ASN American Society of Nephrology

KIDNEY WEEK EDITION

# Kidney News

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# Scrutiny Continues Over Use of Race in Estimated GFR

By Eric Seaborg

As calls for social justice and unrest reach into every corner of American life, the controversy over the inclusion of race as a factor in calculating estimated glomerular filtration rates reached more milestones as ASN and the National Kidney Foundation (NKF) formed a task force to reassess the practice, a congressional committee chair sought information from medical societies about the use of race in clinical algorithms, and more institutions moved away from the practice.

The issue even hit the mainstream media with a story from *Consumer Reports*, "Medical Algorithms Have a Race Problem."

The NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease is co-chaired by Cynthia Delgado, MD, and Neil R. Powe, MD, MPH, MBA. Delgado is an associate professor of medicine at the University of California, San Francisco, where Powe is also a professor of medicine.

Formed in August, the task force has begun its deliberations and plans to issue its initial recommendations by the end of 2020.

"We have been charged with examining the inclusion of race in the estimation of GFR and its implications for the diagnosis and subsequent management of patients with or at risk for kidney disease," Delgado said. "We have also been charged with recognizing that any change in eGFR reporting must consider multiple social and clinical implications, be based on rigorous science, and be part of a national conversation about uniform reporting across healthcare systems. Those are just two of the five charges that we have gotten."

The task force includes 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 recommendations will be vetted by an eGFR Advisory Board, Delgado said, and "go through a series of checks by members of the nephrology community at large, including patients and patient advocacy groups, to make sure that we are all in agreement with what we recommend."

"We have been diligently working on this for months," Delgado said. She noted that ASN has been playing a "key behind the scenes role on efforts to promote diversity, equity, and inclusion among kidney health professionals and to work toward eliminating health disparities in the communities that we serve."

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## Kidney Week Scientific Sessions

### THURSDAY

**Human Genome Editing: Responsible Pathway Forward**
*State-of-the-Art Lecture*: Victor J. Dzau, MD

**Tubular Cell Metabolic Reprogramming in Renal Fibrogenesis**
*Barry M. Brenner, MD, Endowed Lectureship*:
Katalin Susztak, MD, PhD

**Kidney Care and the COVID-19 Experience**
*Christopher R. Blagg Endowed Lectureship*: Nicole (Nicki) Lurie, MD, MSPH

**Drug Targeting of the Podocyte Actin Cytoskeleton**
*Michelle P. Winn, MD, Endowed Lectureship*: Mario Schiffer, MD, MBA

**Managing Electrolyte Abnormalities on Continuous Renal Replacement Therapy (CRRT)**
*Burton D. Rose, MD, Endowed Lectureship*: Ashita Tolwani, MD, MSc

### FRIDAY

**Reducing Physician Distress: Organizational Approaches to Improve Physician Well-Being**
*State-of-the-Art Lecture*: Tait D. Shanafelt, MD

**Rationale for Personalized Medicine Approaches to the Management of CKD-Associated Osteoporosis**
*Jack W. Coburn, MD, Endowed Lectureship*:
Glenn M. Chertow, MD, MPH

**Understanding Cellular Oxygen-Sensing Mechanisms: Implications for Medicine**
*Homer W. Smith Award Lecture:* Sir Peter John Ratcliffe

### SATURDAY

**Global Efforts to Curate the Genome**
*State-of-the-Art Lecture*: Heidi Rehm, PhD

**How the Unknown Unknowns Cause the Increased Peripheral Vascular Resistance**
*Robert W. Schrier, MD, Endowed Lectureship*:
Friedrich (Fred) C. Luft, MD

**From Genes to Medicines: The Arc of Discovery for Kidney Diseases**
*Donald W. Seldin Young Investigator Award*:
Anna Greka, MD, PhD

### SUNDAY

**RNA Biology and Medicine: A Journey of Unexpected Discovery**
*State-of-the-Art Lecture*: Joan A. Steitz, PhD

**Developing Actionable Patient Safety Outcome Metrics for Dialysis**
*Celeste Castillo Lee Memorial Lectureship*:
Allison Tong, PhD, MPH

*Presentation of ASN Awards*

## Inside

**Preparing for a COVID-19 Surge**
Scarce Resources Report urges nephrologists to take the lead in planning

**Diabetic Kidney Disease**
Gut microbiota and diabetes, the DKD pandemic, and use of SGLT2s in solid organ transplant and AKI

**Clinical Trials**
Patients as partners: why wait?

**Detective Nephron**
A case of type 2 diabetes mellitus with an elevated hemoglobin A1c

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**Reference: 1.** Fishbane SN, Singh AK, Cournoyer SH, et al. Ferric pyrophosphate citrate (Triferic®) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. *Nephrol Dial Transplant*. 2015;30(12):2019-2026.

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# KidneyNews



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# ASN Kidney Week—New in 2020

## Kidney Week Reimagined: A Fully Digital Meeting

ASN has been honored to host the world's premier meeting in nephrology for 50+ years. While we have all enjoyed the various sites at which past annual meetings have taken place, Kidney Week has not succeeded because of a specific location.

This year's meeting is offered in a fully online format with educational presentations delivered live-streamed, simulive, and on-demand; ePosters; digital exhibit hall; virtual networking opportunities; and more. Annual Meeting content will launch October 22, recorded, and will be available on the meeting website through December 4.

Questions? Check out FAQs, or email education@asn-online.org.

## Early Programs

ASN is hosting five Early Programs this year, preceding the Annual Meeting. For each program, on-demand presentations will be available starting October 14, and live-streamed sessions will take place October 19–21.

- Advances in Research Conference: Single-Cell Biology
- Basic Research Forum for Emerging Kidney Scientists: A Partnership Between APS and ASN
- Critical Care Nephrology: 2020 Update
- Glomerular Diseases: 2020 Update
- Maintenance Dialysis

## ePosters

Thousands of ePosters can be viewed on-demand starting October 22 at 10:00 a.m. EDT. ePoster features include:

- Interactive interface to browse through uploaded posters
- Keyword search and multiple indices to quickly find uploaded posters
- Various communication tools (with Kidney Week login)

## More CE Credits and MOC Points

With Kidney Week being a "reimagined" blended learning activity this year, ASN will offer up to 75 continuing education credits for physicians, nurses, and pharmacists and up to 75 ABIM MOC Points. Instructions for claiming credits/points will be available in October.

## Networking and Interactive Opportunities

ASN will offer unique opportunities to network with other participants and exhibitors at Kidney Week 2020 Reimagined through Attendee Connect. Attendee Connect matches you with other participants based on your registration information and presents opportunities to chat, email, and have video meetings.

Kidney Week will also have a digital photo booth, wellness activities, an EXPLORE: Scavenger Hunt, fun ways to experience Denver and San Diego virtually, and the Kidney Week forum, which will allow participants to interact in a chat forum. All sessions have a chat/discussion board and allow participants to interact with faculty and one another.

## Also on offer:

- Daily state-of-the-art lectures during the plenary sessions (October 22–25, 9:00–10:00 a.m. EDT)
- Race and equity sessions
- COVID-19 sessions, events, and abstracts


# Preparing for the Surge

## Nephrologists Prepare for Fall COVID-19 Surge, Increased Dialysis Demand

By Bridget M. Kuehn

As the COVID-19 pandemic started sweeping across the United States this spring, hospitals began preparing for a surge in critically ill patients by increasing the numbers of intensive care unit (ICU) beds and trying to secure more ventilators. But they were "blindsided" by a huge increase in the need for renal replacement therapy among COVID-19 patients and the resulting shortages in dialysis nurses, equipment, and supplies, said Anitha Vijayan, MD, professor of medicine at Washington University in St. Louis.

"We were completely caught off guard by the proportion of patients with acute kidney injury who required dialysis," said Sumit Mohan, MD, associate professor of epidemiology and medicine at Columbia University in New York City. Some New York hospitals documented rates of AKI higher than 30% (1).

As hospitals across the country brace for a potential second surge of critically ill COVID-19 patients, ASN and the Department of Health and Human Services are urging nephrologists to take a leading role in preparations. The two organizations hosted two 90-minute roundtable sessions to identify best practices for managing a dialysis surge. The insights gleaned during the sessions have been summarized in a the Scarce Resources Roundtable Report (2).

""The collaboration between ASN, CMS [Centers for Medicare & Medicaid Services], Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and ASPR [Office of the HHS Assistant Secretary for Preparedness and Response] demonstrates how successful public-private partnerships can be in helping hospitals identify the resources they need to care for these patients," said Kristen Finne with the HHS COVID-19 Ambulatory Care and Dialysis Team, Health Care Resilience Working Group. "These roundtables were instrumental in identifying best practices and lessons learned from the early days of the pandemic that can be used today across the country and showed the importance of nephrologists collaborating within hospital response structures to ensure COVID-19 patients had access to the dialysis care they needed to improve patient outcomes." Finne is also director of the HHS emPOWER Program and senior program analyst, HHS/ASPR/EMMO/Readiness.

### Machines and disposables

As the number of ICU beds at Michigan Medicine increased from 100 to 250 to accommodate the surge of COVID-19 patients this spring, Michael Heung, MD, MS, professor of nephrology at the University of Michigan, and his colleagues scrambled to bring in more continuous renal replacement (CRRT) machines. They purchased a couple more CRRT machines and borrowed unused hemodialysis machines from outpatient centers. But acquiring the necessary renal replacement supplies became a challenge, as suppliers limited hospitals to purchasing 110% of their usual supplies, Heung said.

"Everybody was trying to get more supplies around the country," Heung said. "We were having double the volume, so [110%] wasn't good enough."

At the epicenter of the pandemic in New York City, Mohan and colleagues were running twice as many CRRT machines and deployed a machine-sharing protocol to further double the capacity. To meet their excess demand for dialysate, the CMS, in collaboration with ASPR and the Strategic National Stockpile, helped them find some additional small suppliers, Mohan said. They also began using dialysis machines to make ultra-pure dialysate in-house and sought FDA guidance and public health department approval to use it if they ran out of commercially produced dialysate.

"We developed, tested, and deployed our production system, but we were fortunate that we never pulled the trigger on their direct use because we came right up to the precipice of running out of commercial dialysate] but never fell off the cliff," he said.

### Staffing

Most hospitals only have a small team of skilled dialysis nurses and other nurses can't be easily trained so many teams were working overtime, said Faith Lynch, MSN, RN, who leads a 10-nurse team as clinical nurse manager at New York University Winthrop in Mineola, New York.

"We were working like 6 to 7 days a week, night and day, trying to dialyze patients," said Lynch, who is also Acute Care Specialty Practice Network Leader at the Nephrology Nurses Association. To extend their capacity and cover for nurses who became ill, the team began cohorting patients in groups of four cared for by two nurses. Eventually, they were able to add traveling nurses to the team.

Many patients with severe COVID-19 experienced excessive blood clotting, which further exacerbated supply and skilled staffing shortages by causing frequent filter clogs and requiring anticoagulation protocols, noted Vijayan, who co-authored the Scarce Resources Roundtable Report.

### Early planning is critical

The report recommends that hospitals create a scarce resources plan now and begin making preparations for potential shortages of skilled dialysis nurses, renal replacement machines, and renal replacement supplies.

"You need everyone involved," Vijayan said. "You need critical care nursing, pharmacy, you need the nephrologists involved, everyone needs to come to the table to develop a protocol."

Lynch also emphasized the need to involve nurse managers, administrators, and frontline nurses in both preparations and implementation.

"Nurses that are actually dialyzing the patients are the ones that are dealing with the reality," she said.

Developing a staffing surge plan and cross-training nurses who can help train dialysis nurses in advance is also critical. The report recommends establishing a "buddy system" where nurses not familiar with CRRT can work with ICU nurses thereby increasing the number of dialysis machines that the trained ICU nurse can support. Staffing plans need to take into account possible quarantine following exposure, as well as reassigning those who are immunocompromised or at high risk from COVID-19, Mohan said.

The plans need to be flexible and able to adapt to changing circumstances. For example, a shortage of machines led Mohan and his colleagues to develop an alternating 24-hour protocol, which was associated with an increase in the use of supplies and increased nursing burden.

Training also needs to begin now to implement new protocols such as citrate anticoagulation, which Vijayan noted cannot be learned on the fly. "If you don't institute the protocol properly it will lead to more patient safety events," she said.

Starting planning as early as possible and including nephrologists, who are most familiar with the supply chain and knowledgeable ways to do dialysis creatively, from the beginning is key, Heung said.

"It's critical," he said. "Nephrologists absolutely need to be taking the lead." ■

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# Scrutiny Continues

*Continued from page 1*

## Congressional action

While significant racial disparities have long been present in the United States healthcare system, the dramatic racial health inequities caused by COVID-19 created a renewed focus and sense of urgency among ASN members to address and dismantle the systems inhibiting Black Americans from receiving equitable care. In May, ASN provided testimony to the House Committee on Ways and Means on the disproportionate impact of COVID-19 and kidney diseases on communities of color that highlighted dramatic racial health inequities in the US healthcare system.

On the heels of that hearing, the *New England Journal of Medicine* published "Hidden in Plain Sight—Reconsidering the Use of Race Correction in Clinical Algorithms," which questioned the use of race in algorithms used in cardiology, nephrology, obstetrics, and urology. That spurred committee chair Richard E. Neal (D-MA) to write to ASN President Anupam Agarwal, MD, "to request an update about any work underway to investigate and change such clinical decisions support tools that fuel racial inequities in care." Neal sent similar letters to other medical specialty organizations and requested a response by Sept. 25.

As part of the 7000-word response of behalf of ASN, Agarwal noted: "ASN agrees that unlike age, sex, and body weight, race is a social, not a biological, construct. Adjusting for race in these eGFR equations may not address the diversity within self-identified Black or African American patients as well as other racial or ethnic minority groups."

The response further states: "ASN also recognizes that the causes of racial health inequities are multifactorial: disparities within kidney diseases are not limited to algorithms but have complexities that will need to be addressed beyond the NKF-ASN Task Force."

In addition to her work on the task force, Delgado has been involved in responding to the request from the House committee. "I think this is a perfect opportunity for us to align ourselves with the House Ways and Means Committee so that we can focus on improving patient care. I think our response will create an opportunity for a dialogue," she said.

## How institutions are responding

Many of the colleagues Delgado has heard from around the country have expressed their eagerness to see the task force recommendations, but many hospital and academic centers are acting on their own to respond to concerns they are hearing from their own staffs about eGFR reporting practices. Beth Israel Deaconess Medical Center (BIDMC) was one of the earliest to make a change, in 2017, according to Melanie Hoenig, an associate professor of medicine at Harvard Medical School who spearheaded the effort at BIDMC.

It all started in the spring of 2016 during a class for medical students when she was talking about the African American coefficient that says that African Americans at a higher creatinine level can have the same eGFR as non-African Americans: "A medical student asked pointedly, 'Why would there be a correction factor for a healthier value for the group at greatest risk of kidney disease?'"

That led to a literature review, meetings with people who helped create the formulas, and consultations with a variety of people, such as the head of the clinical laboratory and the chief of medicine. Hoenig said their investigation found "the use of race in clinical medicine is flawed and problematic. Ultimately, we agreed to change the language of the report to remove race but provide the two values generated by the eGFR formula." The lab report indicates a range for the eGFR.

