 Day 0 Day 0	Retrospective case series
Bessen SY, et al	1	MTX	15 mg/week PO	+4 weeks	Case report, MTX initiated after increase in sUA
Botson JK, Peterson J	10	MTX	15 mg/week PO	-1 month	Prospective case series
Freyne B	1	MMF and Cyclosporine	3000 mg/day PO‡ 100 mg/day PO‡	-14 years	Case report of a heart transplant patient
Berhanu AA, et al	1	AZA	50 mg/day PO§	-2 weeks	Case report

TABLE 1: Studies of Pegloticase 8 mg Biweekly With Immunomodulation[28-38]

All patients were administered infusion reaction prophylactic medications prior to each infusion. AZA, azathioprine; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; PO, by mouth; SubQ, subcutaneous. *Adapted from Keenan RT, et al. *Semin Arthritis Rheum.* 2021;51(2):347-352.[38] †Day 0 defined as the day of first pegloticase infusion, with - and + indicating started prior to and after the first pegloticase infusion, respectively. ‡Total daily dose of a twice per day dosing schedule. §Transient increase in AZA to 100 mg/day at week 71 of pegloticase therapy.

has been used by providers to help mitigate immune response.[20,21,24,26,27]

Over the last three years, case reports and case series, open-label studies, and a proof-of-concept randomized controlled trial have been published in which adult patients with uncontrolled gout treated with pegloticase were also given a form of concomitant immunomodulation, including oral and subcutaneous MTX, MMF, LEF, and AZA.[28-37]

The first randomized control trial to evaluate the efficacy and safety of concomitant immunomodulation with pegloticase compared with pegloticase monotherapy was recently published: RECIPE (Reducing Immunogenicity to Pegloticase). In this investigator-initiated, phase 2, proof-of-concept study, 35 adult patients with uncontrolled gout were randomized (3:1) to receive either MMF or placebo for two weeks prior to starting pegloticase (8 mg every 2 weeks for 6 months). Thirty-two patients received at least 1 dose of pegloticase and were included in the analysis, with 3 patients discontinuing prior to the first pegloticase infusion. During the trial, patients continued to receive pegloticase and either MMF 1 g twice daily or placebo for 12 weeks, after which MMF was discontinued to assess the durability of therapeutic response through 24 weeks. The primary endpoint was the proportion of patients who reached and maintained response to therapy (defined as sUA levels ≤6 mg/dL at 12 weeks). At week 12, 86% of patients (19/22) randomized to receive concomitant pegloticase and MMF achieved sUA levels ≤6 mg/dL versus 40% of patients (4/10) who received pegloticase and placebo (P=0.01). In the pegloticase and MMF arm, no infusion reactions were reported (0/22); in the pegloticase and placebo arm, 30% of patients (3/10) had an infusion reaction. The most commonly reported adverse events in the pegloticase and MMF arm versus the pegloticase and placebo arm were: musculoskeletal, 41% vs 10%, respectively; gastrointestinal, 18% vs 10%; respiratory, 18% vs 0%; and infections, 9% vs 0%.[37]

A randomized controlled trial investigating the use of concomitant oral methotrexate, the study of Pegloticase (KRYSTEXXA) Plus Methotrexate in Patients With Uncontrolled Gout (MIRROR; NCT03994731), is currently underway.[39]

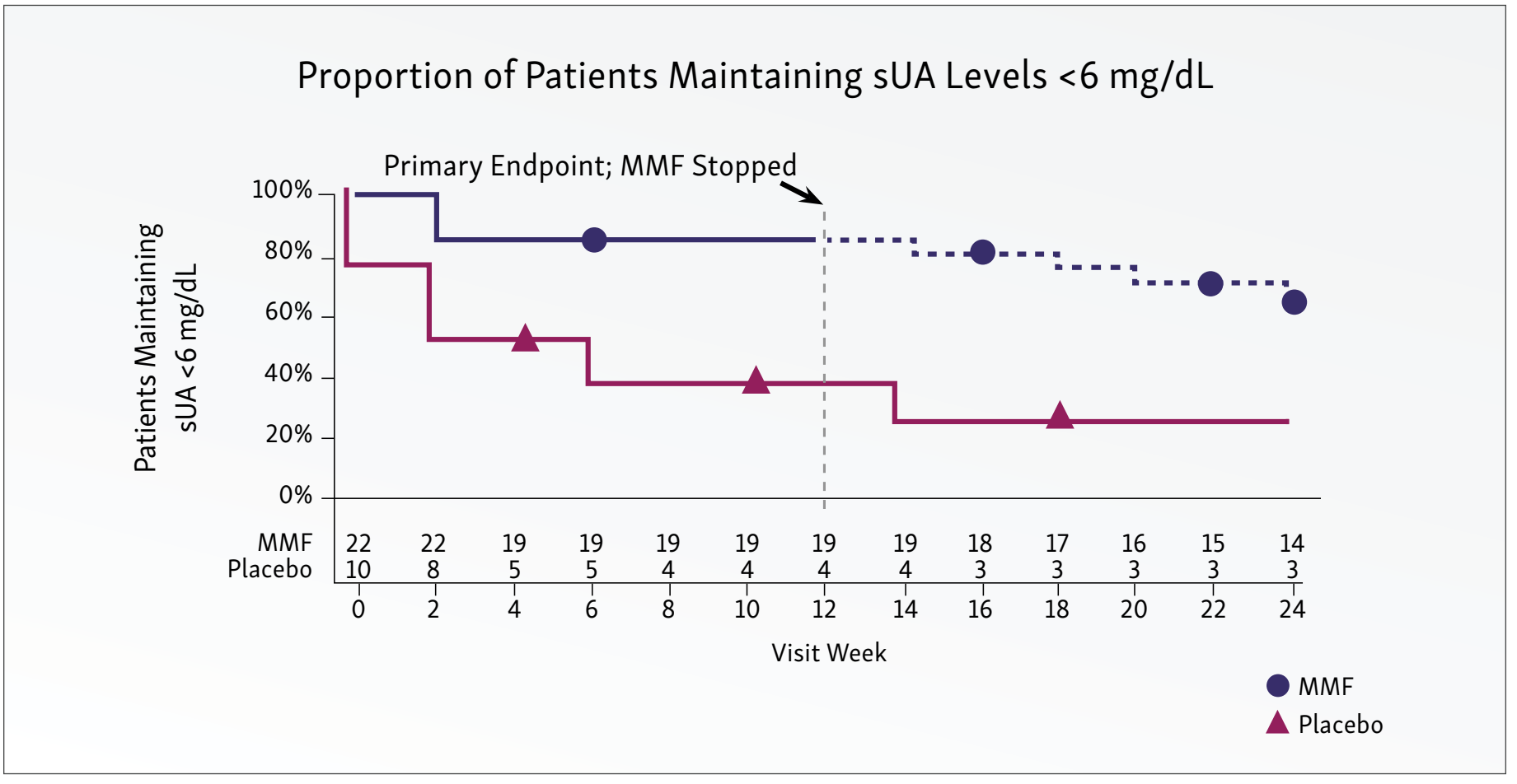


FIGURE 4: Proportion of Patients Treated With KRYSTEXXA and MMF Maintaining Target sUA Levels at Week 24 (Kaplan-Meier Estimates)[37]
In a secondary analysis, a greater percentage of patients maintained sUA <6 mg/dL through Week 12 and Week 24 in the MMF group (Kaplan-Meier estimates).

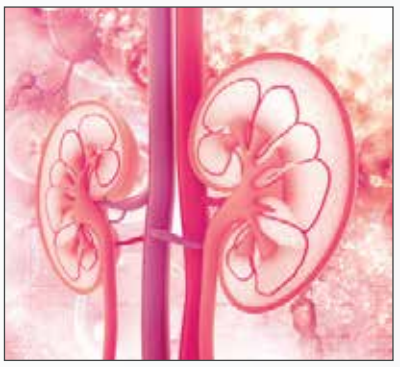
"It is nice to have a treatment option for patients who have severe, uncontrolled gout."
– **Dr. Abdul Abdellatif**

A LOOK AT TRANSPLANT PATIENT POPULATION DATA

Dr. Abdul Abdellatif

Gout is a significant concern for patients who have undergone a kidney transplant. Patients with kidney transplant and gout suffer from higher rates of overall transplant-related complications. In a retrospective study of patients who have undergone kidney transplant, 40.4% of patients with gout (n=1504) developed transplant-related complications versus 34.6% of patients without gout (n=4581).[40]

The Prospective Study of Pegloticase in Transplant Patients (PROTECT) study is an ongoing phase 4, open-label trial evaluating the use of KRYSTEXXA in adult patients with uncontrolled gout who were receiving stable doses of immunosuppression following kidney transplantation. Early data suggest that KRYSTEXXA can be safely used in treating uncontrolled gout in kidney transplant patients. A total of 5 of 15 patients completed 24 weeks of treatment and 2 patients discontinued (1 due to loss of response and 1 due to concerns over COVID-19). Eight patients were still receiving treatment. All patients experienced a rapid decrease in sUA levels after initiating KRYSTEXXA therapy. Most patients had an sUA level <1 mg/dL at the last available assessment, and estimated glomerular filtration rate remained stable in all 5 patients throughout treatment with KRYSTEXXA. At the time of this data cut, 12 patients experienced an adverse event, most events have been mild-to-moderate in intensity, and no anaphylaxis or infusion reaction events have been reported. The most common adverse event experienced was gout flare (n=7).[41,42]



CONSIDERATIONS FOR UNCONTROLLED GOUT IN MY RENAL TRANSPLANT PATIENTS

"Some of my patients have debilitating gout, so having a safe and efficacious treatment option for them is important. Because immunosuppressive medications can decrease the development of antidrug antibodies, there may be a potential for a high percentage of renal transplant patients to achieve a complete response. The PROTECT study will be an informative addition to the growing body of research supporting immunomodulation. I know that some providers may be hesitant to place patients on an infusion every 2 weeks, yet, this can be an effective treatment option when conventional therapy does not bring sUA levels down enough. In fact, patients will be appreciative that you tried to control their uncontrolled disease. Many of my patients do not realize their urate burden is the cause of many of their symptoms. It is encouraging to see the impact when they respond to therapy."