"Since race is a social construct and cannot be measured, use of race in the formula is fraught with problems and we feel that this practice should be abandoned. We hope that the joint task force from the ASN and NKF will also come to this conclusion," Hoenig told *Kidney News*.

Task force co-chair Powe, who is also chief of medicine at Zuckerberg San Francisco General Hospital, said in contrast to the "well-vetted process" used at BIDMC, at his institution, "A small group dictated what happened."

He said the change in the eGFR reports involved "changing the language and not the values themselves. [The new reports] just attach the label high muscle mass to African Americans and low muscle mass to other races."

An alleged greater muscle mass among African Americans is often cited as the reason for higher creatinine levels, but Powe said: "People have been taught in medical school that the reasons creatinine levels are high have to do with muscle mass, but that is just a little dogma, and there are many other things that affect creatinine levels," including tubular secretion, extra-kidney elimination, and the amount of meat in the diet. "The group that wanted to change to muscle mass now wants it changed to something else. They realized that what they initially did was not well thought out." He fears that other institutions will fall victim to "advocacy efforts" rather than a thoughtful process of considering all the ramifications.

But the University of Washington, Vanderbilt University, and several hospitals affiliated with Brown University all simply dropped the use of the African American coefficient after an extended process. These institutions reported going through a careful process with input from many perspectives, but they also said that in the end it was not a difficult or controversial decision internally.

The change at the University of Washington came after a three-year process, according to Rajnish Mehrotra, MD, MS, interim head of the division of nephrology and editor-in-chief of *CJASN*. "The considerations that led us to the decision were the imprecision of the estimate itself, that a precise estimate is rarely imperative in clinical practice, and concern about using race as a biologic variable when it is actually a social construct," Mehrotra said in an email to *Kidney News*.

"We presently report only a single value of eGFR using the CKD-EPI equation for all individuals without using the race coefficient. So, the value for non-blacks, as per the CKD-EPI, is reported for all individuals," Mehrotra said. "The implementation has been widely accepted by all stakeholders, and I do believe the implementation has been successful. I credit the long time period over which we discussed this and the engagement with a broad range of stakeholders."

Vanderbilt also dropped the African American reporting with "no replacement for race-related or adjusted reporting," according to Alp Ikizler, MD, director of the division of nephrology, noting that "race is not a reliable proxy for genetic difference and this is especially true in the US given the level of admixture that is present here."

"The process required input from multiple parties including but not limited to leadership, clinical pathology, information technology, and most importantly clinicians. Once everyone was on board, the change was seamless," he said. But it is too soon to judge the impact on patient care, and "we need to follow it up with quantitative [and] qualitative work to understand the impact of this change on Black people."

Three teaching hospitals affiliated with his institution also dropped the use of race as a variable in estimating eGFR, said Douglas Shemin, MD, director of the division of kidney diseases and hypertension at the Alpert Medical School of Brown University. "We didn't make this decision lightly," Shemin said. We had people from general internal medicine, pathology, nephrology, kidney transplantation, etc., all involved. The decision was unanimous."

"Our take-home point to our trainees is that they should look at the creatinine level in every single patient and make an assessment about what they think the actual glomerular filtration rate is based on clinical signs," Shemin said. That assessment should include muscle mass and other potential factors.

The use of a race coefficient dates back to the Modification of Diet in Renal Disease (MDRD) study, in which all patients had their GFR measured by the kidney iothalamate clearance gold standard. The researchers concluded that African Americans had higher creatinine levels vis a vis a given GFR, leading to the use of a correction factor in the MDRD estimating equation.

Proponents of the value added by the equations tend to point to the MDRD and the evidence base of the equations and say the equations have served the nephrology community better than any alternative so far. But others question: How can you base a coefficient on "African American," when, given the genetic and ancestral diversity of this population, you can't define what it means? How reliable is an eGFR when one of the factors used—Black or not—is itself an estimate?

Even the terms of the debate can be muddled. "By dropping the race coefficient," Powe said, "you are ignoring the data on African Americans that were in the study. It is saying, 'Let's just assign the [value of the] majority race. It is kind of saying, 'White is right.'"

But Shemin considers the opposite to be the case, that using the coefficient singles out African Americans: "It is not African Americans vs. Caucasians; it is African Americans vs. anybody else."

Andrew Levey, MD, chief of the division of nephrology at Tufts Medical Center who led much of the ground-breaking work on the estimating equations, said: "We always recognized that race was not the biological process by which African Americans differed from non-African Americans in the relationship between GFR and creatinine, but we thought it had too big of an effect to be overlooked. We understood that race was not a binary categorical variable, and that it wasn't the biologic process, but that it stood in for something that was important." The same consideration is true for age and sex, he said: "These are not the true biological variables, they are just easier to ascertain than the true biological variables."

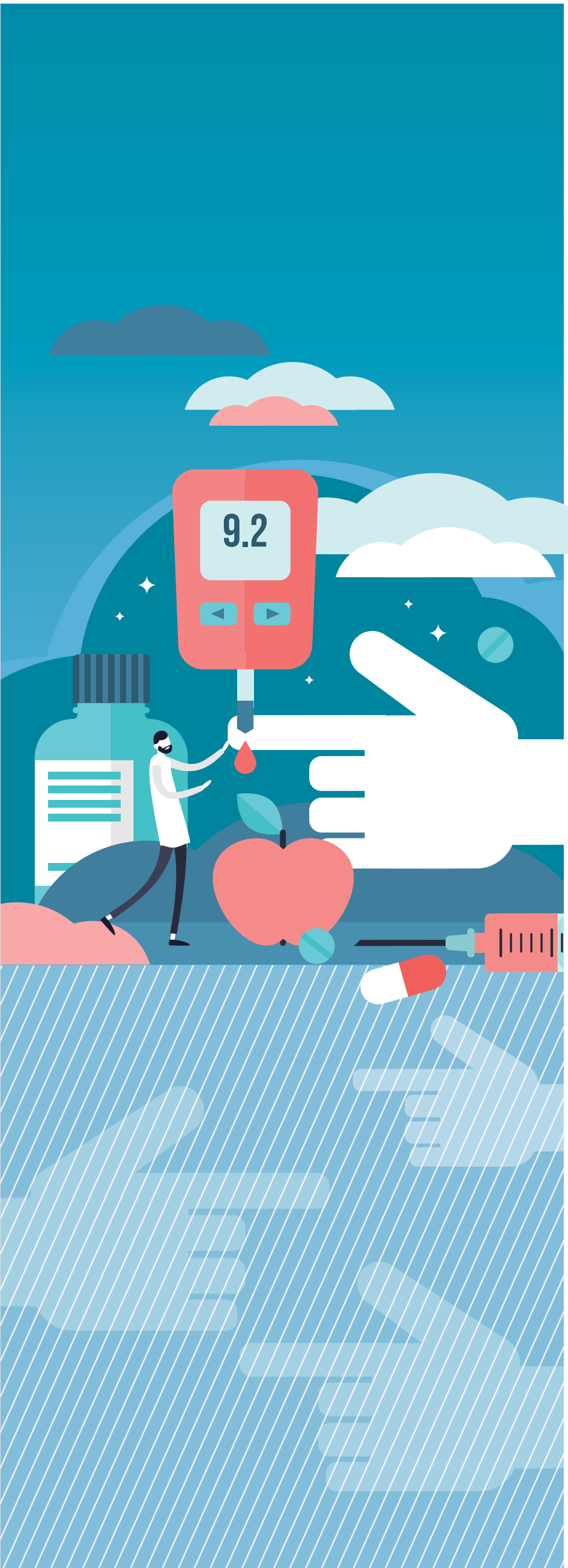
The 1999 MDRD study tried to identify the source of the variation with the statement "on average, black persons have higher muscle mass than white persons," and the contentiousness of that statement has helped undermine confidence in the equations themselves considering that "neither the MDRD researchers nor any of the cited studies provided any evidence that Blacks indeed have higher muscle mass than whites," wrote Vanessa Grubbs, MD, in a recent "Perspective" in *CJASN*. Shemin said that as part of his institution's deliberations he reviewed the literature and could find no support for the assertion, nor any study that "looks at body weights and definitely shows that creatinine production is higher in blacks than whites."

Just the same, Powe cautions against moving too quickly to discard a tool that has worked well: "What you hear the advocates of changing say is that these equations are hurting patients because they are leading to them not being on the wait list for a transplant, or being referred to a specialist. They cite anecdotal cases of individuals they may have taken care of. The advocates say that [the equations] caused harm, but there is no evidence of that other than the anecdotes," Powe said. The disparities in care long pre-dated the use of the equations, and there is no evidence that the equations exacerbated them, he said. He worries that dropping the coefficient will lead to less accurate diagnoses and potential overtreatment among African Americans.

Richard Lafayette, MD, professor of nephrology at Stanford University Medical Center, agrees: "While a higher eGFR may bias toward waiting longer for transplant, it also biases toward being able to wait longer to start dialysis, waiting longer before meeting the worrisome diagnosis of chronic kidney disease, and a lower likelihood of being biased against by insurance. The key thing is to feel that the GFR prediction is accurate. The race correction is generally in the right direction by about the right amount, but can vary quite a bit individual by individual. Thus, a discussion should be undertaken with patients of any race, and other measures of kidney function can be considered."

As the medical student in Hoenig's anecdote might counter, as a population, the African American community is chronically undertreated. Overtreatment might be a preferred alternative, especially when early treatment can be beneficial when it comes to conditions like chronic kidney disease and transplantation.

But Powe notes that there is no evidence that the equations have anything to do with inequities that were in place before the equations existed: "If you want to truly address health inequities, let's find the real drivers of them rather than scapegoating the equations." ■



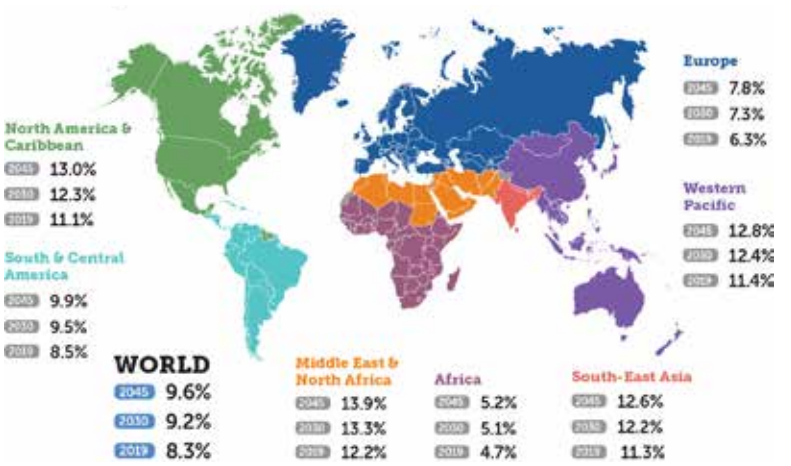

# The Pandemic of Diabetes and KIDNEY DISEASE

By Robert G. Nelson and Meda E. Pavkov

The rising prevalence of diabetes, hypertension, and obesity is largely responsible for a global pandemic of chronic kidney disease (CKD), which is associated with adverse health outcomes, including kidney failure, cardiovascular disease, and death. The public health and societal burdens associated with this pandemic are considerable because of the high cost of treating these patients and the loss of productivity from disability. These problems are greatly amplified among those in low-income and middle-income countries, where 78% of the nearly 700 million persons with CKD reside. In this review, we briefly examine the role of diabetes in this pandemic of CKD.

The International Diabetes Federation estimates that in 2019, 463 million adults worldwide had diabetes, of whom 90% had type 2 diabetes (1). Half of those with diabetes are unaware they have the disease, and 79% of them live in low-income and middle-income countries. The International Diabetes Federation projects a 65% increase in the number of people with diabetes by 2045; thus, within 26 years, 762 million people, or 9.6% of the adult world population, are expected to have diabetes (Figure 1). Factors responsible for the increasing prevalence of diabetes include population growth and aging, the frequency and severity of obesity, and exposure to diabetes in utero, which now affects one in six live births globally. The prevalence of diabetic kidney disease is increasing worldwide alongside the rising prevalence of diabetes, so the magnitude of the pandemic of diabetic kidney disease is expected to increase into the foreseeable future.

**Figure 1. Prevalence of diabetes among adults (20–79 years) in International Diabetes Federation Regions, by age-adjusted comparative diabetes prevalence [1].**




Serial cross-sectional surveys of adults with diabetes by the National Health and Nutrition Examination Survey found that the prevalence of diabetic kidney disease in the United States (defined by a persistent urine albumin-to-creatinine ratio of ≥30 mg/g, or a persistent estimated GFR [eGFR] of <60 mL/min per 1.73 $m^2$), has not changed appreciably during 1988 to 2014. The prevalence was 28.4% from 1988 to 1994 and 26.2% from 2009 to 2014; thus, about 8 million of the more than 30 million people in the United States who have diabetes are affected (2). The prevalence of persistent albuminuria, however, declined from 20.8% to 15.9% during that study period, and the prevalence of persistently low eGFR increased from 9.2% to 14.1%. The lower prevalence of albuminuria over time was observed only among non-Hispanic white adults and those younger than 65 years, whereas the higher prevalence of low eGFR was observed among all ages and races or ethnicities. The increasing average duration of diabetes and improvements in diabetes management over time may be re-

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# The Pandemic of Diabetes and Kidney Disease

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sponsible for the evolving clinical presentation of diabetic kidney disease (2). Estimates from the 2017 global burden of disease study of diabetic CKD among 21 geographic regions are generally consistent with these findings, suggesting that within diabetic populations in most regions, the prevalence of diabetic kidney disease has remained fairly stable since 1990; however, there are important regional differences. For example, the highest prevalence of diabetic kidney disease is found in Oceania and Eastern Europe, whereas the lowest is found in Western Europe (Figure 2) (3). Despite the relative regional stability of diabetic kidney disease prevalence among those with diabetes, the rapidly increasing prevalence of diabetes worldwide means that the total number of cases of diabetic kidney disease will continue to increase in proportion to the prevalence of diabetes.

The proportion of incident ESKD attributable to diabetes among the general population also varies widely among countries, ranging from 10% to 67% in 2016 among countries that report these data (Figure 3) (4). In the United States, 47% of incident ESKD in 2016 was attributable to diabetes. Many of the countries with high proportions of incident CKD attributable to diabetes have experienced steep increases in the number of people with ESKD during the past 2 decades in response to a rising prevalence of type 2 diabetes. Malaysia, South Korea, and the Philippines, for example, have each more than doubled their diabetes-related ESKD incidence during the 2 decades ending in 2016 (Figure 4). Declines in incident ESKD due to diabetes have been observed among some European countries, including Austria, Belgium, Denmark, Finland, and Sweden, where a high proportion of diabetes is type 1 (1).

An Australian study in which analyses were restricted to the diabetes population found that the annual incidence of ESKD was stable among those with type 1 diabetes but increased progressively among those with type 2 diabetes; the increase was caused in part by a trend toward an earlier age at onset of type 2 diabetes (5). Moreover, the incidence of ESKD was four times as high among indigenous people with diabetes than among nonindigenous people, with poorer nutrition, higher blood pressure, obesity, recurrent infections, smoking, and limited access to healthcare playing roles in this disparity.

In the United States, improvements in diabetes care have contributed to a 68% decline in cardiovascular events from 1990 to 2010 among people with diabetes (6). A decline in ESKD incidence attributable to diabetes was also observed during the same period, but it was more limited (28%), partly because cardiovascular disease is an important competing health event, and the dramatic reduction in cardiovascular disease events increased the likelihood that people with diabetes would progress to ESKD (6). Unfortunately, these declines in diabetes complications stalled or reversed after 2010, particularly among young and middle-aged adults, and the reasons for the resurgence in diabetes complications are unclear. Factors may include the increasing prevalence of obesity and also inconsistent clinical care, which is attributable in part to rapidly escalating costs that make care unaffordable for many (7). The effects of a resurgence in diabetes complications on future trends in diabetic kidney disease are uncertain because a disproportionate increase in fatal cardiovascular events could ameliorate the risk of diabetic kidney disease.

The onset of type 2 diabetes among youth is a rapidly emerging problem that affects populations worldwide and is driven by an increasing prevalence and severity of obesity among children and adolescents. Intrauterine exposure to maternal hyperglycemia, which occurs among one in six live births worldwide, further enhances the risk of obesity and type 2 diabetes among the offspring during childhood and adolescence, and it impairs the development of the fetal kidneys, reducing nephron development among humans and in animal models. Among adolescents and young adults with youth-onset diabetes, the prevalence of diabetes complications—particularly diabetic kidney disease—and other comorbidities is higher among those with type 2 diabetes than among those with type 1 diabetes (8).

Among the Pima Indians, a group of Native Americans living in central and southern Arizona, the contribution of youth-onset type 2 diabetes and of hyperglycemia in utero on the development of ESKD have been studied extensively because of the rapidly increasing prevalence of youth-onset type 2 diabetes among this population since the 1960s. The onset of type 2 diabetes among Pima Indians younger than 20 years is associated with a nearly fivefold increased incidence of ESKD between 25 and 54 years of age, compared with later onset of diabetes, and the longer duration of diabetes by middle age among those who received their diagnoses before the age of 20 years is largely responsible for this finding (9). Intrauterine diabetes exposure increased nearly fourfold among the Pima Indians during the 30 years from 1967 to 1996, and the prevalence of youth-onset type 2 diabetes doubled during this period (10). This intrauterine exposure to diabetes was associated with a fourfold higher incidence of diabetes-related ESRD in individuals before the age of 45 years than in those without this exposure (11).

Development of the fetal kidneys is also adversely affected by low birth weight, preterm birth, and vitamin A deficiency during pregnancy—exposures more likely to occur among persons from low-income and middle-income countries and among disadvantaged persons from high-income countries (12). Together, the effects of youth-onset type 2 diabetes and factors that adversely affect developmental programming of the kidneys are likely to exert a growing influence on the pandemic of diabetic kidney disease among populations worldwide in the coming years.

In conclusion, a global increase in the prevalence of diabetes is fueling a pandemic of diabetic kidney disease. The increasing prevalence and severity of obesity among children and young adults is shifting the onset of type 2 diabetes to younger ages and into the childbearing years, which is adversely affecting fetal kidney programming and further exacerbating the pandemic. Improvements in medical management have increased longevity, resulting in an aging population that is also at increased risk for diabetes and its complications. Advances in medical care have slowed the progression of diabetic kidney disease, but in low-income and middle-income countries and disadvantaged people in high-income countries, who together bear much of the disease burden, treatments are costly and may not be readily available to patients. These observations illustrate the urgency of identifying the underlying pathogenetic mechanisms of diabetic kidney disease and finding new, more efficacious therapies to treat them. Efforts to prevent the development of type 2 diabetes, or to delay its onset with lifestyle interventions, are also fundamental to stopping this advancing pandemic.

**Figure 2. Prevalence of diabetic kidney disease among 21 geographic regions, stratified by sex, in 1990 and 2017, per 1000 capita [3].**

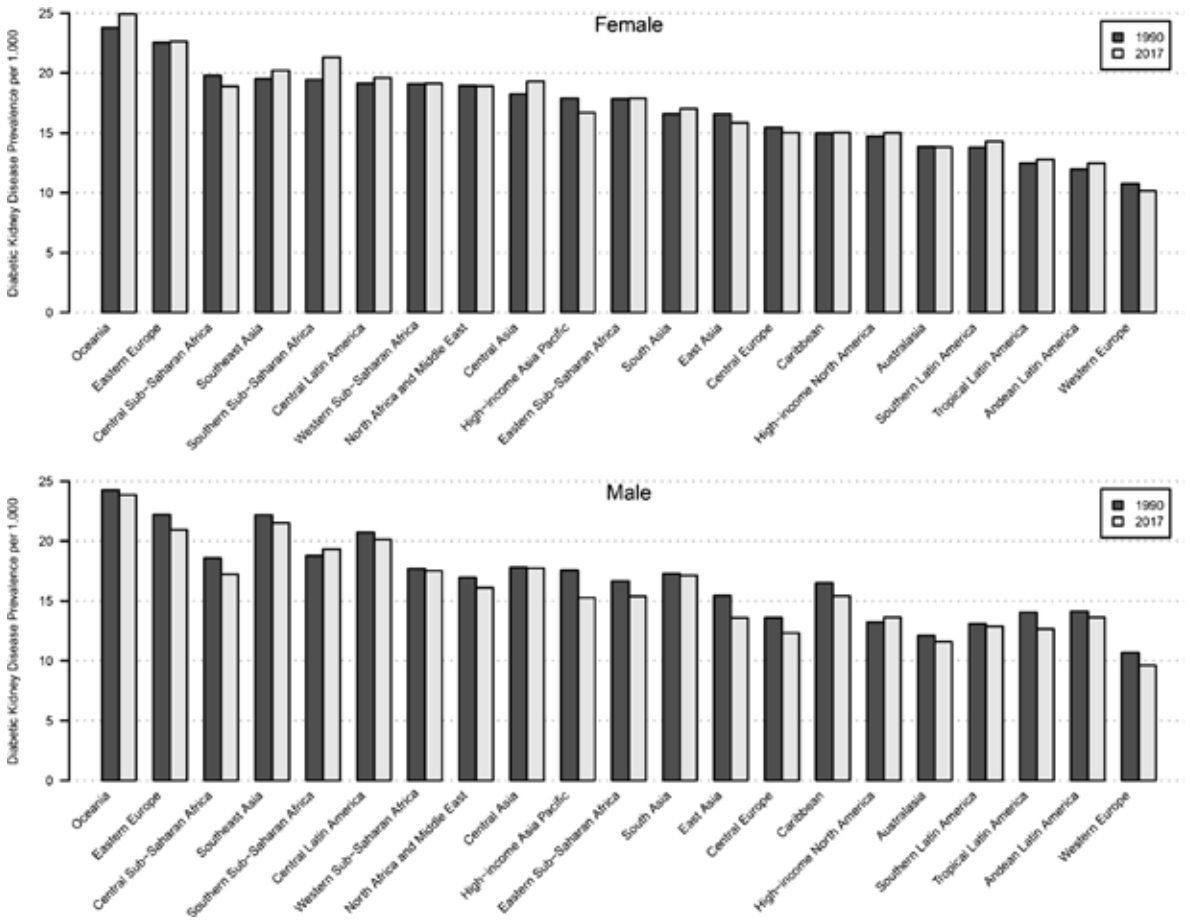
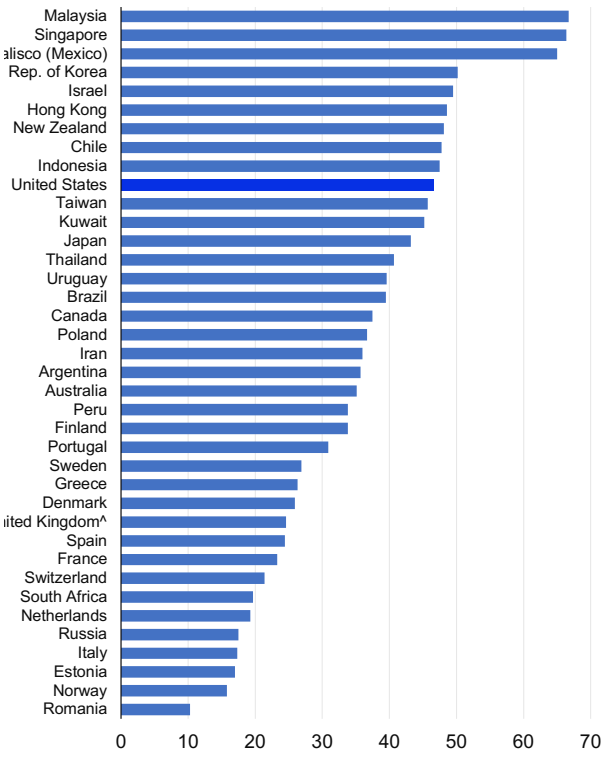



**Figure 3. Percentage of incident ESKD caused by diabetes in 2016, by country [4].**



**Disclaimer**
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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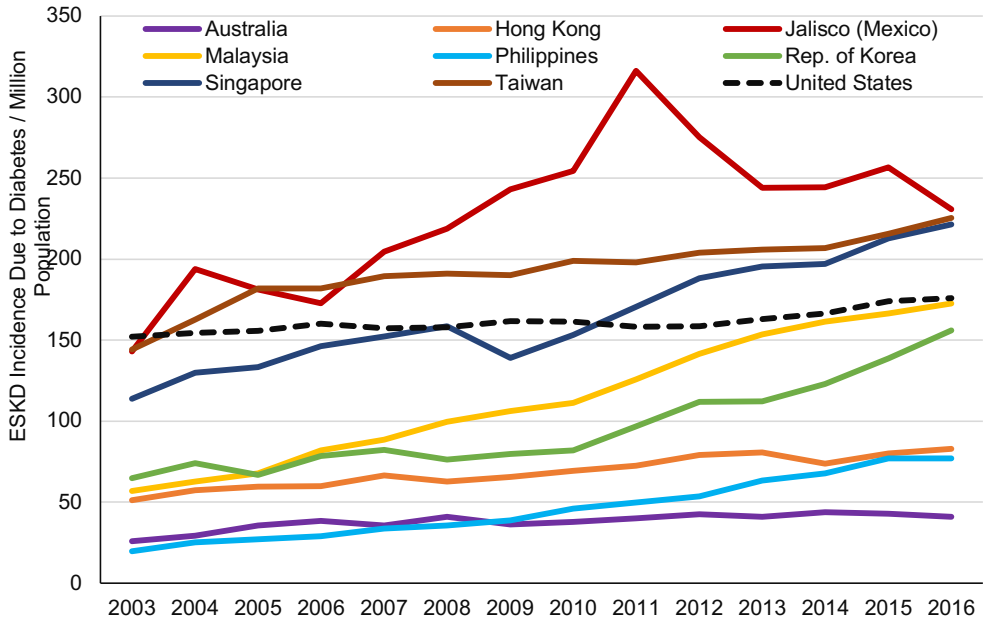
**Figure 4. Trends in the unadjusted incidence of diabetes-related ESKD, 2003–2016 [4]. The countries with the largest average yearly change in ESKD incidence from 2003 to 2016 are represented, plus the United States.**




# SGLT2s Show Promise for Kidney Protection

## Benefits Seen in Patients with and without Diabetes

By Bridget M. Kuehn

Results from 2 large clinical trials of sodium-glucose cotransporter 2 (SGLT2) inhibitors presented at the European Society of Cardiology (ESC) Congress 2020 show that the drugs may offer substantial kidney-protecting benefits.

The hotly awaited results of the Phase III Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial showed a 39% reduction in a composite outcome of sustained reduction in estimated glomerular filtration rate of at least 50%, end stage kidney disease, or renal or cardiac death in patients taking the drug compared with patients taking a placebo (1). The trial, which was stopped early because of the strong benefit (2), enrolled 4304 patients with chronic kidney disease from 386 centers in 21 countries and included patients with diabetes and without. All participants were already taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Comparable benefits were seen in patients with and without diabetes.

"The DAPA-CKD trial has shown dapagliflozin's potential as a long-awaited new treatment option for patients with chronic kidney disease," said lead author Hiddo Heerspink, PhD, professor in the department of clinical pharmacy and pharmacology at the University Medical Center Groningen in the Netherlands in a press briefing at ESC Congress 2020.

### Heart *and* kidney benefits

Results of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial were also presented and published during the meeting (3). The trial enrolled 3730 patients with heart failure with reduced ejection fraction who were simultaneously treated with the drug and standard heart failure therapy.

It showed that empagliflozin reduced the risk of hospitalization for heart failure by about 30% compared with placebo in both patients with and without diabetes. Previously, results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial demonstrated that dapagliflozin reduced the risk of worsening heart failure or cardiovascular death in patients with or without diabetes (4).

"We believe the important results of DAPA-HF and EMPEROR-Reduced trials should be sufficient to establish SGLT2 inhibitors as a new standard of care for patients with heart failure and reduced ejection," said lead author Milton Packer, MD, distinguished scholar in cardiovascular science at Baylor University Medical Center in Dallas, Texas.

In addition to demonstrating heart benefits, empagliflozin slowed the progressive kidney function decline seen in patients with heart failure and reduced by 50% the risk of a composite end point of needing chronic dialysis, kidney transplant, or sustained declines in estimated glomerular filtration rate.

### Class benefits

The results of the DAPA-CKD trial showed a comparable magnitude of kidney benefit to the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of the SGLT2 inhibitor canagliflozin, which was also stopped early in July 2018 (5).

"DAPA-CKD really reinforced a major point from CREDENCE, how the SGLT2s are great drugs to reduce the need for dialysis and improve mortality in patients who have diabetic kidney disease," said Christos Argyropoulos, MD, PhD, chief of the division of nephrology at the University of New Mexico School of Medicine, who noted diabetes contributes to about 40% of cases of chronic kidney disease. "It also added the twist that the drugs may work to the same degree and improve the same outcomes in patients who don't have diabetes but do have chronic kidney disease."

There are currently multiple theories about how

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## SGLT2s

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SGLT2 inhibitors protect the kidneys, but Argyropoulos said they likely help by stopping hyperfiltration and the resulting damage that occurs when the kidneys overwork.

"A big part of kidney disease development and progression is the kidneys sensing that something has happened to them and trying to compensate by working extra," he said. "This process, called hyperfiltration, causes secondary kidney damage, which makes more kidney tissue stop working." The SGLT2s seem to be able to slow the kidneys down and make them last longer, he said.

There are still some questions that need to be answered about this class of drugs. For example, it would be helpful to know who is likely to have rare but serious side effects like diabetic ketoacidosis.

"The next thing that we would have to do is find ways to use these drugs more safely, or at least detect these complications," Argyropoulos said.

It will also be important to manage or prevent common side effects, such as genital yeast infections in both men and women taking the drugs. Although these infections are easy to treat, repeated infections may make patients want to stop taking the drugs, Argyropoulos said.

The growing number of trials supporting substantial kidney benefits of SGLT2 inhibitors is a major development for the field of nephrology, Argyropoulos said. In fact, he said it's likely the biggest development since the emergence of ARBs and ACE-inhibitors.