– **Dr. Abdul Abdellatif**

To learn more, visit KRYSTEXXAHCP.com.

IMPORTANT SAFETY INFORMATION CONTINUED

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.

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KRYSTEXXA pegloticase

REFERENCES

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Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA at the end of this advertisement.

KRYSTEXXA® pegloticase

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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. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Many Family Members Do Not Fully Understand the End-of-Life Wishes of Patients on Chronic Dialysis

By Tracy Hampton

Toward the end of life, people undergoing maintenance dialysis often receive intensive treatments, and some may lack the cognitive capacity to make critical decisions about their care. Therefore, family members and trusted friends can play an important role in helping ensure that end-of-life care is aligned with patients' values, goals, and preferences. A new study published in the *Clinical Journal of the American Society of Nephrology* examined whether such close contacts have a good understanding of these patients' wishes (1).

For the study, investigators surveyed family members and close contacts in two US metropolitan areas to determine their level of involvement in each patient's care and prior discussions about care preferences. The team also compared patient and family member responses to questions about end-of-life care. (The researchers used the word "family" to include partners and friends.)

Among 997 enrolled patients, 511 indicated that they did not want the study team to contact a family member, and 104 did not have anyone to list. A total of 382 provided contact information for one or more family members, although listed family members of 210 patients either could not be contacted or chose not to participate. In the end, 187 family members of 172 patients verbally consented to participate in the study and completed the survey.

"Perhaps the most striking finding was how hard it was to enroll family members. Many patients were unwilling to provide the names of family members who we could contact, and approximately 10% of patients indicated that they did not have a family member or friend to list," said lead author Fahad Saeed, MD, an assistant professor of nephrology at the University of Rochester Medical Center.

After analyzing the survey results from those who agreed to participate, Dr. Saeed and his colleagues found that family members were relatively involved in each patient's care, and many lived with the patient. Most family members indicated that they had spoken with the patient about treatment preferences, but fewer than one-third had spoken about whether the patient would want hospice or would want to stop dialysis if he or she were to become sicker.

Also, although family members had a fair understanding of patients' wishes pertaining to CPR, they had much more limited insights into how patients would respond to a range of questions about other aspects of end-of-life care, such as whether they would want to receive mechanical ventilation, the value placed on life prolongation, preferred place of death, and prognostic expectations.

"When we talked with family members of people on dialysis, most did not have a clear idea of what patients would want if they were seriously ill or dying," said Dr. Saeed. "Because [families] are often in the position of making important medical decisions for people undergoing dialysis when they become seriously ill, these findings show how important it is for patients to discuss their wishes with those close to them and for clinicians and health systems to find ways to support these conversations."

Alvin H. Moss, MD, who was not involved with the study and is a professor of medicine and the director of the Center for Health Ethics and Law at West Virginia University Health Sciences Center, noted that the findings are consistent with previous studies. "There is an urgent need—made more apparent by the pandemic—to improve advance care planning between patients with kidney disease and their families and between patients/families and the nephrology clinicians caring for them," he said. He pointed to the recently completed Pathways Project, in which nephrology nurse practitioners and social workers, with the permission of attending nephrologists, conducted advance care planning and improved documentation of patients' wishes. He added that more studies are needed to determine the best way to implement advance care planning interventions in the outpatient setting and in dialysis centers.

"The ideal is that patients would have their wishes known and respected. Since patients report that many high-intensity interventions at the end of life are unwanted, it is reasonable to expect that there would be more referrals to hospice and fewer hospitalizations at the end of life, resulting in more peaceful deaths for patients and less complicated grief for families," Dr. Moss said.

Reference

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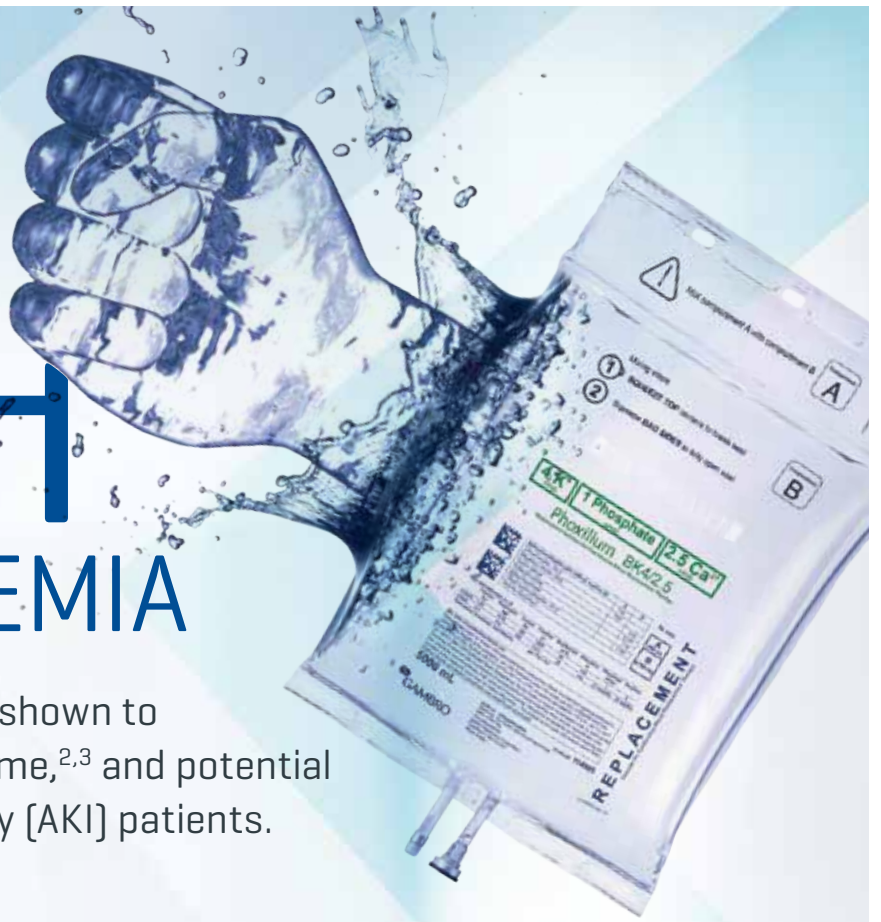

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Warnings and Precautions

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USMP/MG144/20-0006a 09/20

The ASN *AKI!Now* Initiative
Defining Excellence in the Prevention and Care of Patients with Acute Kidney Injury

By Jorge Cerdá, Samir M. Parikh, Jay Koyner, Anitha Vijayan, and Erin Barreto, on behalf of the *AKI!Now* initiative

In hospitals and in the community, the incidence of acute kidney injury (AKI) is high and rising worldwide. At the societal level, AKI is increasingly recognized as a major public health burden (1). For the individual patient, severe AKI is a life-altering event with profound immediate and future consequences. Recently, the COVID-19 pandemic has highlighted the impact of AKI in hospitalized patients with SARS-CoV-2 infection.

AKI is not a single disease, but a syndrome caused by multiple mechanisms in patients with different comorbidities and several potential treatment targets. By developing the ***AKI!Now*** initiative, ASN is committed to defining excellence in AKI prevention and care, aiming to describe pathogenic mechanisms, transform management, reduce morbidity and mortality, and improve short- and long-term outcomes (2).

To achieve these goals, ***AKI!Now*** has established four workgroups that will design a broad educational program bridging the continuum from basic investigations to clinical studies, focusing on early recognition, intervention, and effective therapies with a patient-centered focus (Figure 1).

The **Public Awareness and Education Workgroup** leverages existing educational platforms and develops novel educational tools for health professionals and patients. This workgroup launched the interactive ***AKI!Now Compendium***, a searchable database of AKI-related resources within the ASN library of offerings. Further goals of the workgroup include the promotion of AKI quality initiatives, emphasizing the role of continuous quality improvement to enhance AKI recognition and care (3). These initiatives extend not only to the nephrology community but importantly, they aim to expand into all domains of clinical practice by interacting and developing new knowledge together with all medical and surgical specialists, recognizing that AKI recognition and management often rest on non-nephrology practitioners. Woven through all educational efforts is the acknowledgment that patients and their families are an intrinsic part of the recognition and healing process.

The focus of the **Basic Science: AKI-Specific Early Interventions Workgroup** is broad, spanning from molecular and cell biology research to investigator education. The group will pursue goals to promote collaborative and inclusive discovery research that translates more effectively to patients, including:

- Developing a centralized, searchable database portal that provides a resource for the research community
- Lowering entry barriers for researchers interested in AKI by developing interactive educational content
- Promoting greater collaboration among AKI basic researchers, translational investigators, and researchers in other fields
- Articulating a preclinical roadmap that facilitates the translation of new discoveries to novel therapies
- Enhancing communication around AKI innovation by fostering an open and vibrant community of patients, researchers, clinicians, and other stakeholders to promote a culture of continuous innovation

The **AKI Recognition and Clinical Interventions: Artificial Intelligence (AI) Workgroup** has outlined objectives in three key domains:

1. *Patients.* Generate input in designing and implementing fair and equitable AI tools, and identify clinical scenarios based on personal and caregiver experience that could be improved with AI.
2. *Clinicians.* Incorporate clinician input in the design, value, and implementation of fair and equitable AI tools, and identify clinical uncertainties that may benefit from new AI tools.
3. *Researchers.* Evaluate current AI processes with a focus on removing implicit bias; develop novel, feasible, and effective AI tools to address gaps identified by patients and clinicians; and develop and implement AI methods with novel sensors for more sensitive assessment of kidney function and injury to advance the science of AKI diagnosis and treatment.

This project, with involvement from a multi-disciplinary group of collaborators, aims to promote efficient and effective use of AI for quality improvement in AKI care, such as the **NINJA** (**N**ephrotoxic **I**njury **N**egated by **J**ust-in-time **A**ction) (4).

Specific deliverables include developing risk-stratification and prediction tools; intelligent alert tools; decision support for bundled care compliance; and decision support for implementing pragmatic clinical trials. Importantly, this work will fill gaps to validate available AI tools and to develop new AI tools that do not currently exist, to deliver highly useful AI implements to improve AKI care and research and reduce costs.

The **AKI Recovery Workgroup** aims to identify challenges and opportunities to improve post-AKI care (5–7); research options to include a wide spectrum of interventions spanning from the role of the angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and sodium-glucose cotransporter 2 inhibitors (SGLT2i), to the importance of physical, mental, and cognitive rehabilitation; and to develop tests and supportive strategies that build capacity for delivery of post-AKI care.

Survivors of AKI are a high-risk, growing population, with potentially poor long-term outcomes. How to care for patients after AKI remains ill-defined and with substantial practice variation. In fall 2021, the workgroup will host two focus group sessions to outline challenges and opportunities in developing evidence-based practice in post-AKI on dialysis (AKI-D) care and to determine gaps in care of AKI survivors.

In conclusion

AKI is common, serious, underrecognized, and strongly associated with increased risk of progressive adverse outcomes. Early recognition is essential, and AI improves pattern recognition and awareness, prevention, and management. Developing AKI-specific therapies is indispensable; a better understanding of AKI basic science will lead to the development of effective treatments. Post-AKI recovery care is necessary to alleviate long-term sequelae that severely impact individuals and society. Such efforts will require close interaction and cross-pollination as the most effective pathway to achieve better AKI outcomes, in close collaboration with patients and their families

During Kidney Week, join ***AKI!Now*** for a Town Hall conversation highlighting the barriers and facilitators to quality care for patients with AKI.

Workgroup members

AKI!Now *Chair*: Jorge Cerdá, MD, MS, FASN

Public Awareness and Education Workgroup: Jorge Cerdá, MD, MS, FASN (Chair); Guarav Jain, MD, FASN; Marla Levy; Andrew Lewington, MD; Kathleen Liu, MD, FASN; Etienne Macedo, MD, PhD, FASN; Marlies Ostermann, MD, PhD

Basic Science Workgroup: Samir M. Parikh, MD, FASN (Chair); Anupam Agarwal, MD, FASN; Amandeep Bajwa, PhD; Jorge Cerdá, MD, MS, FASN; Leslie Gewin, MD; Sanjeev Kumar, MD, MBBS, PhD; Sherry Mansour, MD, MS; Mark D. Okusa, MD, FASN

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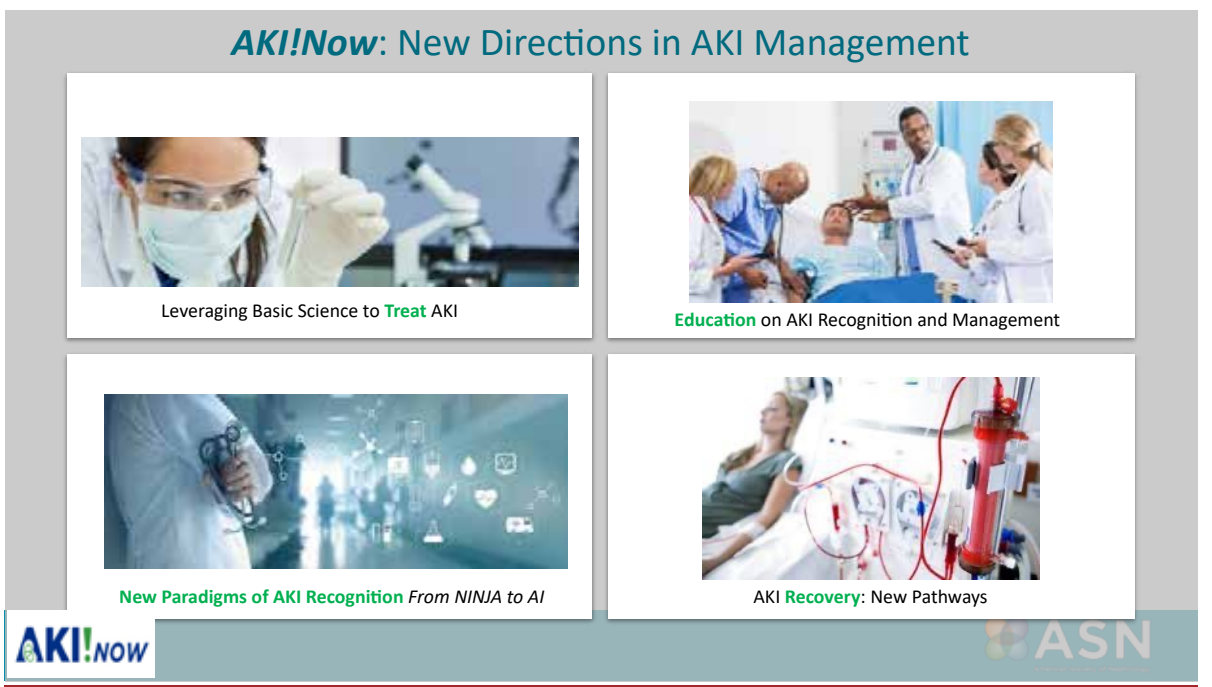
Figure 1.



Recovery Workgroup: Erin Barreto, PharmD, MS, FASN (Co-Chair); Anitha Vijayan, MD, FASN (Co-Chair); Emaad Abdel-Rahman, MD, PhD, FASN; Leslie Gewin, MD; Javier A. Neyra, MD, MS, FASN; Samuel Silver, MD, MS, FASN

The authors report no conflicts of interest.

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ASN Diabetic Kidney Disease Task Force
Embracing the Promise of Kidney Health

By Katherine R. Tuttle and Bonnie Freshly

The past 18 months have brought to the kidney community an explosion of innovative therapies that have ushered in a wave of promise for the treatment of diabetic kidney diseases (DKDs).

Globally, 476 million adults are living with diabetes (1), of whom 40% will develop DKD (2). The impact of DKD on patient quality of life is extensive, and the care of these patients is complex, requiring the thoughtful intersection of specialties and ongoing communication for quality management of care.

To date, the standard of care for treatment of DKD has been an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), yet these agents remain underutilized in clinical practice (3).

A series of trials clearly demonstrate that sodium-glucose co-transporter-2 inhibitors (SGLT2is) and non-steroidal mineralocorticoid antagonists (MRAs) improve survival along with kidney and heart health. Notably, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial also extended these observations to non-diabetic patients with albuminuric CKD.

- CREDENCE (SGLT2i): Canagliflozin reduced risks of substantial loss of kidney function, kidney failure and death due to kidney disease, and cardiovascular (CV) outcomes (4).
- DAPA-CKD (SGLT2i): Dapagliflozin reduced risks of substantial loss of kidney function, kidney failure, hospitalization for heart failure, and death from CV and all causes (5).
- FIDELIO (non-steroidal MRA): Finerenone reduced risks of substantial loss of kidney function, kidney failure, kidney disease death, and CV outcomes (6).