"We are really talking about a once every 20 years type of event for nephrology." ■

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## Take Action to Increase Access to Immunosuppressive Medication

ASN needs your help to ensure kidney transplant patients are able to access life-saving immunosuppressive medications.

Congress has introduced the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act (H.R. 5534/S. 3353), bipartisan legislation that would remove Medicare's three-year limit for coverage of immunosuppressive drugs.

According to a pre-pandemic Department of Health & Human Services report, hundreds of kidney transplant patients lose their transplant due to an inability to afford immunosuppressive medication. This is not only costly to the health of the patient, but also to Medicare as the patient returns to dialysis. A recent analysis by the non-partisan Congressional Budget Office found that extending coverage of immunosuppressive drugs would save Medicare $70 million over a period of 10 years.

ASN and stakeholder organizations have urged Congress to pass this legislation before time runs out. However, your legislators need to hear from you as a constituent. Urge them to pass the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act, which will save lives and taxpayer dollars.

Visit the following link and send a pre-composed email to your members of Congress: www.asn-online.org/policy/lac.aspx. ■

# Gut Microbiota and Diabetes
## An Evolving Relationship

By Wei Ling Lau

The adult gut harbors 100 trillion bacteria. This is tenfold greater than the number of cells in the human body. The abundance and diversity of bacteria increase from the stomach ($10^2$ to $10^4$ cells/mL) to the colon (>$10^{12}$ cells/mL) as oxygen tension decreases. Given the vast number of microorganisms concentrated in the intestinal tract, it is not surprising that the products of bacterial metabolism modulate the health of the host. The gut microbiome has been implicated in the pathophysiology of numerous chronic diseases, including diabetes mellitus (DM), obesity, heart failure, dementia, chronic kidney disease, and cancers.

Across these chronic disease states, there appear to be two commonly observed derangements of the gut microbiome. First, there is decreased bacterial production of short-chain fatty acids (SCFAs), such as butyrate, acetate, and proprionate. SCFAs are a major nutrient source for the epithelial cells lining the intestinal tract; thus, they contribute to the integrity of the intestinal barrier. Deficient production of bacterial SCFAs leads to an unhealthy epithelial barrier, or "leaky gut," which allows translocation of toxins from the gut lumen into the bloodstream. Relevant to the pathogenesis of DM, SCFAs also modulate the host's appetite and energy expenditure, and they increase glucose-stimulated insulin secretion (Figure 1).

Second, there is a shift in the bacterial metabolic profile in such a manner that instead of primarily fermenting carbohydrates, there is increased catabolism of proteins and amino acids, which generates toxins that exert systemic effects. Tryptophan is metabolized into indole by intestinal bacteria and is subsequently sulfated in the liver to form indoxyl sulfate. P-cresol sulfate is derived from phenylalanine and tyrosine and is conjugated by gut microbes to p-cresyl sulfate. Bacterial metabolism of quaternary amines (e.g., phosphatidylcholine, L-carnitine) yields trimethylamine, which is rapidly oxidized in the liver to produce trimethylamine N-oxide (TMAO). Indoxyl sulfate, p-cresyl sulfate, TMAO, and other bacteria-derived metabolites have traditionally been labeled "uremic toxins" because they were initially studied in the setting of chronic kidney disease. It may be time to change this terminology because these microbiota-derived toxins have now been implicated in nonkidney-related diseases. For example, blood TMAO levels are strongly associated with DM, and dietary restriction of precursors of TMAO results in improved insulin sensitivity and glucose metabolism. In heart disease research, higher blood TMAO is associated with adverse cardiovascular events in the general population. At the cellular level, the vascular injury induced by these toxins can be explained by increased oxidative stress and inhibition of cell proliferation.

Other pathways that have been implicated in DM include abnormal signaling from toll-like receptors (TLR) TLR2 and TLR5, leading to insulin resistance and increased abundance of gut Firmicutes. Microbiota can also induce lipogenesis in the liver, as well as upregulation of carbohydrate response element-binding protein (ChREBP) and liver sterol response element-binding protein type 1 and (SREBP-1).

Compelling evidence for a central role of the gut microbiome in the development of type 1 DM came from The Environmental Determinants of Diabetes in the Young (TEDDY) study. This multinational study analyzed the stool microbiome from children in the United States and three European countries, starting at the age of 3 months and continuing until they were 10 years old. Expression of microbial genes involved in the biosynthesis of SCFAs was lower in children who experienced type 1 DM than in matched control children. Furthermore, supplementing infants with probiotics within 27 days of life correlated with a decreased risk for the development of type 1 DM. Data from large genome-wide association studies have also identified strong links between bacterial SCFAs and risk for the development of type 2 DM.

Beyond impairment of glucose metabolism and insulin secretion, the gut microbiota also drive diabetic kidney disease. Baseline blood phenyl sulfate levels predict 2-year progression of albuminuria, and this bacterial-derived toxin has been shown in animal studies to induce podocyte damage. There is increased expression of *Escherichia-Shigella* and *Prevotella* bacteria in patients with diabetic nephropathy, compared with diabetic individuals who lack kidney disease. It has been proposed that increased levels of *Escherichia-Shigella* species contribute to the pathophysiology of diabetes by promoting breakdown of the gut epithelial barrier and by producing ethanol, which leads to disordered SCFA metabolism. Finally, frequent use of antibiotics (which disrupts the balance of normal intestinal flora) has been shown to correlate with the severity of diabetic nephropathy in patients with type 1 DM.

With all this accumulating evidence pointing to an integral role for the gut microbiome in the pathophysiology of DM, several studies have attempted to manipulate the microbiota as a novel way to treat DM. These interventions can be in the form of prebiotics (nondigestible food ingredients that can stimulate growth and/or activity of beneficial gut bacteria); probiotics (living organisms ingested in food or supplements that are believed to improve the health of the host); or symbiotics, which combine both prebiotics and probiotics.

The results so far have been mixed, and at best the impact on glycemic control is small. The largest studies have come from Malaysia and Australia. In the Malaysian study, non–insulin-dependent type 2 DM patients with baseline hemoglobin A1c 7.6% were randomized to placebo versus a probiotic formulation (68 patients per group). Probiotic therapy decreased A1c by 0.14%. In the Australian cohort, 156 nondiabetic overweight individuals were randomized to placebo versus probiotics; there was no change in A1c after 6 weeks, and, perplexingly, the probiotics group ended the study with a higher average fasting glucose level. Finally, a smaller study of 70 patients with type 2 DM in Iran found that symbiotic therapy stabilized A1c and microalbuminuria but did not improve serum or urinary markers of kidney function. General limitations of studies involving probiotics include the following: 1) we may not yet know the right mix of bacteria that will promote health, 2) selection of an appropriate high-risk population so as to detect meaningful changes in clinical outcomes at study completion, and 3) study duration that is too short to enable detection of differences between the treatment and placebo groups.

In summary, the gut microbiome modulates host metabolic pathways and risk for the development of DM (Figure 2). Key mechanisms include disturbances in the production of short-chain fatty acids and activation of toll-like receptors. Furthermore, bacteria-derived toxins from the gut contribute to insulin resistance and to vascular and podocyte damage. We do not know at this time how to manipulate the natural diet to engender a less pathogenic microbiome; and more work is needed to clarify the role of prebiotics and probiotics in diabetes management. ■

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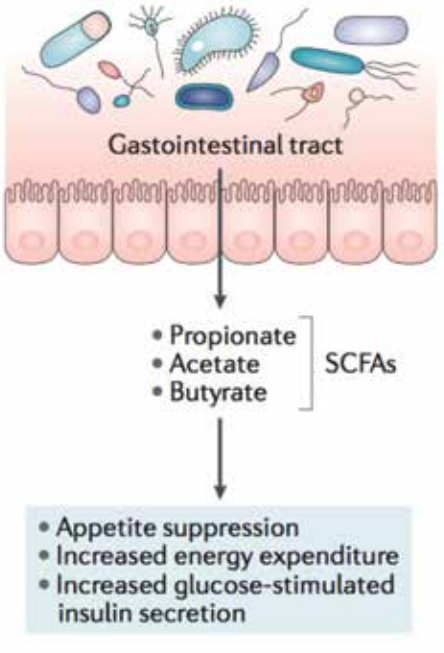


**Figure 1. Short-chain fatty acids (SCFAs) generated by the gut microbiota include propionate, acetate, and butyrate, which are essential nutrients for intestinal epithelial cells. SCFAs modulate host energy and glucose metabolism through effects on appetite, energy expenditure, and insulin secretion. Reprinted with permission from Lau WL, Vaziri ND. Gut microbial short-chain fatty acids and the risk of diabetes [Editorial]. *Nat Rev Nephrol* 2019; 15:389–390.**

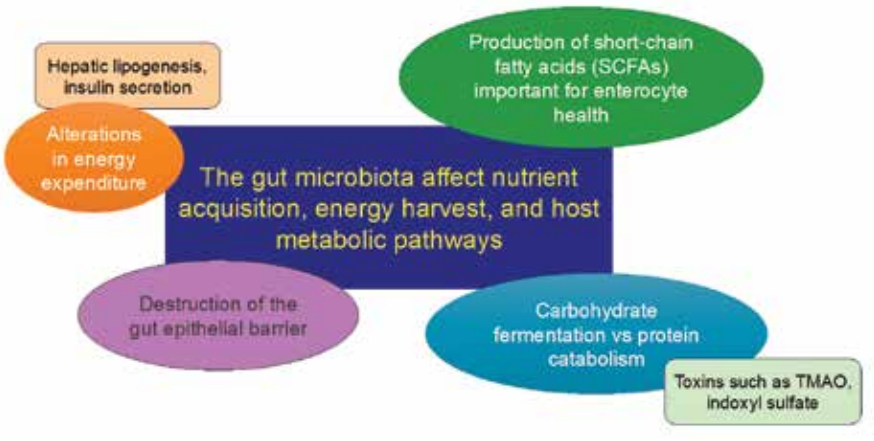


**Figure 2. The gut microbiota affect the acquisition of host nutrients, use of energy, and metabolic pathways, including hepatic lipogenesis and insulin secretion. Short-chain fatty acids (SCFAs) are important as a nutrient source for intestinal cells and for maintenance of gut epithelial integrity, and they have systemic benefits, as noted in Figure 1. A shift toward protein and amino acid catabolism (rather than carbohydrate fermentation) produces bacteria-derived toxins such as indoxyl sulfate and trimethylamine N-oxide.**

# SGLT2 Inhibitors in Solid Organ Transplant Recipients with Type 2 Diabetes Mellitus

By Anju Yadav

The increasing prevalence of type 2 diabetes in recent decades is the primary factor accounting for the substantial global increase in kidney failure. Currently, more than 3 million people worldwide are estimated to be receiving treatment for kidney failure, with predictions that the number will increase to more than 5 million by 2035 (1). Sodium-glucose cotransporter 2 (SGLT2) inhibitors were developed to lower blood glucose levels in patients with type 2 diabetes. These agents were studied in trials to meet the regulatory requirements for cardiovascular safety; in fact, they were found to reduce cardiovascular events. Further analysis of these trials suggested that SGLT2 inhibitors might improve kidney outcomes. The CREDENCE trial was designed to study SGLT2 inhibitors in diabetic kidney disease (DKD) patients with proteinuria, who are at high risk for microvascular and macrovascular complications. For the first time in two decades since renin-angiotensin system blockade was approved for use in DKD patients, this trial with SGLT2 inhibitors has revolutionized their treatment (1).

The three large population-based controlled trials with SGLT2 inhibitors were conducted primarily to assess for cardiovascular safety: 1) the Empagliflozin, Cardiovascular outcomes, and Mortality in type 2 diabetes (EMPA-REG OUTCOME) trial showed that empagliflozin was superior to placebo (2); 2) the Dapagliflozin Effect on Cardiovascular events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial showed that dapagliflozin was noninferior to placebo (3); and 3) the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial showed a lower risk of cardiovascular events in patients treated with canagliflozin than in those who received a placebo (4). A greater risk of amputation, primarily at the level of the toe or metatarsal area, was noted in these studies, and physicians were cautioned (4). Owing to the mechanism of SGLT2 inhibitors, glycosuria leads to an increased incidence of genitourinary infections (both bacterial and fungal) and an initial small decline in estimated eGFR as with renin-angiotensin aldosterone inhibitors (1–4).

The CREDENCE trial specifically studied the role of canagliflozin in DKD and showed a 30% lower risk in the event rate of ESRD, in comparison with the placebo group; doubling of serum creatinine; and cardiovascular death in the treatment group, which also had a lower risk of hospitalization for heart failure, cardiovascular death, myocardial infarction, or stroke, and hospitalization for heart failure. However, this trial excluded patients with nondiabetic kidney disease, with glomerulonephritis treated by immunosuppressive agents, or with a kidney transplant (1).

After solid organ transplantation, there is an increased risk of DKD, because of the recurrence of both pre-transplantation diabetes and post-transplantation diabetes mellitus (PTDM). PTDM has been reported to occur in 4% to 25% of kidney transplant recipients, 2.5% to 25% of liver transplant recipients, 4% to 40% of heart transplant recipients, and 30% to 35% of lung transplant recipients. PTDM occurred in 34.7%, 46.9%, and 56.2% of liver transplant patients at their 1-year, 3-year, and 5-year follow-up visits (5). This leads to substantial microvascular and macrovascular complications after transplantation. These complications eventually reduce the survival of allografts and patients.

SGLT2 inhibitors are an attractive therapeutic option for DKD patients after solid organ transplantation because this population has the most to gain. However, trials and consensus guidelines regarding the use of SGLT2 inhibitors are lacking; hence, they are not used for these patients. Lacking clinical trial data with reported adverse effects, the transplantation community is holding back on prescribing this therapy. In terms of clinical data, only a handful of case series or trials with SGLT2 inhibitors for solid organ post-transplantation patients with DKD, that analyze their efficacy, kidney outcomes, and safety, are available.

A single-center, prospective, double-blind randomized study with empagliflozin in 22 kidney transplant (KT) recipients (22 empagliflozin/22 placebo, 34 male patients) over 24 weeks showed a median change in glycated hemoglobin (HbA1c) by –0.2% (compared with –0.1% in the placebo group) and a reduction of 2.5 kg body weight versus a gain of 1 kg in the control group, with no significant differences in adverse events, interactions with immunosuppressants, or eGFR (6).

A case series of 10 post-KT recipients with PTDM but stable graft function and no recurrent urinary tract infections, treated with empagliflozin in addition to preexisting antidiabetic treatment, showed a stable median eGFR during follow-up for 12 months (7). The median HbA1c decreased by 0.2%. Two patients had urinary tract infections (UTI) with no long-term effect on kidney function, 1 patient had a creatinine increase of 0.3 mg/dL with no incidence of ketoacidosis, and 1 patient experienced a diabetic ulcer, which healed even during therapy with SGLT2 inhibitors.

A report of 10 KT and simultaneous kidney-pancreas transplant recipients who were given canagliflozin, with a follow-up time of >80.5 patient-months, showed a decrease in body weight by 2.1 kg, lower systolic and diastolic blood pressure (–6.5/–4.8 mm Hg), and decreased HbA1c by 0.84% (8). There were no increases in urinary or mycotic infections, acute allograft rejection, or acute kidney injury. A small change in eGFR (4.3 mL/min), similar to that in the general population, was observed.

In a case series, 8 living unrelated KT recipients (2 with a history of diabetes) received SGLT2 inhibitors (empagliflozin and dapagliflozin) and were followed up at 3 and 6 months. Their kidney function remained stable, with minor changes in HbA1c and body weight. Again, no increased incidence of UTI or fungal infection was reported (9).

In the only available report of SGLT2 inhibitors in heart transplant recipients (study group 22, control patients 79), transplant recipients receiving empagliflozin were followed up for 12 months and showed a reduction in body weight (–2 kg median body weight), body mass index (–1.3 kg/$m^2$), and HbA1c, and a reduced need for diuretics (10). There were no large changes in blood pressure or kidney function. This group experienced three adverse events, including dizziness, acute kidney injury, and urinary symptoms, but no UTIs were noted.

None of these case series or studies demonstrated an increased risk of amputation, as reported in CANVAS (4). In the CREDENCE trial there was no significant difference in the risk of lower-limb amputation or rates of fracture (1

The Dapagliflozin in Chronic Kidney Disease (DAPA-CKD) results presented at the European Society of Cardiology Congress 2020 are the first to include nondiabetic CKD patients (32%). The study included 4304 participants from 21 countries randomized to Dapagliflozin and placebo. The primary outcome showed slower eGFR decline with improved ESKD outcomes and renal or CV death (hazard ratio 0.61; number needed to treat, 19). The side effect profile was not observed to be different from placebo. A few post-kidney transplant patients were part of the study. It will be interesting to see the analysis on this small cohort of patients and their baseline characteristics once the study is published.

In conclusion, SGLT2 inhibitors are no doubt an effective therapy for DKD, but their benefits regarding primary or secondary outcomes in solid organ transplant recipients are unclear. Theoretically, they appear to be a reasonable therapeutic choice in solid organ transplant recipients and can potentiate the benefit of transplantation in patient survival. SGLT2 inhibitors can be considered 6 months after transplantation, once allograft function is stable and kidney function is in a steady state.

Randomized controlled trials with SGLT2 inhibitors are warranted to better study the kidney and cardiovascular outcomes in all solid organ transplant recipients. These studies should be able to guide us in timing the initiation of therapy and in analyzing its efficacy, safety, drug–drug interactions, and its long-term impact on the immunologic makeup of individual patients. Both kidney and cardiovascular outcomes along with patient and allograft survival. ■

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# SGLT2 Inhibition and Acute Kidney Injury
## Friend or Foe?

By George Vasquez Rios


*Two patients seek medical care. One is a 45-year-old man with diabetes mellitus type 2 who presents to the emergency department with concerns for diabetic foot ulcer and extensive cellulitis, which did not subside after a short course of Bactrim. His creatinine had increased from 1 mg/dL to 1.3 mg/dL. The second patient is a 52-year-old woman who was referred to the nephrology clinic by her primary care physician because of a "creatinine bump" on her routine laboratory test results. Both patients were recently prescribed dapagliflozin by their endocrinologists. You are consulted for the evaluation and management of "acute kidney injury." What are your recommendations?*

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a novel class of antidiabetic medications that have been demonstrated to improve cardiovascular outcomes in patients with diabetes. SGLT2 inhibitors regulate serum glucose levels by selectively blocking type 2 glucose transporters in the proximal convoluted tubules, thereby reducing the amount of glucose and sodium reabsorbed. Increased delivery of sodium and chloride to the macula densa induces tubuloglomerular feedback, leading to constriction of the renal afferent arteriole and to reduction of intraglomerular pressure and albuminuria. Also, these medications have been shown to reduce cellular oxidative stress and to improve energy balance. Whereas SGLT2 proteins are markedly distributed in the kidney and the gut, the beneficial effect of these medications on distant organs such as the cardiovascular system suggests that there may be additional anti-inflammatory and cardioprotective properties yet to be explored (1).

Three large randomized controlled trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) (2), the Empagliflozin Cardiovascular Outcome Event Trial in type 2 diabetes mellitus patients (EMPA-REG OUTCOME) (3), and the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLAR-TIMI 58) (4) trial showed that SGLT2 inhibitors are associated with improved cardiovascular endpoints in patients with diabetes, such as decreases in myocardial infarction, cardiovascular mortality, and all-cause death. SGLT2 inhibitors have also proved to be beneficial in chronic kidney disease (CKD) patients by decreasing the rates of advanced CKD and kidney replacement therapy needs (5, 6).

Furthermore, the recent clinical trial "Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure" (DAPA-HF) (7), has shown that even nondiabetic patients may also benefit from the cardiometabolic effects provided by this group of medications. In addition, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial (6) states that canagliflozin is safe and effective in reducing the rate of kidney function decline in patients with moderately advanced nephropathy and estimated GFR between 30 and 45 mL/min per 1.73 $m^2$. Despite the promising body of evidence indicating that SGLT2 inhibitors are a new tool in the management of diabetic kidney disease (DKD), some concerns have been raised regarding their association with adverse kidney outcomes, including acute kidney injury (AKI), especially in the setting of excessive diuresis and/or reduction of renal blood flow resulting from severe afferent renal constriction (8). The purpose of this review is to discuss the role of SGLT2 inhibitors in AKI and to visit some of the putative mechanisms involved.

## SGLT2 inhibitors: individual experience versus clinical evidence

In 2016, the U.S. Food and Drug Administration strengthened the existing warning on SGLT2 inhibitors, most notably canagliflozin and dapagliflozin, after a report of 101 patients in whom AKI developed after they began taking these medications without another identifiable culprit. AKI was seen within 1 month after the medication was started in approximately 50% of the cases. Although some of these patients experienced improvement after the medication was withheld, some of them required hospitalization and kidney replacement therapy. Thus, a warning label revision was added, and clinicians were requested to be judicious in the prescription of these medications.

Certainly, SGLT2 inhibitors could contribute to AKI by inducing volume depletion because of their natriuretic and osmotic properties, especially in patients who are already dehydrated or are exposed to medications that block the renin-angiotensin-aldosterone system, nonsteroidal anti-inflammatory drugs, or antibiotics, as in the stem case (9, 10). Furthermore, in the distal renal tubules, glucose can be exchanged for uric acid by luminal GLUT9, which becomes more active in the presence of glycosuria (11). This could result in increased tubular levels of uric acid, which may induce crystal deposition, inflammation, and oxidative stress, as shown in some preclinical models of tubular injury (12). Moreover, even though acute SGLT inhibition normalizes oxygen tension in the renal cortex, it may cause hypoxia in the renal medulla of anesthetized diabetic rats, rendering them susceptible to ischemic insults (13).

Although any of these mechanisms can contribute to the development of AKI in patients taking SGLT2 inhibitors, it is important to consider a few aspects of diabetes as a disease process.

First, patients with diabetes are at increased risk of AKI when they routinely use other substances such as antibiotics, nonsteroidal anti-inflammatory drugs, and contrast material. Second, diabetes per se confers an intrinsic susceptibility to AKI because of the chronic microvascular damage related to systemic inflammation and toxic effects associated with albuminuria. Third, despite the specific effects of SGLT2 inhibitors in different parts of the nephron, it is possible that compensatory mechanisms are responsible for the net benefit provided by these medications, including blood pressure control, natriuresis, and overall increased survival rates (1, 3, 5, 6). For example, erythropoietin (EPO) production by peritubular cells can increase as a response to decreased oxygen tension in the medulla, which could partially explain the rise in hematocrit levels in these patients (14). Ultimately, restoration of EPO levels could contribute to cardiovascular/renal tissue protection because of its immunomodulatory effects (15).

Assessing the detrimental effects of any medication is very challenging without an appropriate control group to identify and remove confounding factors. From a physiologic perspective, SGLT2 inhibitors are expected to induce mild increments of serum creatinine because they tend to reduce intraglomerular pressure and consequently reduce the GFR (10). Often in clinical practice, sudden "creatininemia" raises caution among clinicians, who may in turn discontinue the "offending" agents, as in the case of the second patient in the stem problem. However, a recent post hoc analysis of a placebo-controlled clinical trial showed that serum creatinine increments in patients exposed to dapagliflozin were not associated with tubular injury, as measured by the urinary kidney injury molecule-1 (16). Furthermore, when compared with patients in the placebo-controlled group, patients using dapagliflozin presented a lower renal inflammatory profile, noted through the evaluation of urinary IL-6 levels (mean percentage change from baseline in the dapagliflozin group: –24 [95% CI 37.9 to –7], p = 0.01) (16). Moreover, in a propensity-matched cohort study, Nadkarni et al. (9) found that AKI was 60% less frequent among users of SGLT2 inhibitors when compared with the control group (adjusted hazard ratio: 0.4 [95% CI 0.2–0.7], p = 0.01) in the Mount Sinai cohort. Likewise, AKI was 50% less frequent in patients using SGLT2 inhibitors when evaluated in the counterpart Geisinger cohort (adjusted hazard ratio: 0.6 [95%

CI 0.4–1.1], p = 0.09). Thus, whereas SGLT2 inhibitors have the potential to exacerbate AKI in patients who have other ongoing insults on an individual level, from a population standpoint, it appears that these agents confer net kidney-protective effects. Furthermore, they are not associated with an increased risk for AKI, which is consistent with the long-term kidney benefits on progressive DKD and kidney failure witnessed in the large randomized controlled trials (17–19). Table 1 shows the reported incidence of AKI in major clinical trials.

## SGLT2 inhibitors, erythropoietin, and fibrosis: benefits from bench to bedside

SGLT2 inhibitors play a role in renal cell energy and oxygen preservation. Medications in this group decrease the absorption of glucose in the proximal tubules, a process that is otherwise energy dependent and that requires intense activity from the ATP-Na/K pump. Intracellular ATP depletion and oxygen consumption affect the energetic balance of renal tubular epithelial cells, thereby limiting their ability to recover from an insult (20). Furthermore, oxygen consumption and the generation of reactive oxygen species promote mitochondrial dysfunction and a dysregulated inflammatory state (21). The proximal tubules are especially vulnerable to hypoxic states and mitochondrial dysfunction, which can induce renal tubular epithelial cell apoptosis, necrosis, and epithelial cell transformation. The latter, which is largely influenced by oxidative stress and hypoxic conditions, involves the differentiation of resident peritubular fibroblasts that would otherwise produce EPO into activated myofibroblasts responsible for collagen synthesis (22). Therefore, SGLT2 inhibitors can ameliorate the cellular stress induced by hypoxia and inflammation-mediated fibrogenesis, which have been identified as key mechanisms of diabetic kidney disease (DKD). Furthermore, short-term canagliflozin treatment has been found to protect against in vivo myocardial ischemia-reperfusion injury in nondiabetic rats (23), a property that has been reproduced in the kidney by dapagliflozin (24).

The relationship between low EPO levels and progressive DKD has been previously assessed in clinical studies. Patients with diabetes have lower EPO levels than do nondiabetic individuals regardless of their kidney function. Furthermore, in a prospective analysis by Fujita et al. (25), low EPO levels—even below the upper normal limit (23.7 IU/L)—predicted rapid kidney function decline independently of other traditional prognostic factors such as hemoglobin level, estimated GFR, and urine albumin–creatinine ratio. Moreover, an indirect correlation between worsening glycosylated hemoglobin levels and EPO levels has also been demonstrated elsewhere. Therefore, it is presumed that SGLT2 inhibitors may alleviate cellular metabolic stress, reduce tissue tubular/peritubular inflammation, and allow to some extent the reversion of myofibroblasts to EPO-producing fibroblasts. The latter effects, along with cardiorenal axis regulation, may be associated with the relatively early cardiovascular and survival benefits provided by these medications in the acute and chronic settings (26).

## Areas of uncertainty

Whereas the SGLT2 inhibitors show promise in the management of DKD, with no statistical data supporting an association with AKI, current labeling recommends dose reductions on the basis of estimated GFR, arguably because of the diminished glucose-lowering effect with reduced kidney function. Despite the statement in the CREDENCE study that the use of canagliflozin is safe and effective in improving cardiovascular outcomes in diabetic patients with an estimated GFR between 30 and 45 mL/min per 1.73 $m^2$, it is unknown whether these results can be extrapolated to patients with more advanced stages of kidney disease (27). Also, it is unknown whether we can extrapolate the latter findings to other SGLT2 inhibitors because of the intraclass difference in pharmacodynamics. Additionally, more data from underrepresented populations and patients in extreme old age is needed because these populations have been shown to be at increased risk of AKI and higher lifetime risk of CKD. The benefit of using SGLT2 inhibitors in patients with active disease (e.g., infection, myocardial infarction) needs to be further investigated regardless of the AKI risk. Moreover, it is unknown whether patients with mild "permissible" serum creatinine increments experience better outcomes compared with those who do not show such increments. Further studies are needed to assess how permissible clinicians should be in their practice.

## Conclusion

SGLT2 inhibitors have been demonstrated to improve cardiovascular and kidney outcomes and to reduce mortality rates among diabetic patients. Large meta-analyses and post hoc studies have failed to find an association between SGLT2 inhibitors and AKI. On the contrary, a potentially protective role has been suggested based on their cardiometabolic, cytoprotective, and anti-inflammatory properties, although this warrants further investigation. Although anecdotal cases of AKI after the initiation of SGLT2 inhibitors exist in the literature, other factors, including dehydration, infection, and nephrotoxins were poorly assessed. In a patient with signs of volume contraction, sepsis, or an active decompensating disease, it is reasonable to withhold the medication until the patient's underlying medical problems have been solved (sick-days). However, SGLT2 inhibitors may be continued in patients in stable condition who show mild creatinine increments with no other obvious explanation. Follow-up and clinical judgment may be important in this scenario. Finally, clinicians should consider the use of SGLT2 inhibitors in the appropriate setting and based on the dose specifications available until additional data are obtained. Additional studies including patients from underrepresented populations, with a wider age range, and with more advanced kidney disease are warranted ■.