To disseminate knowledge about these new therapies and brainstorm with the provider community on best practices to increase prescription of SGLT2is and MRAs to patients with DKD, the American Society of Nephrology (ASN) Diabetic Kidney Disease Collaborative (DKD-C) Task Force convened a series of three strategy conferences in 2020 and 2021. Each of these conferences assembled a multi-disciplinary group of stakeholders, including nephrologists, government representatives, pharmacists, healthcare system leaders, patient advocates, and industry partners. The second conference invited partnership with primary care providers, and the third highlighted collaboration with cardiologists and endocrinologists.

1. The first strategy conference, which was held in Washington, DC, in January 2020, defined barriers and solutions. For example, barriers in early identification may be addressed by earlier referrals and recruitment of local champions. A position paper highlighted a set of deliverables, including development of educational materials and a patient-oriented campaign.
2. The second conference, which highlighted collaboration with primary care providers, took place virtually on April 20, 2021. Outcomes included the identification of DKD care best practices and recommendations for the implementation of new therapies for DKD.
3. The capstone conference took place virtually on June 16, 2021. Conference participants considered a multispecialty approach to ensure the implementation of therapies.

The DKD-C Task Force will soon release its summation of these conferences, highlighting barriers such as therapeutic inertia in a fragmented silo care model, high costs, and inconsistent messaging and data. The Task Force will recommend constructively disruptive solutions to improve healthcare delivery. Throughout all recommendations, the importance of engaging and educating patients is of primary importance. The ASN DKD-C Task Force challenges healthcare colleagues to embrace the promise of SGLT2i and MRA therapies by establishing them as a standard of care for DKD.

With each conference identifying a need for greater education, the Task Force has embarked on development of a web-based educational module for DKD. Under the direction of Chairs Dr. Amy Mottl and Dr. Christos Argyropoulos, this module utilizes a case-based strategy focused on the patient journey:

Diagnosis and Pathophysiology
Diet, Exercise, Medical Weight Management
Racial and Socioeconomic Disparities
Awareness, Detection, and Intervention
Glycemic Targets
Glucose-lowering Agents (including SGLT2i)
Hypertension Treatment
Renin-Angiotensin System Blockade (including ACE inhibition, ARBs, and MRAs)
CV Disease Evaluation and Treatment
Acute Kidney Injury, Nephrotic Syndrome, and Indications for Kidney Biopsy

The module will feature knowledge checks that prompt the learner to consider treatment strategies for clinical case scenarios. As new therapies emerge, the module will be updated to reflect current evidence.

The advent of breakthrough therapies for DKD has ushered in an exciting new era for patients and healthcare professionals. The ASN DKD-C Task Force, through initiatives such as the strategy conference series and the DKD education module, is a trustworthy source of information, communication, and collaboration across specialties and disciplines that together aspire to achieve better health and life for patients with DKD.

ASN DKD-C Task Force members

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NTDS: Educational Initiatives in Pursuit of Transformational Change

By Alan S. Kliger and Bonnie Freshly

Since its creation in 2016, Nephrologists Transforming Dialysis Safety (NTDS) has worked with the Centers for Disease Control and Prevention (CDC) in its mission to "enhance the quality of life for people with kidney failure by engaging nephrologists as team leaders in transformational change that continuously improves the safety of life-sustaining dialysis." The first goal of NTDS was to target zero infections in dialysis patients. NTDS created a series of *Targeting Zero* infection-prevention webinars and online educational resources for the kidney community, which provide practical, evidence-based guidance for providers and can be accessed on demand at viewers' convenience. Since 2017, NTDS has produced 7 webinars with over 12,000 views. NTDS continued this series on September 28, 2021, with "Management of [*Clostridioides difficile*] *C. diff* [infection] (CDI) in Outpatient Hemodialysis Settings." This webinar describes risk factors for CDI and transmission dynamics of *C. diff* and utilizes case scenarios to show common pitfalls and best practices to stop *C. diff* transmission. The webinar will soon be available on demand on the ASN Learning Center.

Fall 2021 brought the release of two online, case-based learning modules: one on Antibiotic Prescribing and the other on Optimizing Hemodialysis Vascular Access Planning. These resources, which offer continuing education (CE) for both physicians and nurses, incorporate case scenarios, video instruction, and links to community resources. They also feature knowledge checks that allow the learner to consider treatment decisions based on key points in the case scenarios.

- The "Antibiotic Prescribing" case-based module demonstrates key concepts in antibiotic treatment, including a standard process for blood culture collection, the use of the SBAR (situation, background, assessment, and recommendation/request) for improving communication, application of antibiotic stewardship principles to treat methicillin-susceptible *Staphylococcus aureus* (MSSA) infections, infection source determination, the importance of repeat blood cultures, and optimization of care transitions from the hospital back to an outpatient dialysis facility.
- "Optimizing Hemodialysis Vascular Access Planning" similarly uses a case-based format to present core concepts to improve safety and mitigate infections by reducing catheters. Chapters address central venous catheter (CVC) reduction strategies, planning for hemodialysis (HD) access, patient-centered selection of the "right" vascular access, arteriovenous (AV) fistula cannulation using the buttonhole technique, the role of endovascular AV fistulas, and future innovations in HD vascular access.

Coming soon to the ASN Learning Center is "The Patient Voice," a case-based infection-prevention and patient safety training tool, designed by dialysis patients for patients. In this moving session, patient advocates describe their experience with multiple treatment modalities to feature key recommendations in improving patient and provider communication. Understanding these experiences is key to creating an environment in which patients feel safe to ask questions and raise concerns with their providers. The patient advocates strongly underline that patients are the experts on how chronic kidney disease (CKD) affects them and remind us that there is more to their lives than dialysis or transplantation. These patient-teachers underscore that when the patient and provider each acknowledge one another as human beings, richer and deeper communication improves care.

In 2020, NTDS examined the feasibility of using an electronic catheter care audit tool to reduce catheter-related infections. A pilot study conducted in seven outpatient HD facilities adapted CDC's catheter care audit tools (catheter connection, catheter disconnection, and exit-site care) in an interactive electronic audit tool. Feedback from participating staff was favorable, and many felt the use of the electronic audit tools facilitated patient and staff engagement. In the next phase, the Vascular Access Workgroup will modify the electronic audit tools to engage patients to act as observers of catheter care and hand hygiene. The electronic tool will include educational materials to teach patients about the procedure before they act as observers. The updated audit tools will be trialed in several pilot facilities in the spring of 2022.

Finally, NTDS partnered with CDC to examine the hypothesis that principles of human factors engineering can be used to improve processes of care in dialysis facilities. Experts in human factors engineering from Carilion Clinic at Virginia Tech worked with NTDS and CDC to observe how staffs work in complex outpatient dialysis environments to identify barriers and facilitators to infection prevention and to propose solutions that make infection prevention easier and more intuitive. After completing human factors assessments at six dialysis facilities around the country, the engineers described their findings related to infection prevention in a final report. The human factors team agreed, "The current process of dialysis is complex, sometimes surpassing human capabilities and augmenting human limitations." Details of the findings from the first six human factors assessments will be submitted for publication later in 2021. In 2020, the COVID-19 pandemic caused postponement of additional site visits. The workgroup is eager to restart this work when it is safe, with two additional in-center assessments and four assessments of home dialysis facilities, including assessments of 12 patients in their home.

With these and future initiatives, NTDS will continue its pursuit of transformative care that improves the lives of patients living with kidney diseases. Additional information about all NTDS projects can be found on the ASN website (https://www.asn-online.org/ntds/). ■

Alan S. Kliger, MD, Chair of Nephrologists Transforming Dialysis Safety (NTDS), and Bonnie Freshly, MEd, CMP, ASN Excellence in Patient Care Project Specialist on behalf of the NTDS Project Committee, report no conflicts of interest..

Nova POC Creatinine/eGFR Method is More Accurate than Laboratory Method: Large Medical Center Study

In a 670 patient study funded by the International Society of Nephrology, the South Africa Medical Research Council and the University of Witwatersrand, Johannesburg, South Africa, the Nova POC StatSensor Creatinine/eGFR meter was more accurate than the central laboratory IDMS-traceable Jaffe methodology in estimating GFR when both methods were compared to MEASURED GFR (iohexol).[1]

- StatSensor measurements showed less proportional and constant error than respective IDMS Jaffe measurements when compared to iohexol measured GFR (mGFR).[1]
- StatSensor showed better accuracy than the IDMS Jaffe methodology at identifying patients with mGFR's <90 mL/min/1.73 m^2.[1]
- Of particular interest in the study, StatSensor showed better accuracy than the laboratory Jaffe methodology in the 60-89 mL min/1.73 m^2 range, where individuals with early disease may benefit renal protective measures.[1]