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*Continued on page 16*

**Table 1. Analysis of major clinical trials evaluating cardiovascular and renal outcomes associated with SGLT2 inhibitors**

| | SGLT2 inhibitor | Inclusion criteria | eGFR (mean+/- SD), mL/min/1.73m² | AKI T - arm | AKI P- arm | Hazard Ratio (95%CI) | P value |
|---|---|---|---|---|---|---|---|
| CANVAS (n = 10,142) | Canagliflozin | A1c: 7% – 10.5% | T – arm: 76.7 ± 20.3<br>P – arm: 76.2 ± 20.8 | 3$ | 4.1$ | NA | 0.33 |
| DECLARE-TIMI 1758 (n =,160) | Dapagliflozin | A1c: 6.5% – 12% | T – arm: 85.4 ± 15.8<br>P – arm: 85.1 ± 16 | 125/8574 (0.014) | 175/8569 (0.02) | 0.69 (0.55-0.87) | 0.002 |
| EMPA-REG (n = 7020) | Empagliflozin | A1c: 7% – 10% | T – arm: >90: 1050, 60-90:2425, <60: 1212<br>P – arm: >90: 488, 60-90:1238, <60: 607 | 45/4685 (0.009) | 37/2333 (0.015) | N/A | <0.05 |
| DAPA-HF (n = 4744) | Dapagliflozin | EF≤40%, NYHA II,III, IV | T - arm: 66.0 ± 19.6<br>P – arm: 65.5 ± 19.3 | 23/2373* (0.009) | 46/2371* (0.019) | NA | 0.007 |
| CREDENCE (n = 4401) | Canagliflozin | A1c: 6.5% – 12% | T – arm: 56.3 ± 18.2<br>P – arm: 56.0 ± 18.3 | 86/2200 (0.039) | 98/2197 (0.044) | 0.85 (0.64 – 1.13) | NS |

*The DAPA-HF trial reported 'serious adverse effects of acute kidney injury'. No hazard ratio data provided; T-arm: 'Treatment' arm, P-arm: 'Placebo' arm; NA: non-available, NS: non-statistically significant; UACR: urine albumin-creatinine ratio; $ Values reported as: event rate per 1000 patient-year

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*Continued from page 15*

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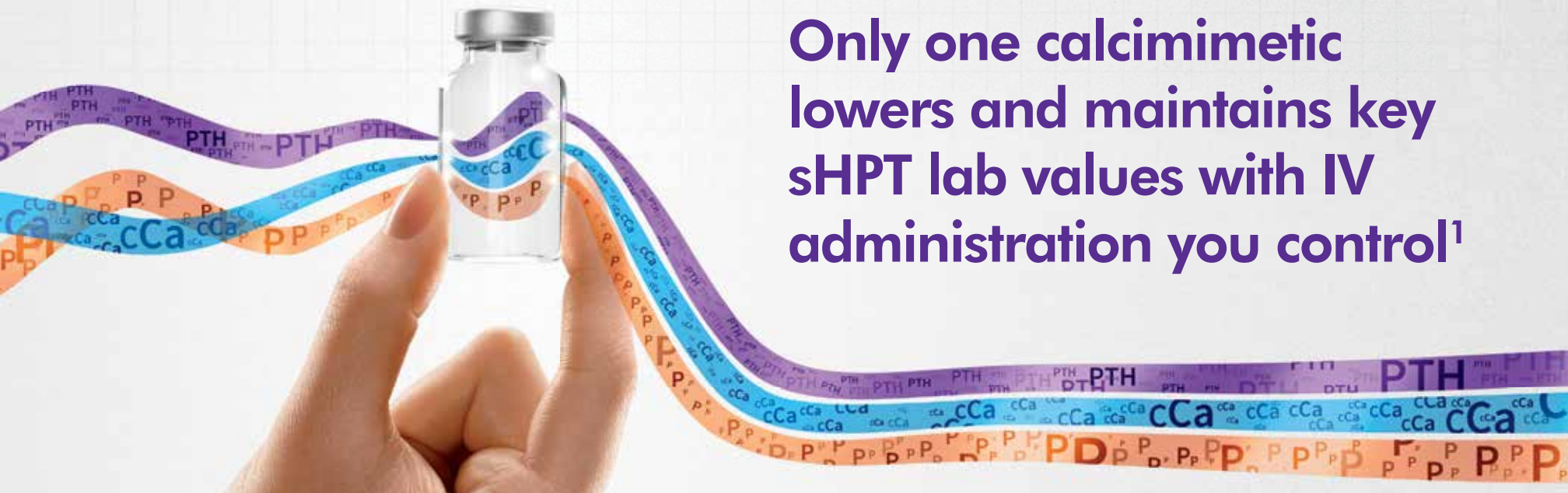


# Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

**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 pruritic rash, urticaria, and face edema, 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 pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) 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.

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.

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.

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. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

## 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)

**Manufactured for:**
**KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.**
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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

# Practice Pointers

## The KDIGO Clinical Practice Guideline on Transplant Candidate Evaluation and Management Exhaustive, Authoritative, and Essential

By Terrence Jay O'Neil

The patient sitting in your office is in her low 30s, with an estimated GFR to match. She comes to you on referral from her primary care practice, unsure why she was referred, but the reason is pretty obvious to you. She has apparently been losing 5 grams of protein in her urine for some time—just how long isn't clear because the proteinuria was first noticed 3 years ago but wasn't quantitated, and this is the first time she has been referred to a nephrologist. She is moderately obese and takes three medications for her hypertension, including an angiotensin-converting enzyme inhibitor. But, kidney ultrasonography done at your request as she was being referred shows her kidneys to be larger—not smaller—than normal size. And, she says, a pack of cigarettes lasts her about a week.

Oh, and her hemoglobin A1c is 8%, so she has type 2 diabetes, too.

You will obviously be fully employed just dealing with the current here-and-now of the disease state this young woman is experiencing. Just trying to keep her from having to say "hello" to a dialysis unit staff somewhere fairly soon is going to be rough.

She has a quintuple whammy of risk factors, including diabetes, hypertension, nephrotic-range proteinuria, declining GFR, and smoking, along with that anomalous result on ultrasonography suggesting there may be something more at work on her kidneys that hasn't even been suspected so far.

But, since she reports having been adopted, you aren't going to get off easy with a family health history.

Darn! This is going to be complicated, and you'd better be able to do something positive for her quickly.

But, you also like to think ahead, and you are well aware that if you can't find a way to forestall further kidney function loss, she may have a life with dialysis to look forward to. And nobody should face that kind of future. So, you'd like to refer her for a possible kidney transplantation at the earliest appropriate time.

But what is that time, and where do you go for the most authoritative step-by-step guidelines on how to prepare her for transplantation candidacy and referral? Where do you find thoroughly vetted recommendations, not only for the technical step-by-step of candidate evaluation but also for the insights that could keep her from facing a complication during transplantation or in its immediate aftermath?

Or, for that matter, how do you anticipate and forestall a possible future repeated decline into kidney failure from an undiagnosed additional condition, despite the new transplant?

You might strongly consider using the "Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation" released by Kidney Disease: Improving Global Outcomes (KDIGO) in the April 2020 issue of *Transplantation*, the journal of The Transplantation Society and the International Liver Transplantation Society. The Guideline is intended to provide recommendations for evaluation of individual aspects of a candidate's profile in such a manner that each risk factor and comorbidity is considered separately. The goal is to assist the clinical team to assimilate all data relevant to an individual, consider this within their local health context, and make an overall judgment on candidacy for transplantation.

KDIGO is a respected international nonprofit organization established in 2003 by the US National Kidney Foundation, transformed into an independent multinational organization in 2012, and currently headquartered in Brussels, Belgium. Its mission is to develop and implement evidence-based kidney disease guidelines.

To produce the Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation, KDIGO convened a 23-person executive committee and a 16-person work group. Other publications by the organization include guidelines for acute kidney injury, anemia in chronic kidney disease (CKD), CKD evaluation and management, mineral and bone disorders, diabetes, and blood pressure management.

### A comprehensive, proactive approach

This Guideline, available on the KDIGO website https://kdigo.org/guidelines/ for free download, has been under development since 2016. It is both comprehensive and extremely detailed, addressing in its 103 pages of text and supplements every candidacy issue for both adult and pediatric patients. Subjects such as access to transplantation, patient demographic and health status factors, and immunologic and psychosocial assessment are covered, but the Guideline does not address issues specifically involving candidates for combined kidney transplantation with another organ. Transplantation education is also not covered. The subjects considered cover the entire clinical course from the first consideration of the need for kidney replacement therapy to the kidney transplantation surgery itself. The full Guideline text is available at https://kdigo.org/wp-content/uploads/2018/08/KDIGO-Txp-Candidate-GL-Exec-Summary-FINAL.pdf.

The document stresses a proactive approach, beginning with a plea for all patients in CKD stage 4 and stage 5 to be fully informed about transplantation as an option, and for these individuals to be referred at least 6 to 12 months before the onset of kidney failure, with the optimal outcome being transplantation before dialysis initiation (so-called preemptive transplantation).

It also stresses avoiding out-of-hand dismissal of the feasibility of transplantation for those with amyloidosis, myeloma, hepatitis C, or other infectious diseases, and even active cancers until it has been determined that completed treatment cannot render the patients acceptable candidates. According to the Guideline, assessment of older candidates should consider potential frailty rather than simply chronologic age. Psychosocial assessment is stressed for both pediatric and adult patients because the outcomes hinge on compliance and aspects of lifestyle affected by the patient's psychosocial environment.

Smoking comes in for special notice, with computed tomography of the chest being advocated to detect occult lung cancers in users with more than 30 pack-years and regular plain chest radiographs for those with less smoking history. Exclusion solely on the grounds of obesity is discouraged, but where it is severe enough to interfere with the surgery or postoperative healing, pretransplantation counseling and attempts to lower body mass index are stressed.

Advice is given for the management of anticoagulant and antiplatelet medications and their complications. The treatment of patients with massively enlarged polycystic kidneys is also discussed, as is the referral strategy and treatment of those with, or at risk for, diabetes mellitus. If the potential candidate's cause of the kidney damage is either unclear or suspected to be complex, a definitive biopsy diagnosis is urged because of the potential for some conditions to recur in the transplanted organ. Evaluation for transplantation in the presence of cardiac and pulmonary disease, peripheral arterial disease, gastrointestinal disorders, neurologic conditions, bone and mineral disorders, and immune system abnormalities is discussed in detail.

An exhaustive list of the literature search terms for each major subject heading is given in an appendix to the main body of all KDIGO Guidelines. Another supplement gives the details of each study included in the review, along with evidence-quality tables for each.

This Guideline is a must-have for nephrologists who wish to have on hand a reference in their digital libraries that is informed by the best and most current evidence. KDIGO recognizes that the accumulation of new research and experience eventually renders all guidelines obsolete, and other guidelines it has already published have undergone appropriate revision and updating.

### And the patient?

Oh, and your patient? You got her blood pressure under better control and convinced her to lose some weight, which improved her hemoglobin A1c and further helped her blood pressure. You prescribed a sodium-glucose cotransporter-2 inhibitor. You also convinced her to join a tobacco-cessation program. Based on what you can find of her past records, her GFR has been dropping at about 4 to 5 mL/min per year. That implies that you will have to refer her to a transplantation center at a GFR of 20 mL/min, given the 3- to 5-year waitlist time for kidney transplants, so she can have 6 to 12 months from listing before she reaches 10 to 12 mL/min and needs dialysis.

You also have a kidney biopsy scheduled a month from now to look for the very real possibility that those large kidneys that are only managing an estimated GFR in the 30s are not hiding something that could recur after transplantation.

Based on the KDIGO guideline for CKD management, you are seeing her every 4 months and continuously re-evaluating the downward slope of the GFR to see whether your interventions are slowing the progression. You have also connected her to other specialists for interventions that have been shown to slow progression: a nutritional medicine specialist, a pharmacologist, a nurse educator, and a clinical social worker.

She is being well cared for by you, using the best available science. Congratulations. ■

*Terrence Jay O'Neil, MD, FASN, COLUSAFMC(Ret), is an affiliate nephrologist at the James H. Quillen VA Medical Center, and clinical professor of medicine at Quillen College of Medicine, East Tennessee State University, in Johnson City, TN.*

# Patients as Partners in Clinical Trial Development—What Are We Waiting For?

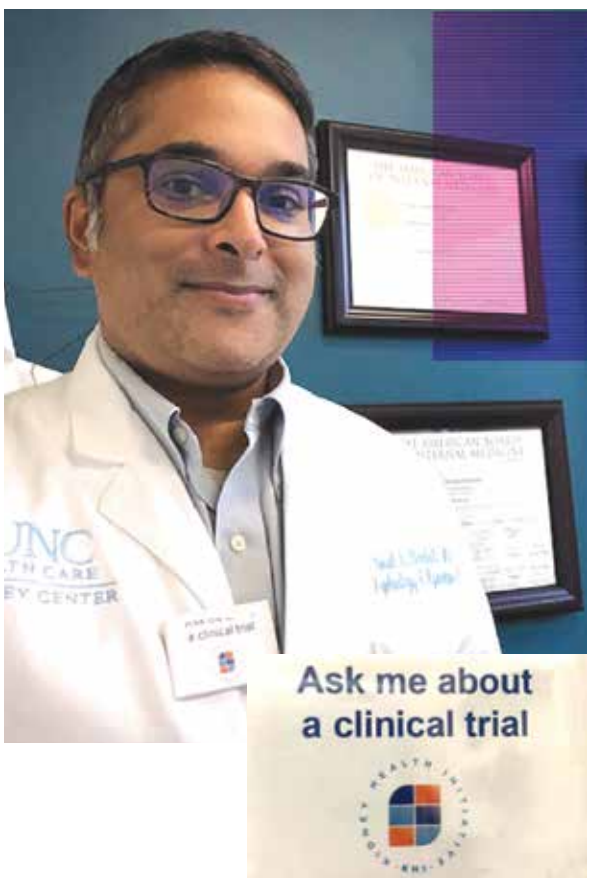
By Barbara S. Gillespie

*"I'm upset because no one has offered me a clinical trial. When I asked about a trial in clinic today, my nurse did not know what to say."*

—Nichole Jefferson

The climate of kidney drug and device development has certainly improved in the past two decades, from advances in trial design to higher numbers of trials being funded and conducted, as well as increased investment in kidney pipelines. But to fully realize the goal of the 2019 Advancing American Kidney Health executive order—reducing the number of Americans progressing to kidney failure by 25% by 2030—more collaborative work must be done. Although the efforts and results of past years can be itemized, it is often recognized that the least tangible change is in fact the one that is hardest to improve: culture change. Nephrology stakeholders must partner closer with the very people we are trying to positively impact—our kidney patients—to accelerate development of new and innovative therapies. Put simply, we need, or shall I boldly suggest that we demand, a culture shift in nephrology to view trial participation as an option for care.

When a patient is diagnosed with chronic kidney disease (CKD), nephrologists and care teams need to make the patient aware of the possibility of enrolling in a trial. Two informal surveys (one conducted by NephCure and the other by patient advocate Kevin Fowler) highlight that 69%–78% of CKD patient respondents noted that their physician never mentioned trial participation to them, but if the physician would take a few minutes to explain the potential benefits of a trial, that conversation would influence 73% of respondents to participate.




Vimal Derebail, MD, FASN, UNC Kidney Center

In the past, there may have been a supply issue. In 2000, there were only 5 nephrology trials registered on ClinicalTrials.gov; however, by 2018, there was a 110-fold increase, to 544 trials (1). Specifically, the landscape for rare kidney diseases was dry in 2015, with only 2 primary hyperoxaluria (Ph)2 or -3 trials for focal segmental glomerulosclerosis (FSGS) and none for immunoglobulin A nephropathy (IgAN). Four years later, in 2019, the drought was over, with 24 Ph2 or -3 trials collectively for those 2 diseases, an increase of 92% (or more than an 11-fold increase) (NephCure). We have gone from famine to feast and have more CKD trials than ever to offer. We need to create the urgency and demand and promote a culture in which every CKD patient is offered the chance to participate in a study—whether interventional, an observational registry, or qualitative research. After a diagnosis of CKD, it should not be a matter of if they will participate in a study but rather, which one will best serve their needs.

In 2017, the International Society of Nephrology (ISN) Global Kidney Health Summit proposed a stretch goal of "30 by 30": 30% of CKD patients should be involved in relevant clinical trials by 2030 (2). Thus, regardless of what hat you wear—patient or researcher or clinician—what will you do to get us to those goals?

*"Happiness and fulfillment are so much more than a measurement from a blood test. . . . When the outcomes are prioritized with the patient in mind, patient satisfaction rockets."*

—Jonathan Haydek (*CJASN* 2019)

Not every patient can participate in a study, but many opportunities exist to solicit a patient's disease insight in supporting study design, planning, and regulatory decision-making. Patients are the experts of their disease, so it is critical to engage their feedback on what should be measured and addressed in clinical studies. There are several mechanisms to obtain their insight. We need to make studies more relevant and patients more willing to participate in these studies. The following is a start, but by no means is the list complete.

## Patient-Focused Drug Development (PFDD)

The PFDD is a framework enacted by the 21st Century Cures Act (2016) that mandated that the US Food and Drug Administration (FDA) engage patients in disease-specific public meetings to learn more about their disease. It falls under 1 of 4 titles, notably, the one dedicated to speeding up clinical development. The others are patient experience data (see below), as well as facilitating novel trial designs and real-world evidence. Collectively, the aim is to generate more data that can serve as evidence to help inform research.

To date, three externally led PFDDs have focused on CKD and have been cohosted by the National Kidney Foundation (NKF): Alport syndrome, complement 3 glomerulopathy (C3G), and IgAN. At the IgAN meeting, Norman Stockbridge, MD, PhD, FDA director of the Division of Cardiovascular and Renal Products, emphasized that the FDA staff was eager to hear from patients about their symptoms, limitation of current therapies, and willingness to undergo potential risks associated with trials investigating novel agents. Figure 1 shows one of the questions designed for audience response and one patient's subsequent reaction.

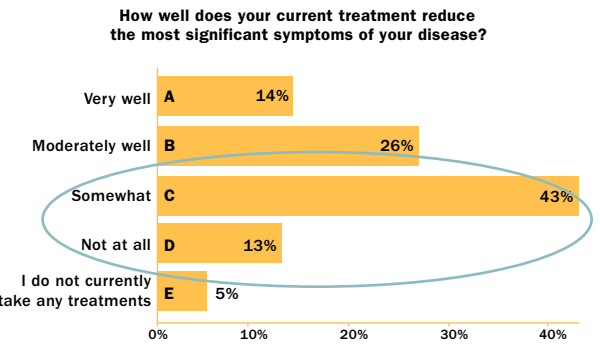
An upcoming Voice of the Patient report will summarize the discussion and findings of the IgAN PFDD. Healthcare providers, patients, and caregivers also had the chance to attend the FSGS PFDD on August 28, 2020.

## Patient Experience Data

This effort also falls under the 21st Century Cures Act and targets how to speed up clinical development. The first instance of a drug label incorporating a novel section, titled "Patient Experience," occurred in late 2017. The drug label articulated how 77% of patients preferred the subcutaneous (SC) administration of Rituxan Hycela over the intravenous (IV) Rituximab infusion, primarily because it required less time. (These were lymphoma patients enrolled in the formulation study of the new SC injection.)

The first time a device received an expanded indication, based on a formal patient preference study, occurred for the home hemodialysis (HD) NxStage machine. Initially, this device had been approved in 2005 for use with a care partner at home and then received clearance for nocturnal dialysis in 2014. But, the FDA granted a label expansion for patients to use it at home without a care partner present, based on patients' willingness and assessment of risk tolerance captured in the formal patient preference survey. The effect is liberating, as this label expansion increased the independence of patients to perform home dialysis. These examples underscore how patient feedback directly affects regulatory decision-making.

**Figure 1. Patient reaction to question about current treatment reducing disease symptoms**




"I'm newly diagnosed and 43% upsets me…that *43% is the problem*…are we willing to take the risk [in trial participation]? I know I am"

—Mike, IgAN patient

Courtesy IgAN patient-focused drug development meeting hosted by the NKF and IGA Nephropathy Foundation of America, August 2019

## Standardized Outcomes in Nephrology (SONG)

These are global surveys that compare priorities of patients and caregivers with those of healthcare providers. One of the goals is to determine which outcomes should be routinely measured in future trials. SONG-HD highlighted

how providers are biased toward outcomes of mortality, hospitalizations, and vascular access in contrast to patients who were more concerned with the ability to travel, dialysis-free time, and dialysis adequacy. Patients noted that their definition of dialysis adequacy was not the lab value dialyzer clearance of urea dialysis time/volume of distribution of urea (Kt/V; on which providers and payors focus) but rather, how they feel relative to receiving the amount of dialysis that is right for them. In other words: ***"Patients focus on living well with CKD rather than dying from it"*** (3). In the SONG-Glomerular Disease Workshop in 2019, patients prioritized developing cancer higher (#5) than the providers did (#8), once again displaying a discrepancy between those who manage disease and those who suffer from it.

## Patient-Centered Outcomes Research Institute (PCORI)

This nonprofit, nongovernmental organization was authorized by Congress in 2010 with the mission of "promoting evidence-based information that comes from research guided by patients…." One recent joint PCORI/academic effort sought to identify barriers and generate solutions for cultivating a research-ready dialysis community by convening patients, dialysis staff, researchers, and dialysis organizations in a workshop (4). Some attendees also generated a video explaining research to target patient audiences (available at the University of North Carolina website, http://news.unchealthcare.org/som-vital-signs/2019/june-13/unc-researchers-featured-in-pcori-ada-video-for-international-conference?utm_source=vs-email&utm_medium=email&utm_campaign=24). Patients and researchers may view the PCORI website to participate in PCORI-sponsored efforts in nephrology.

## Workgroups to Identify Renal Endpoints

Several data-driven efforts have been underway to assess potential trial endpoints across many indications in CKD, resulting in at least 8 publications since 2014 (5–12). Two papers reflecting the inclusion of CKD patients in multi-stakeholder workgroups were published in 2018, recommending and defining trial endpoints for vascular access and HD catheters (6, 10). These papers were the output of workgroups from the Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology (ASN) and FDA, which has invited patients onto subsequent workgroups that define endpoints in other indications. The NKF has hosted 3 workshops since 2008, examining albuminuria, proteinuria, and glomerular filtration rate (GFR) decline and slope as endpoints. Notably, patients participated in the most recent one in 2018, which convened the FDA and European Medicines Agency with researchers and nephrologists.

## Patients' Reaction to Published Research

In January 2018, *CJASN* introduced a new editorial section, termed Patient Voice, where invited patients share their response to research published in the same issue. Additionally, the ISN Advancing Clinical Trials (ACT) initiative convened a Patient Engagement Workgroup. The initial effort will be to invite patients to provide perspectives on selected publications highlighted on the ISN Global Trial Focus website. These perspectives are important, as they should help guide research planning and areas of focus. We need to remember that without patient participation in these studies, there would be no data generated and no papers to publish. The following are the words of one patient but a sentiment echoed by many:

***"Sponsors should acknowledge us with a thank you note and share study updates throughout and the study results at the end."***

—Janine Reed

Considering the large investment in time and emotional and physical energy that patients commit to research when agreeing to participate in a study, this is a small and easy-to-fulfill request.

## NKF's Patient Network

This will be the first of its kind CKD Patient Registry in the United States where patients can register and enter their health data. This information will be linked to electronic medical records where possible. Among the aims of the registry will be to collect patient-reported insights on their CKD, facilitate patient-centered trial designs, and expand patient participation in trials. There is also the potential for post-trial surveillance so that patient data can be continuously captured even after the trial ends. Providers across the spectrum who touch CKD patients (i.e., primary care, diabetologists, cardiologists, and nephrologists) should promote enthusiasm for this registry (planned launch, fall 2020) and encourage patients to sign up so its benefits can be fully realized.

***"The trial didn't go great for me, but it was enriching to contribute something back, and my experience gives some value, since the drug will be tested in other kidney diseases too."***

—Jesse Morales

Please don't hesitate to promote the voices of the rising chorus of CKD patients who have been waiting long enough. Explore ways to seize a culture change in catalyzing nephrology to be more research ready, whether through participation in a trial or any one of the current efforts that employ patients' insights to ultimately improve our goal in finding more therapies. Change starts with grass-roots efforts that can be as simple as wearing buttons on white coats of study staff to encourage patients to "Ask me about a clinical study" and empower patients to serve as peer mentors to other patients by sharing their research-related experience to encourage others. Whether or not you act as an investigator, start the discussion in your clinic today. Inject a sense of urgency about the importance of clinical research into your discussions with patients, because in the words of my research colleagues: "Patients can't wait, and neither should we." ■

*Acknowledgment: I would like to thank the many patients who have taken the time to share their journey and thoughts with me, which include many who are not directly quoted here but have opened my eyes to issues I would not have otherwise recognized.*

*Barbara S. Gillespie, MD, FASN, is vice president, Therapeutic Head of Nephrology, Covance, and adjunct professor, Division of Nephrology and Hypertension, University of North Carolina.*

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

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

# Detective Nephron

**Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.**

**Nephron** What do you have for us today, my dear apprentice?

**Henle** I have a 67-year-old white man with a history of type 2 diabetes mellitus, with an elevated hemoglobin A1c (8.1%) and a history of moderate hypertension, who is now here with proteinuria.

**Nephron** Stop… why are you talking like a textbook today?

**Henle** Trust me; you are going to love this one!

**Nephron** It better be a case of some exotic chemotherapy causing thrombotic microangiopathy (TMA) and not diabetic nephropathy—although sodium-glucose cotransporter-2 (SGLT2) inhibitors have made diabetic nephropathy interesting as well. Nevertheless, go on!

**Henle** (*curious*): Hmm.... what is with everyone and TMA these days? Getting back to the case, he was in his usual state of health until a few months ago, when he noticed his blood pressure getting worse, requiring more than two medications for management.

**Nephron** What was his creatinine 6 months ago?

**Henle** It was 0.7 mg/dL 1 year ago and 1.3 mg/dL 6 months ago.... thank you for your interruption. Also, his urine albumin-to-creatinine ratio 3 months ago was 0.3 g/g.

**Nephron** (*angry*): And let me guess: now the creatinine is 1.6 mg/dL, and he has proteinuria of 5 g/24 h.

**Henle** (*surprised*): There you go again—you are stealing my thunder. Yes, and yes, but it is 6 g/24 h. You are off slightly. Only trace edema on examination. Cholesterol is stable, and serum albumin is slightly low at 3.4 g/dL.

**Nephron** Is there any hematuria?

**Henle** Yes, a bit, and some red blood cell casts as well. Hmm….

**Nephron** I am sure they did serologies before they called you.

**Henle** Better yet, I even got you a kidney biopsy!

**Nephron** (*startled*): Stop right there. Before we go any further, let me summarize this. You have a diabetic patient with worsening renal function and rising proteinuria. Wait... I can't say "renal" any more—kidney function.

**Henle** (*wondering to himself about quick decision by Nephron*): Yes; correct. By the way, no new medications, such as quinine, nonsteroidal anti-inflammatory drugs, hydralazine, or protein pump inhibitors. Just on the usual: glipizide, metformin, lisinopril, and amlodipine. Of course, no SGLT2 inhibitors.

**Nephron** Oh, oh, no! This is a good one. Glad you brought this case to me. I am assuming this is paraproteinemia related, since you think I am reading too much onconephrology these days.

**Henle** (*trying to remember*): Ha-ha… perhaps not. The kidney biopsy was done, and it showed….

**Nephron** (*jumping in*): TMA.

**Henle** (*with a smirk*): Hmmm. You are too much. Stop interrupting. The mesangial areas showed diffuse and focal nodular expansion by matrix material with segmental mesangiolysis and microaneurysm formation. A few glomeruli displayed variable ischemic changes. The arteries displayed moderate intimal fibrosis, and the arterioles showed prominent afferent and efferent hyalinization. Immunofluorescence was negative for significant glomerular immune complex deposition. Electron microscopy revealed glomerular basement membranes with global thickening. Segmentally, there was subendothelial widening with segmental glomerular basement membrane duplication and mesangial cell interposition. Focally, within these areas there was an accumulation of flocculent and electron-lucent debris with mild layering of new basement membrane material. Basically, the pathologic findings showed renal TMA in a background of diabetic nephropathy.

**Nephron** (*shocked*):This is impressive! What are you: a poetic renal pathologist? And thank you for reading the pathology report verbatim. You could have saved a lot of words and ink and said, "diabetic nephropathy with superimposed TMA." I trust you.

**Henle** (*jumping in*): As I mentioned earlier, no secondary cause—no cancer found, no rheumatologic disease. No paraproteinemia to explain the TMA finding. To my knowledge, diabetes should not do this. With the diagnosis of TMA, a review of peripheral blood smears and laboratory parameters was undertaken. Peripherally, there were no schistocytes, and the vitamin B12 level was 770 pg/mL. The von Willebrand factor-cleaving protease (ADAMTS13) was 110% of reference range activity, ruling out any ADAMTS13 deficiency and thrombotic thrombocytopenic purpura. No diarrhea was noted, which suggests that there was no typical hemolytic uremic syndrome, or evidence for the presence of Shiga toxin. The platelets remained in normal range despite the drop in hemoglobin over the course of the year.

**Nephron** Good work, apprentice, on your search for the cause of TMA. We often forget to do that. How do you categorize TMA?

**Henle** (*not sure*): Well, most of the world likes to call this stuff hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), or atypical HUS. I think the better way is to define it by the pathophysiology, such as ADAMTS13-mediated TMA, complement-mediated TMA, Shiga toxin–mediated TMA, drug-induced TMA, metabolism mediated (cobalamin deficiency), coagulation mediated, and finally secondary systemic diseases–associated TMA. Interestingly, there are two mechanisms of drug-induced TMA: immune mediated (quinine) and direct endothelial injury. Some of the chemotherapies and targeted therapies might fall into that category.

**Nephron** Perfect! Pathobiology-based discussion is always the best way to discuss anything, rather than names like TTP, HUS, and atypical HUS.

**Henle** But here I am confused. We checked for all potential causes in our patient. Complements were normal, but in complement-mediated TMA 60% of patients might have normal complements. The entire complement cascade workup was performed, but—you know—I will get the results in 2022.

**Nephron** (*interrupting*): Is there anything on his physical examination?

**Henle** Nothing specific except for some trace edema bilaterally in the lower extremities. His blood pressure was high at 150/90 mm Hg.

**Nephron** Use of tonic water? Because that might contain quinine, which leads to an immune-mediated TMA.

**Henle** Perhaps this patient has a complement cascade factor deficiency and a "second hit" occurred. But what is that second hit?

**Nephron** Any diabetic neuropathy or retinopathy?

**Henle** Yes, diabetic retinopathy. Big deal.…

**Nephron** Let's go to his bedside

***Henle and Nephron exit.***

**Nephron** Sir, we have a question for you. Do you get any specific injections for your diabetic eye disease?

**Patient** "Yes, Avastin."

***Henle responds with shock.***
***A few hours later:***

**Henle** He had experienced progressively blurry vision and was seen by an ophthalmologist, who prescribed intravitreal vascular endothelial growth factor (VEGF) inhibitor therapy a year ago. He was receiving intravitreal injections of bevacizumab (Avastin) (1.25 mg) in both eyes (2.5 mg injected total) every 2 months until he had a more severe episode of recurrent macular edema. This necessitated switching to monthly intervals. This was also deemed necessary because of the possible development of early central retinal vein occlusion, which could impair vision. According to this dosing schedule, the patient received bevacizumab at a total of 20 mg in both eyes to date.