Nova Biomedical StatSensor Creatinine Meter

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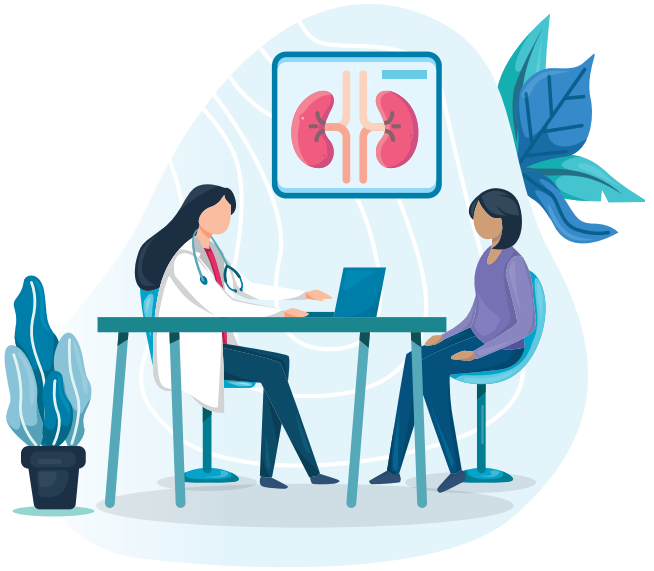

Leadership Opportunities for Women in Nephrology

By Susanne B. Nicholas, Nisha Bansal, Leslie Gewin, and Lisa M. Curtis

Women are underrepresented in leadership positions in medicine, in part, from the "glass ceiling" (an invisible barrier to advancement) (1), the "leaky pipeline" (the loss of women along the path to advancement) (2), the "broken rung" (the very first "step up" from junior level to an initial leadership position less frequently offered to women) (3), and the "labyrinth" (the advancement of women but with routes that have additional known and unknown challenges creating "twists and turns") (4). Although not specifically addressed in this article, there should be recognition that women in underrepresented racial/ethnic minority groups as well as the LGBTQ+ community may have additional barriers (5, 6), some of which may be countered through the recommendations provided here.

Per the 2018–2019 State of Women in Academic Medicine report by the Association of American Medical Colleges (7), women comprise 48% of medical school graduates and represent 41% of faculty of medical schools, yet only 29% of division chiefs and 18% of department chairs and deans are women. These disparities extend to nephrology as well (8). Among nephrology and affiliated societies, leadership by women has been infrequent. Since its inception in 1966 until recently, the American Society of Nephrology (ASN) has had only four female compared with 51 male presidents; the International Society of Nephrology (ISN) has had only three female compared with 24 male presidents since its inception in 1960; and three women presidents out of 24 have led the National Kidney Foundation (NKF). The American Physiological Society (APS), first founded in 1888, with its notable Renal Section, has had 8 women of 92 presidents, with the first elected to serve in 1975 (Dr. Bodil M. Schmidt-Nielsen, a comparative physiologist who studied the kidney). Of five leading nephrology journals, one has a female editor-in-chief, and only about 20% of deputy or associate editors are women. Despite these grim statistics, this has been an historic year. For the first time ever in nephrology, the current presidents of all three organizations—ASN, ISN, and APS—concurrently are women (Drs. Susan Quaggin, Agnes Fogo, and Jennifer Pollock [whose expertise is also in nephrology], respectively). This is a triumph to be celebrated and a testament that women are and should be promoted as accomplished leaders and visionaries.

Striving for gender equity in leadership should be a high priority for organizations and will benefit all key stakeholders, men and women alike. In a study of elderly hospitalized patients, those treated by female internists had lower mortality and lower rates of readmissions compared to those cared for by male internists (9). Research in other industries has shown that women's presence in leadership is associated with a more participatory leadership style and greater motivation, innovation, and productivity (10).

Whereas leadership may be defined as "the act or an instance of leading" (11), an even better working definition considers the qualities or characteristics of a leader. Some well-known traits of a good leader include integrity, self-awareness, gratitude, influence, empathy, courage, respect, ability to delegate, and being an effective communicator. These characteristics allow an individual to lead in any environment, as the position of a leader does not necessarily require a title. Not everyone will become president of ASN, ISN, NKF (current president-elect is Dr. Sylvia Rosas with her term as president to begin in October 2022), or APS, but anyone can be appreciated and recognized for her or his leadership qualities to advance policies that are important to her or his organization. Leadership skills are best intentionally learned and honed with practice, and in the following sections, we have outlined some ways in which women in nephrology can position themselves to attain leadership positions.

Lead early

In early career stages, it is often a misconception that leadership is something that happens later in a career when a certain level of accomplishment is achieved. In fact, leadership can and should happen early and throughout a career trajectory. Finding opportunities as a nephrology fellow, in clinical practice or in research, may offer opportunities to identify strengths and weaknesses or likes and dislikes that may translate into future career opportunities or prevent wrong turns. As women and men transition to their first post-training position, it is tempting to focus on just getting to the next step, whether that is getting promoted, getting the first federal grant, or establishing the practice. Although these milestones are all essential to advancement, they don't preclude finding opportunities to contribute through leadership. Just as there is a need to identify a niche within research, finding a way to lead with a new role or to bring a new idea to fruition can be equally important to your long-term goals. Paths often diverge from original plans, and these additional roles may position individuals for novel opportunities that were not imagined at the start of a career. In later career stages, this early exploration may position individuals with prior experience and a track record that can open doors to additional, more elevated leadership opportunities. Whenever these leadership opportunities are undertaken, increasing experience may combat "imposter syndrome," as discussed below, and increase willingness to accept new opportunities.

Mentors are beneficial

For women in nephrology interested in pursuing leadership positions, it is important to seek out mentors and sponsors who can support or help in developing your vision for your career path. An excellent mentor (whether peer-peer, near-peer, or senior) will nurture and respect you, as well as provide enthusiasm, listen attentively, and direct you on approaches to advance your career. Be aware that as a mentee, it is your responsibility to foster the relationship, as well as initiate and arrange regular meetings. Be flexible when identifying mentors. Although your role model(s) and mentor(s) may not physically look like you, they may possess the relevant qualities that you admire, such as confidence, humility, courage, and leadership. More men than women are in leadership positions, and men may have different insights than women due to their individual experiences, so having mentors of either sex may be advantageous. Women and underrepresented minorities are typically less likely to have a mentor (12, 13), and thus, actively and intentionally pursuing these relationships is of paramount importance. On the other hand, your sponsor, typically a more senior-level individual, will actively promote, advocate, and boost your career by including you in professional networks and introducing you to key individuals in your field. She or he will suggest participation in programs you may not have considered and will push you toward positions that are aligned with your long-term goals. This can serve as an enormous boost to your career advancement, so accept the challenge whenever possible. Identifying sponsors willing to support you is enhanced through active network development and visibility at conferences and meetings. Be familiar with the expectations of mentors and sponsors as well as your role in promoting and fostering these relationships, as they will be highly beneficial to keeping you focused and on track, particularly when the relationships are continually nourished.

Seek opportunities

The timing of advancement to leadership positions will vary. In order to guide your decision in pursuing leadership roles, you should research the qualifications of the intended position to determine whether they are within your trajectory and seek advice from others who have either been in the position or are currently in the desired position. Finally, seek out objective and impartial recommendations from trusted colleagues. Depending on your professional career track, become more informed about the possibilities and opportunities within your local, regional, and national organizations. Continually visit their respective websites to know when new prospects for specific leadership roles become available. Keep your resume and curriculum vitae regularly updated (e.g., monthly) so that you are equipped and prepared for the right moment(s). Make your colleagues, mentors, and sponsors aware of your aspirations to enhance your reach to opportunities. Women in Nephrology (WIN) provides opportunities for mentoring at all academic levels and actively sponsors its past and current members for available leadership roles in nephrology.

Beware imposter syndrome

Women offered leadership opportunities may experience the imposter syndrome (14). The imposter syndrome is the feeling that a person is ill prepared and doesn't really deserve the position being occupied. It is present among both genders but is more prevalent in women, especially in those of underrepresented minorities in medicine/science (15), and is common among physicians and scientists. The imposter syndrome generates anxiety and emotional distress in the potential leader. Transitioning into a new role may exacerbate these feelings of self-doubt, as there is naturally a learning curve for new work environments and tasks (16). Overcoming the imposter syndrome is critical to the confidence and creativity required of successful leadership.

Choose wisely

When embarking on a new leadership opportunity, several challenges must be addressed. First, the decision of whether to accept the leadership position is critical. Taking on a new leadership role often requires relinquishing other duties or activities, both professional and personal. A leadership opportunity may be exciting, but the decision to accept/reject should take into consideration how the position fits into a professional's overall career goals as well as an individual's personal commitments. For instance, a physician-scientist may be presented with a leadership opportunity in clinical operations. However, if the scientist's overall career goal is to build a strong research program, such a leadership position will not further the individual's overall career goals. The "balance" between personal and professional responsibilities may be tilted differently at points along your career trajectory and necessarily will inform these decisions. Distinguishing between the reluctance to accept a leadership position due to imposter syndrome or due to realistic evaluation of priorities is challenging but if considered carefully, can lead to confidence in the decision. Discussing

career opportunities with role models or mentors holding positions that you are considering helps with this decision. A strong professional network can facilitate this process, but some women may lack the senior professional contacts or may not have role models who face similar professional and personal challenges, thus making the path forward less clear or increasing the chances of turning down leadership opportunities.

Be resolute

Other challenges in accepting a new leadership opportunity include both self-advocacy and self-investment to strengthen the likelihood of success. New leaders should be proactive in asking for the resources they need to carry out their leadership tasks. Women often do not feel empowered for self-advocacy and may be hesitant to demand the support the job requires. A new leadership position often requires a new set of skills, and courses in leadership (Table 1) are valuable tools to ensure professionals are prepared for their new roles. Attendance at gender-specific conferences related to professional development has been shown to improve self-advocacy and leadership skills among women physicians (17).

Education is key

Finding the right position or role in which to say "yes" requires the same diligence as finding your niche. Leadership may involve "soft" skills that are not typically taught in either medical or graduate student training. Many resources exist that offer education in these soft skills at various career levels. Formalized commercial programs may be directed to different levels of careers, involve different amounts of time investment, and may be open to all registrants or may require nomination or selection for the opportunity (Table 1). Common among these programs is the opportunity to explore self-awareness of strengths and weaknesses, but they may also extend to real-world implementation. Individual institutions may have leadership programs as well, but caution should be advised in discerning the difference between leadership and management. Both components may be integral to a role, but leadership often requires more of an intentional "stretch" to achieve.

Over its 35+ years' experience, WIN has always placed a high value on the dissemination of information about leadership. Its programs on career development have included the nuts and bolts of private practice and academia but also sessions related to skills attainment and practical tips in finding and succeeding in leadership roles. A new offering from WIN that began in 2020 is a 1-day Leadership Conference dedicated to sessions pertinent to leadership in a variety of career tracks across the pipeline (Table 1). A strength of this program is that the speakers include a mixture of well-known leaders in nephrology and those at all levels of the workforce pipeline. This open event gives participants the opportunity to engage in networking and to find role models and sponsors for different careers within nephrology. Developing a network is often the best way to identify sponsors and advocates, in addition to mentors, who are essential to gaining visibility that then leads to future opportunities for leadership. Whatever resources are accessed, gaining this essential leadership training should be a continuing education experience as challenges change throughout the trajectory of a career. As noted by Sheryl Sandberg, "The ability to learn is the most important quality a leader can have" (18).

Finding ways to lead, at all levels, expands the dynamic range of the work, enhances career fulfilment for women in nephrology, and contributes to success of organizations. This is the perfect time for us to collectively promote women into leadership positions across all areas of nephrology. ■

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All authors are members of the Women in Nephrology Executive Council.

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Table 1. Selected list of leadership training opportunities

Program title	Career level	Link	Comments
Women in Nephrology Leadership Conference	Physicians and scientists at all levels from fellow to professional in private practice, academia, and industry	https://www.eventbrite.com/e/win-leadership-conference-2021-developing-future-leaders-in-nephrology-tickets-93202153149	1-day conference; open to all September 24, 2021
Nephrology Business Leadership University	Clinical fellow	https://nbluniv.org/event/nblu-2021/	5-day conference; open to all
Executive Leadership in Academic Medicine (ELAM)	Senior women faculty at associate or full professor	https://drexel.edu/medicine/academics/womens-health-and-leadership/elam/	1-year program; requires nomination
Leadership Development Seminar for Women Faculty in Medicine and Science	Women physicians or scientists at assistant or associate professor	https://www.aamc.org/professional-development/leadership-development/seminar-women-faculty-medicine-and-science	3-day conference; open to all
Career Advancement and Leadership Skills for Women in Healthcare	Physicians and healthcare professionals	https://womensleadership.hmscme.com/?RefID=ce-hoc&utm_source=harvard-online-learning&utm_medium=referral&utm_campaign=ce-hoc	3-day course; open to all; November 1–3, 2021
Being a Leader and the Effective Exercise of Leadership	Physicians and healthcare professionals	https://beingaleader.org/	Presented annually in the summer

Beyond Preeclampsia, Soluble FLT1 in Kidney Disease

By Isaac Yang and Tomokazu Souma

Vascular endothelial growth factor (VEGF or VEGF-A) is a powerful vascular growth factor and is important for maintaining glomerular health. Clinically, an anti-VEGF state induces glomerular injury. For example, excess placental production of soluble Fms-like tyrosine kinase (sFLT1), a decoy receptor for VEGF, causes preeclampsia. Moreover, patients treated with VEGF inhibitors show glomerular pathologies and hypertension. Recently, Wewers et al. report a comprehensive review on the role of circulating sFLT1 in kidney diseases other than preeclampsia (1).

The kidney vasculature is particularly dependent on VEGF-VEGF receptor 2 (VEGFR2) signaling for its development and maintenance (1, 2). Podocyte-derived VEGF is critical for glomerular health, and tubular epithelial cell-derived VEGF is essential for developing peritubular capillaries. Although downregulation of VEGF signaling causes glomerular injury, excess VEGF is also detrimental to renal pathologies, including diabetic nephropathy (1). Therefore, VEGF expression must be regulated tightly for healthy glomerular and vascular functions, and the role of sFLT1 reflects the specific role of VEGF in each condition. Importantly, sFLT1 exerts its function locally and systemically. sFLT1 can be introduced into circulation and inhibits the proangiogenic function of VEGF in remote organs. sFLT1 can also control cellular functions locally by modulating local VEGF availability and directly activating intracellular signaling pathways independent of VEGFR signaling (1, 2).

To summarize the results of clinical studies testing the roles of circulating sFLT1 in multiple kidney diseases, the authors selected peer-reviewed articles published between 2009 and 2020, which investigated the association of sFLT1 and kidney function in chronic kidney disease, acute kidney injury (AKI), and kidney transplantation. Most studies show that the elevated circulating sFLT1 level is associated with adverse outcomes, such as lower estimated glomerular filtration rate (eGFR), slower recovery from AKI, and delayed graft function. However, one report suggests that a high level of sFLT1 could be more beneficial than harmful in coronary artery disease in patients with kidney disease (Figure 1) (1). Finally, the authors discuss several unanswered questions that need to be addressed before considering therapeutic removal of circulating sFLT1. For example, it is essential to answer whether sFLT1 is a pure biomarker of metabolic disturbances, or its elevation is harmful and causing disease. In summary, this review establishes the status quo for future mechanistic and clinical studies to better understand the role of sFLT1 in kidney diseases. ■

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The authors report no conflicts of interest.

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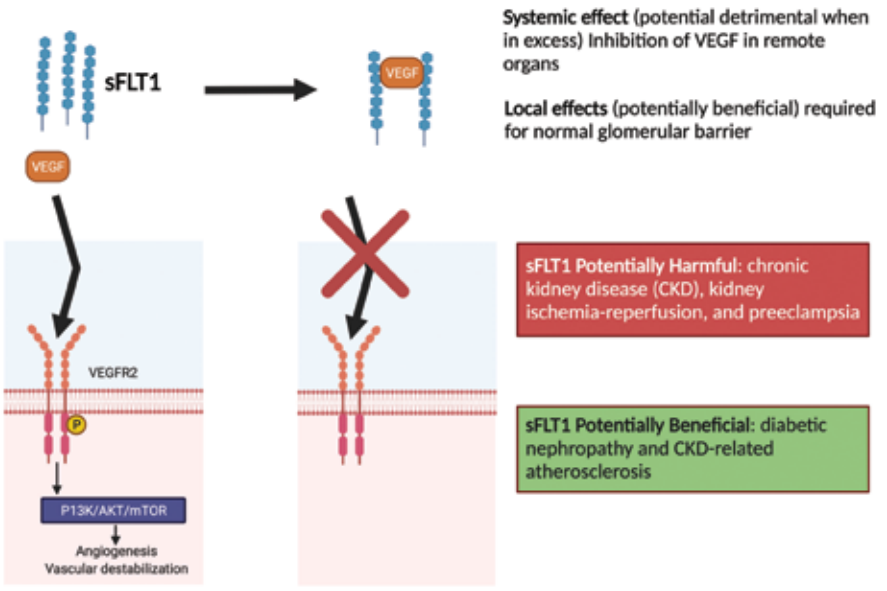
Figure 1. sFLT1 is a natural antagonist for vascular endothelial growth factor (VEGF)



PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin.

High Complication Rates in Youth with Type 2 Diabetes

Sixty percent of patients with youth-onset type 2 diabetes experience diabetic complications by the time they reach young adulthood, according to long-term follow-up data published in *The New England Journal of Medicine* (1).

[The] risk of complications… increases with age, such that a majority of patients are affected by their mid-20s.

In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, patients with youth-onset type 2 diabetes were assigned to metformin alone, metformin plus rosiglitazone, or metformin plus intensive lifestyle intervention. Patients were then transitioned to metformin alone or metformin plus insulin. The current analysis presents observational follow-up data from 2011 to 2020 in 500 patients.

About 65% of participants were female; 73% were Hispanic or non-Hispanic Black. At follow-up, mean age was 26.4 years and mean time since diabetes diagnosis was 13.3 years. Participants had annual follow-ups for diabetic complications, including annual assessment of diabetic kidney disease, hypertension, dyslipidemia, and nerve disease, plus two assessments for retinal disease.

During follow-up, at least one diabetic complication occurred in 60.1% of patients and at least two complications in 28.4%. Cumulative incidence was 67.5% for hypertension, 54.8% for diabetic kidney disease, 51.6% for dyslipidemia, and 32.4% for nerve disease. Prevalence of retinal disease increased from 13.7% in the follow-up period 2010–2011 to 51.0% in 2017–2018.

Rates of adjudicated, clinically identified complications were 3.73 per 1000 person-years for heart, vascular, and cerebrovascular events; 12.17 per 1000 person-years for all eye disease events; 6.70 per 1000 person-years for liver, pancreas, or gallbladder events; 2.35 per 1000 person-years for nerve events; and 0.44 per 1000 person-years for kidney events, including end-stage kidney disease.

Risk for developing any microvascular complication was about 50% higher for Hispanic and non-Hispanic Black participants, compared to non-Hispanic White patients. In adjusted models, significant risk factors included glycated hemoglobin level, body mass index, insulin sensitivity, hypertension, and dyslipidemia.

As the prevalence of youth-onset type 2 diabetes continues to rise, there is little information about the associated risk of diabetic complications. These longitudinal data show a high risk of complications that increases with age, such that a majority of patients are affected by their mid-20s.

Patients of minority race/ethnicity are at higher risk of complications. The researchers call for studies exploring early aggressive management of glycemia and risk factors in youth-onset type 2 diabetes. ■

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Ronak Lakhia, MD
Role of Cis-Regulatory Elements in Autosomal Dominant Polycystic Kidney Disease

Eugene Lin, MD, MS, FASN*
The Impact of Medicare Advantage on Patients with End-Stage Kidney Disease

Jennie Lin, MD, MS
Endoplasmic Reticulum Stress and Macrophage Function in APOL1 Nephropathy

Alla Mitrofanova, PhD
STING as a Potential Therapeutic Target for Diabetic Kidney Disease

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Regulation of Divalent Cation Homeostasis by Muc1

Yanhua Wang, PhD
Roles of Aldosterone and Phosphatases in Vasopressin Escape

John Merrill Grant in Transplantation

John Yongjoon Choi, MD*
Harnessing Regulatory CD8+ T Cells to Suppress Antibody-Mediated Rejection

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Meredith Posner Schuh, MD
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Rac1 is Required for Renal Tubular Function and Repair

Amanda J. Clark, MD*
NAD+ Biosynthesis Impairment in Acute Kidney Injury

Irma Husain, MBBS, MD
Role of Macrophage AIF-1 in Ischemia Reperfusion Injury and Kidney Allograft Rejection

Felix Poppelaars, MD, PhD
Molecular Imaging: A Novel Tool for Noninvasive Tracking of Disease Activity in Lupus Nephritis

Ghazal Z. Quinn, MD*
Immune Cells in Renal Fibrosis and Chronic Kidney Disease

Sharon Anderson Research Fellow

Mary Hannan, PhD, NP
The Influence of Sedentary Behavior on Health Outcomes in Individuals with Chronic Kidney Disease

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Somatic Mutations in Kidney Disease

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The Role of Glomerular Basement Membrane Glycation and Stiffening in Development of Proteinuria

George B. Rathmann Research Fellow

Konstantin Deutsch, MD
Recapitulating the Human SRNS Phenotype in CRISPR/Cas9 Zebrafish Models by Circumventing NMD

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Caroline M. Hsu, MD*
Predictors of Peritoneal Dialysis Technique Survival

William and Sandra Bennett Clinical Scholars Program

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Identifying the Role of the Interstitial Extracellular Matrix Network During Murine Renal Development

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Oral NaHCO3 Alters K+ Balance and Promotes Insulin Resistance

Riana Parvez, MS
Lineage Convergence in the Regulation of Fluid Homeostasis in the Kidney

** Kidney Week 2021 oral and/or poster abstract presenter*

Maintaining Pandemic-Level Use of Telemedicine in Kidney Care Hinges on Lasting Policy Changes

By Bridget M. Kuehn

At the height of the pandemic, between mid-March and mid-June 2020, Anju Yadav, MD, and her colleagues at the Jefferson Transplant Institute in Philadelphia pivoted from conducting fewer than 5 telehealth visits a month to 250 a month. That pivot allowed kidney transplant patients who were at higher risk of COVID-19 to safely receive posttransplant care. It also allowed evaluation of potential living donors to continue and provided a vital connection to care for transplant patients who developed COVID-19 symptoms.

"The emotional and psychological impact that had on us and COVID-19 patients was tremendous," said Yadav, an assistant professor of Transplant Nephrology at Thomas Jefferson University, in an interview. She explained that daily calls and weekly video visits helped relieve patients' isolation and fear and enabled clinicians to closely monitor their patients and, if necessary, have them admitted to the hospital quickly. Other transplant clinics also used telehealth to triage posttransplant patients with COVID-19 and even to continue to oversee their care while they were hospitalized (1).

Because Yadav's team had been doing telehealth visits for living donor candidates and posttransplant clinics since 2016, they already had the infrastructure in place and were comfortable with the technology, explained Yadav and colleagues in a commentary (2). Emergency policy changes included in the Coronavirus Aid, Relief, and Economic Security (CARES) Act (3) that temporarily expanded Medicaid coverage of telehealth, and the removal of some state licensing requirements also helped. Now, as the pandemic shifts into a new phase, Yadav and other nephrologists say they see a role for expanded use of telemedicine going forward in patient education for chronic kidney disease (CKD), dialysis care, and transplant care.

"The hybrid (telehealth and in-person) care model is here to stay," said Yadav, who noted that although in-person visits at her institution have resumed, one-third of patients continue with telehealth visits. But she and other nephrologists caution that the future of telemedicine in kidney care hinges on more permanent policy changes.

Dialysis day to day

Expanded use of telemedicine in day-to-day dialysis care also helped mitigate potential exposures for dialysis patients. Prior to the pandemic, Medicare would cover telehealth services conducted at local clinics for individuals in rural areas, some home dialysis visits, and remote patient check-ins. But a waiver issued under the CARES Act expanded access beyond rural areas and enabled patients to receive certain types of care via phone or video conferencing in their home, at a dialysis center, or in a hospital.

"There has been urgency to expand the use of technology to help people who need routine care and at the same time keep vulnerable people and those with mild [COVID-19] symptoms in their homes," said Janice Lea, MD, a professor of medicine at Emory University and Chief Medical Officer at Emory Dialysis during a video session at the American Association of Kidney Patients' 2021 Annual Policy Summit (4).

For example, physicians used tablets or other two-way video-conferencing technology to communicate with dialysis patients hospitalized with COVID-19 or for other conditions that put them at risk of COVID-19 to limit both physicians' and patients' potential exposure and to preserve limited personal protective equipment for clinicians providing es-

sential hands-on care, Lea said. It also helped increase the physician workforce during this period of high demand, by allowing physicians on quarantine to continue working remotely, she said.

Many home dialysis patients were already receiving two out of every three visits via telemedicine prior to the pandemic, so that gave providers some familiarity with the services. But the waiver enabled physicians to conduct video telehealth visits at outpatient dialysis centers as well, Lea said. This allowed them to—with the help of an on-site nurse—conduct a physical exam, check vascular access, talk with the patient, or even use a digital stethoscope to listen to the patient's heart. Telehealth was also used for visits with dieticians, social workers, and other staff at dialysis centers to minimize unnecessary exposures, she said. It also enabled virtual meetings with patients' families at a time when family and other visitors weren't allowed in facilities.

Patients really liked the flexibility and privacy of doing some visits via telemedicine at home, said Lea, for example, having discussions with dieticians or reviewing their monthly labs.

"They feel like they are getting more privacy," she said. "They can talk longer, and staff can spend more time with them."

Because of its usefulness and popularity, Lea said, she sees some form of telemedicine continuing in dialysis care after the pandemic. For example, she suggested that using telehealth tools in outpatient dialysis clinics might help reduce emergency department visits for dialysis patients by enabling a nurse or physicians to see and consult with patients virtually to decide whether they need to be seen in person immediately in an emergency room or if they can wait for their next scheduled visit.

"It really is a win-win for everyone," Lea said. "It maximizes the use of the clinician workforce. We don't know if we are going to have future pandemics, so it would be great for us to be able to work out this process and perfect it so we can apply it in the future."

Virtual education could boost use of home dialysis

Another use for telemedicine that is poised to grow post-pandemic is patient education. Manisha Singh, MD, a nephrologist and assistant professor of medicine at the University of Arkansas for Medical Sciences, was part of a team that developed and tested a tele-education program for patients with CKD. The program was designed to help patients understand their condition, how to help slow progression, and make an informed choice about options for care.

"For most patients, I feel home dialysis is a wonderful idea," Singh said. "But for some patients, it is not; they need to know what works best for them."

The team compared the tele-education intervention with face-to-face patient education in the Telemedicine Patient Education Study and found both modalities were remarkably effective (5). Prior to the education programs, 47.1% of the patients randomized to face-to-face education and 52.2% of those randomized to tele-education said they didn't have enough information to choose a modality for kidney replacement therapy. But by the third session, only 7.4% of the face-to-face patients and 13.2% of the telehealth patients felt that way. The number of patients in both groups who chose home dialysis options more than doubled in both groups, with 67.7% of the face-to-face group choosing a home modality and 50.1% of the telemedicine group choosing a home modality.

"The impact was enormous," said Singh. She explained that many patients come in afraid that their diagnosis means their life is over, but they leave feeling empowered by the curriculum.

Interest in transplant also shifted in both groups. About 92% of both groups were interested in a transplant prior to beginning the education program, and that interest dipped to about 88% in both groups after they learned more about transplant. Some patients chose palliative care as well, Singh said.

"When they came into class, the majority of patients wanted transplants," she said. "As some of them learned what transplant entails, they realized it is not for them."

The team did run into some challenges with the telehealth program. For example, people living in rural areas often had very poor internet connections. But they found that even though many patients were older and needed family help to initially log in, they adapted quickly. Having the sessions available at home also enabled family members or caregivers to listen in to live sessions or watch recordings.

When the pandemic hit, Singh and her colleagues were

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Telemedicine in Kidney Care

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able to continue the tele-education program when they had to temporarily stop some in-person options. Now, the program is offered routinely at the University of Arkansas clinics and is available throughout the state of Arkansas. They are working to overcome some of the barriers they encountered with internet access by aiming to make the program available at public health departments or libraries and working with policymakers to expand access to high-quality internet.

They are also working on making the program available nationally through a website currently in development.

"We want to reach out to providers all over the country," Singh said. "Our program is validated and works."

Policy changes needed

Continued use of telehealth is also important to help boost living kidney donations and to boost patient adherence to posttransplant care, said Yadav. She explained that telehealth can help potential donors make an informed decision and limit their costs and inconvenience. Although some funds are available to offset costs, the average living donor spends more than $5000 on costs ranging from travel and lodging for in-person visits and surgery to childcare and time off work (6). But by using telehealth, she and her colleagues have been able to limit pre-surgery visits to one, 2 weeks before surgery. The team has also found the telehealth visits have improved adherence for posttransplant patients who struggle with transportation to in-person visits.

But continued use of telemedicine in transplant care hinges on more permanent policies that support the use of telemedicine beyond rural areas and across dialysis settings. In a recent editorial (7), Fawaz Al Ammary, MD, PhD, Medical Director of Living Donor Kidney Transplantation at Johns Hopkins University School of Medicine, and colleagues argued that geographic restrictions on telehealth for kidney transplantation services should be removed permanently.

State licensing requirements were temporarily lifted during the pandemic, and that helped, but some of those requirements are now back in place. As a result, Yadav and her team have had to limit some telehealth services to in-state patients as they try to complete a prolonged process of getting cross-state licenses. This is a particular challenge for practices like hers that routinely see patients in Pennsylvania, New Jersey, and Delaware. She said more advocacy is needed to permanently change cross-state licensing and enable reimbursement for expanded use of telehealth in transplant care.

"It serves the patients better," Yadav said. "It improves their adherence and their experience." ■

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Friday, November 5

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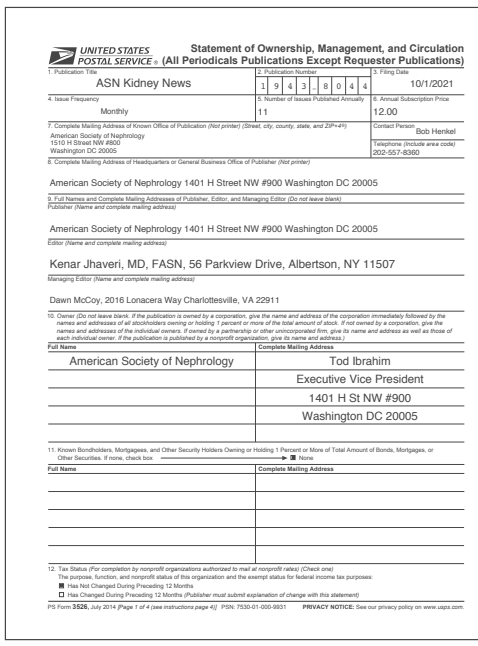

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1. Publication Title	2. Publication Number	3. Filing Date
ASN Kidney News	1 9 4 3 - 8 0 4 4	10/1/2021
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Monthly	11	12.00

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Publisher (Name and complete mailing address): American Society of Nephrology 1401 H Street NW #900 Washington DC 20005
Editor (Name and complete mailing address): Kenar Jhaveri, MD, FASN, 56 Parkview Drive, Albertson, NY 11507
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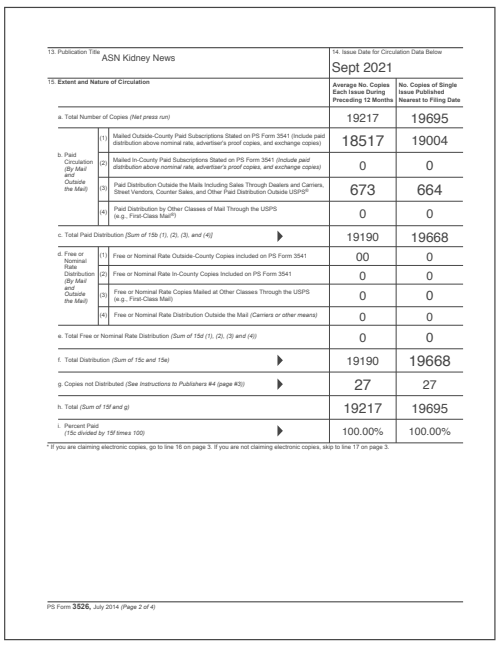

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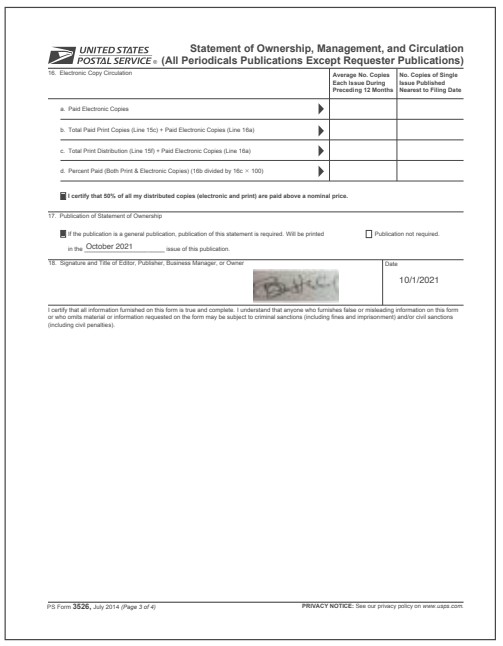

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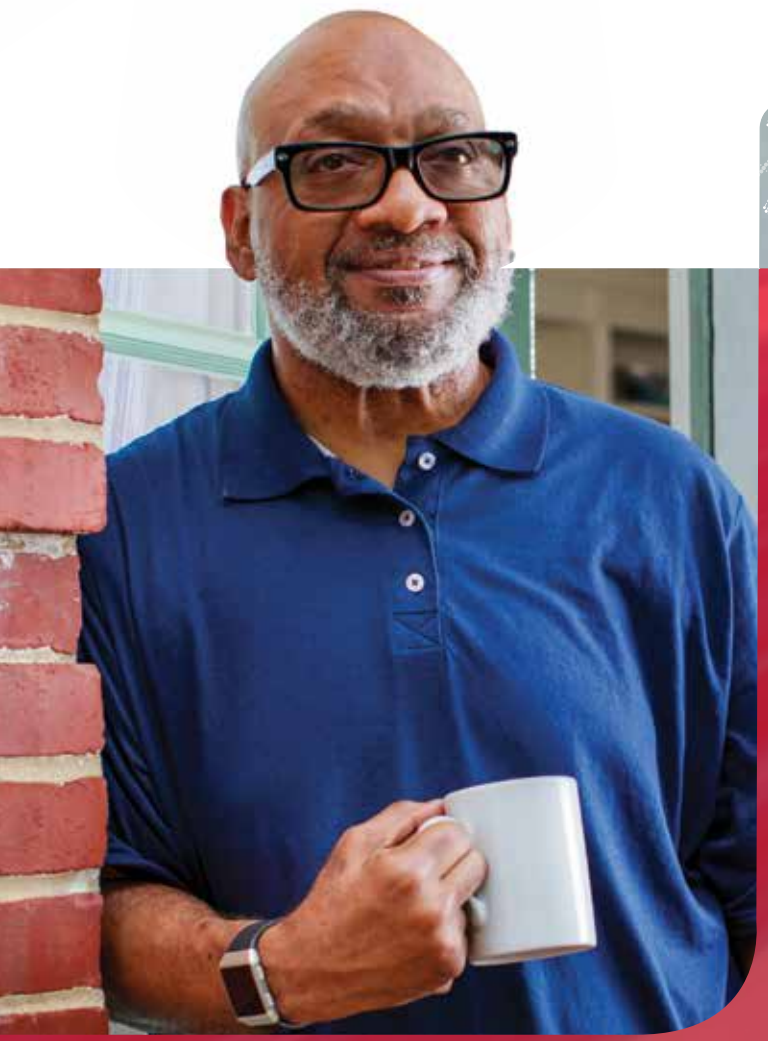

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