**Nephron** Fascinating information. So, you think this intravitreal bevacizumab can cause renal-limited TMA? If so, you are going to give some retina specialists a heart attack.

***Henle, puzzled, leaves the room. He returns a day later.***

**Nephron** And?

**Henle** The US Food and Drug Administration never approved bevacizumab for intravitreal use but did approve aflibercept (Eylea) and ranibizumab (Lucentis) for intravitreal use. The label inserts asserted that the serum drug levels with intravitreal injections were 200-fold lower than the levels achieved by systemic administration, and thus VEGF inhibition would be minimal. So why do we get renal TMA?

**Nephron** (*jumping in*): New data have shown that intravitreal absorption could be significant (≥50% inhibitory concentration) and result in very significant inhibition of systemic VEGF for days to weeks after intravitreal injections. Ranibizumab may be considered as a lower-risk option for diabetic retinopathy in patients with proteinuria because of lower serum levels, shorter t½, and much less VEGF disruption.

**Henle** (*surprised*): There are now published cases that show worsening hypertension, proteinuria, and glomerular disease after intravitreal VEGF inhibition. Kidney biopsy findings range from renal-limited TMA, collapsing glomerulopathy, and FSGS. Most of these findings are in the background of diabetic nephropathy.

**Nephron** The pattern of injury is exactly what is expected with VEGF blockade systemically. Temporal clarity is important to make these associations. An important clinical lesson from these cases is that diabetes per se cannot be blamed for the abrupt rise in serum creatinine and rapid rise in proteinuria.

**Henle** Assumptions are bad in medicine. A systematic process is important for a differential diagnosis in every case, and asking about nontraditional medications is now more important in medicine than ever.

**Nephron** These are also useful teaching cases to dissect the causes of nondiabetic glomerular disease in diabetic patients. These cases are extremely challenging to diagnose, and it is useful to consider the role of intravitreal VEGF blockade in every diabetic patient. Retina specialists should consider measuring urine protein in addition to monitoring blood pressure to document the effect of VEGF depletion on the kidney. Would they do that? I assume that we will see more of this to come.

**Henle** The patient was instructed to talk with his retina specialist. But balance is important in medicine. Loss of vision is far more important to some patients than having to use dialysis. Continuing the agent was the final decision made by this patient. His serum creatinine is now 3.4 mg/dL.

**Nephron** Well done, apprentice. Keep an open mind; never assume. Make sure you have looked at all aspects of your differential diagnosis. Just because someone has a history of diabetes does not mean that the rising creatinine and proteinuria is from diabetic nephropathy. And it is cool that I got to discuss TMA. I think that it is a fascinating diagnosis.

**Henle** (*with a wink*): Do you think hypertension causes TMA or TMA causes hypertension?

**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 Donald and Barbara Zucker School of Medicine at Hofstra/Northwell.* *Special thanks to Dr. Ramy Hanna, assistant professor of medicine at UC Irvine, California, for the case and editorial assistance. Thanks to Dr. Rimda Wanchoo, associate professor of medicine at Zucker School of Medicine at Hofstra/Northwell, for her editorial assistance.* *Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.*

# Taking on Racism

## ASN Panel Addresses Next Steps for Dismantling Systemic Racism in Nephrology

By Bridget M. Kuehn

During ASN's recent webinar on Going Beyond the Statement: Dismantling Systemic Racism in Nephrology, a panel of nephrologists delved deep into the ways structural and overt racism affects patients and the profession and what to do about it (1).

"We hope and envision this will be the start of an important ongoing conversation that engages the broad community of our organization," said ASN's Secretary-Treasurer Keisha Gibson, MD, MPH, who moderated the panel.

Nephrologists and ASN must play a greater role in changing policies, practices, and beliefs that prevent Black, Indigenous, and other people of color from achieving their full potential, said panelist Will Ross, MD, Associate Dean for Diversity and professor in the Division of Nephrology at Washington University School of Medicine in St. Louis. Housing, transportation, and nutrition policies all have major impacts on health, particularly among disenfranchised and under-resourced populations, he said.

"The ASN has realized we can effect change," he said. "We can advocate for those policies; it is in our purview." Ross argued for more use of rigorous implementation of science to ensure the use of evidence-based interventions to reduce health disparities.

Panelist J. Kevin Tucker, MD, director of the Brigham and Women's Hospital/Massachusetts General Hospital Joint Nephrology Fellowship Program, said it was the first time in his 25-year career in nephrology that he felt the profession was having this difficult discussion. He noted that often people dance around the topic because it is so uncomfortable to talk about race and racism with colleagues.

"We have to be willing to have difficult conversations," Tucker said.

### Advocating for equity

The ASN Council and ASN Diversity and Inclusion Committee (renamed the Diversity, Equity, and Inclusion Committee) have begun drafting a road map for addressing systemic racism in nephrology and will dedicate two of its eight mission-based committees to this work starting in 2021, Gibson said. The Health Disparities and Social Determinants of Health Committee will focus on improving social determinants and health disparities and the combined effects of COVID-19 and high-profile acts of racism on patients. The Diversity, Equity, and Inclusion Committee will tackle institutional racism in academic medicine, patient care, research, education, and administration at healthcare institutions. A joint ASN-National Kidney Foundation Task Force has also been created (2) to reassess the use of race in diagnosing kidney disease, as a growing number of institutions around the country eliminate race in estimated glomerular filtration rates (3).

"Success of these efforts will require that this work permeates the entire fabric of our organization," Gibson said, noting that the committees will work closely with the Council and throughout the organization.

### Battling bias

Physicians and institutions also need to consider how their own attitudes or practices might disadvantage people of color. Dana Mitchell, MD, a private-practice nephrologist and chief executive officer of the Global Kidney Center in Houston, Texas, recommended implicit bias training for clinicians and education about other cultures and people to empower clinicians to have better patient interactions.

Overt or implicit biases can come in many forms and may limit patient care options. Gibson noted that her aunt was almost denied access to peritoneal dialysis because her nephrologist was worried that her high school-level education would limit her ability to do home dialysis, but Gibson was able to advocate for her. Criteria for transplant might also disadvantage patients working lower-paying jobs. Vanessa Grubbs, MD, MPH, spoke about a patient who was almost denied a transplant after he was late for dialysis because he could not leave his job as a dishwasher early without fear of being fired. Grubbs is associate professor at the University of California, San Francisco, and a living kidney donor. "If anything, that's all the more reason for him to get a transplant," she said. "With a kidney transplant, he'd be able to work and sustain himself without fear of being penalized for having kidney failure."

A new approach is also needed for the way researchers and journals present studies about health disparities, Grubbs argued. She said they need to stop presenting race as a biological construct and instead acknowledge it as a social construct. Too often, she said, researchers try to attribute health disparities to unknown genetic factors that may not exist.

"We need to stop talking about race as a risk factor, rather than racism as a risk factor," Grubbs said. She recommended that researchers, reviewers, and editors apply new standards for publishing on health inequities, outlined in a *Health Affairs* blog post authored by health equity advocate Rhea Boyd, MD, MPH, and colleagues (4).

### Representation matters

Greater representation of Black, Latino, Indigenous, and other under-represented groups in nephrology is key to improving care for patients, panelists noted.

There is evidence that patients receive better care from physicians who look like them, Gibson said. Yet only 3.8% of nephrology residents are Black (5), and data from the Association of American Medical Colleges show only 5.3% of medical trainees are Latino. Less than 0.3% are Indigenous (6).

Washington University School of Medicine's Ross said having emeritus professor of nephrology Aubrey Morrison, MBBS, as a renal physiology instructor was pivotal to his path to nephrology. Many participants echoed the importance of having nephrology mentors who looked like them in attracting them to the field.

Tucker also emphasized a need to build a better pipeline for under-represented students into medicine and nephrology starting with kindergarten through high school education by addressing school quality and growing resegregation. He also recommended recruiting talent from junior colleges or historically Black colleges and universities (HBCUs).

"We have to look at expanding the pipeline by trying to find talent in places we don't often look," he said. The assurance that nephrology salaries are competitive with other specialties is also essential to recruiting under-represented physicians who are less likely to come from wealthy families and are more likely to carry substantial student loan debt.

### Addressing racism's effects in academic institutions

Grubbs said it is also important to address racism at academic institutions that may hinder admission or advancement for Black trainees. She noted that admissions criteria too often "favor the already highly favored." For example, when she was interviewed for medical school, she was asked about her volunteer work, but she hadn't volunteered because she was working three jobs. The interviewer did not ask about her job experience. Ross recommended that medical school and residency admissions committees use holistic review processes (7) that take into account applicant experiences and attributes in addition to more traditional metrics, such as test scores or grades.

Minority faculty and trainees need to be supported when they face racism in practice, either from within the institution or from patients, Tucker said. He cited an essay by a former Brigham and Women's resident about dealing with a racist patient and not feeling supported (8).

Academic institutions also need to revamp promotion and tenure policies to reward the work of physicians from under-represented groups. For example, minority faculty are often asked to help serve on admissions committees to help improve recruitment or to serve on diversity or inclusion committees, but this work may not be rewarded in promotion or tenured decisions.

"If you want to retain Black faculty, you should pay us," Grubbs said.

Tucker said all faculty, not just an under-represented minority faculty, should be engaged in health equity and inclusion work. "It makes us as a field, as physicians, and as a medical community better if we are all engaged," he said.

Although efforts to build the ranks of under-represented physicians are in progress, Ross argued for greater use of advanced practice nurses from under-represented groups to provide culturally appropriate care to communities of color. He also recommended the use of community health workers who can help patients access basic necessities, such as food and housing, and also navigate the health system.

ASN President Anupam Agarwal, MD, promised to make addressing racism a priority.

"I'd like to commit as ASN president that this is a top priority for ASN within our organization to ensure that all aspects of systemic racism are completely dismantled within our society and going forward for every level, whether it's trainees, clinicians in private practice, faculty, and academia," Agarwal said. "We really need to address this head on. We cannot do this alone. We need your help." ■

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# LOOK BEHIND THEIR STONE AND GET IN FRONT OF A SERIOUS CONDITION[1]

A kidney stone may be a sign of a metabolic stone disease, such as primary hyperoxaluria type 1 (PH1), that can result in progressive renal impairment.[1-3] So, any unusual presentation among stone formers merits further investigation.[1]

Once suspected, confirming PH1 with genetic testing may reduce an often lengthy delay in diagnosis, which may improve the overall outcome.[4-7]

BEHIND THE™ STONE

**Consider genetic testing for your patients when you suspect a metabolic stone disease.[1]**



Alnylam® PHARMACEUTICALS

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# Spectrum of Choices Urged for People with Kidney Failure

By Ruth Jessen Hickman

A recent article in *The New England Journal of Medicine* emphasizes the ethical importance of giving well-educated patients true choices when it comes to management of advanced chronic kidney disease, especially regarding potential dialysis cessation (1). Through coordination with palliative care specialists, nephrologists can offer patients a wide variety of options to help meet their specific personal needs and goals.

Although a vital, life-saving therapy, dialysis can come with side effects and significant psychological, social, and financial pressures on patients. Solomon Liao, MD, is director of palliative care at the University of California, Irvine, and one of the paper's coauthors. He points out that dialysis, especially as pursued in traditional models, may not be the right choice for some elderly and frail patients with multiple medical morbidities, who may not live much longer even with dialysis.

Yet the choice to end dialysis—or to not initiate it in the first place—must be made thoughtfully, by exploring the variety of available options in a non-pressured way, as death may come fairly quickly after dialysis cessation of hospitalized patients.

Kamyar Kalantar-Zadeh, MD, MPH, PhD, a coauthor of the paper, noted that one of the worst times to begin this conversation is when patients with kidney failure are hospitalized and critically ill. Kalantar-Zadeh is a professor of medicine and chief of the nephrology division at the University of California, Irvine.

## Financial incentives could impede clear decision-making

Because of changes made through the Affordable Care Act, hospitals have financial incentives to reduce the length of hospital stays and prevent hospital readmissions within 30 days of a previous hospitalization. This is especially pertinent to people with kidney failure, who often have multiple significant medical morbidities.

The authors expressed concern that these and other factors might lead to undue pressure to get some people with kidney failure off dialysis. The COVID-19 pandemic heightens these concerns, as nephrologists may feel pushed to get their dialysis patients out of needed ICU beds via abrupt dialysis withdrawal and hospice initiation.

"I worry that dialysis patients will become a lower priority," Kalantar-Zadeh said. "We need to make sure that some of these perverse incentives and other important goals do not cause a conflict of interest to compromise patient choice. Patients should not feel forced to stop dialysis, in the same way that patients shouldn't feel pressured to start dialysis."

Kalantar-Zadeh and colleagues noted that when it is discussed, the decision to continue dialysis is often presented in stark opposition to comfort treatments. Yet many integrated options exist that may better meet many patients' needs. For some patients, conservative therapy such as dietary and lifestyle interventions, pharmacotherapy, and active symptom management can help preserve the kidneys and delay the need for dialysis.

Gradual transition to dialysis is another option, perhaps starting at less than standard dialysis frequencies. An expanded palliative care role could be an option for some patients, with patients managed by palliative care professionals both during hospitalization and as outpatients. Dialysis frequency and intensity can also be decreased gradually with a primary aim of reducing symptoms in conjunction with hospice care.

But patients often do not have an idea of the spectrum of options available to them, thinking that standard dialysis is the only choice other than total care cessation. Even other health professionals may lack the understanding of options held by nephrologists, one of the reasons it is critical that nephrologists be included in any discussion of dialysis cessation or transition plans to less aggressive intervention.

Some nephrologists might not begin the discussion early enough, when there is still time for patients and their family members to ask questions, digest the information, and consider their personal goals.

"Physicians fear that if they bring up these issues patients will get mad at them or pull away," said Liao. "But the medical literature shows that patients and families actually appreciate it when doctors bring up these issues." He emphasized the need to have such conversations early in treatment, ideally at dialysis initiation, to be revisited as needs and goals change.

With COVID-19, it is even more important for pa-

tients with kidney failure to have plans about how they would like to be managed in the hospital if they do become sick. Such conversations, Liao noted, can reduce patient anxieties in a turbulent time.

Nephrologists should not hesitate to work in collaboration with palliative doctors, who are expertly positioned to help with symptom management and integrative care approaches. Liao emphasized that every home hemodialysis patient should have a palliative medicine team following their care as well.

Various administrative issues and structural barriers can make collaboration between nephrologists and palliative care professionals challenging, such as credentialing and reimbursement issues at joint clinics. However, academic centers can facilitate exchanges to educate nephrologists about relevant palliative care perspectives and vice versa.

The main goal remains a shared one: making sure patients are given choices, truly informed choices, that uphold their overall health, dignity, and personal hopes. ■

*Ruth Jessen Hickman, MD, is a freelance medical and science writer in Bloomington, IN.*

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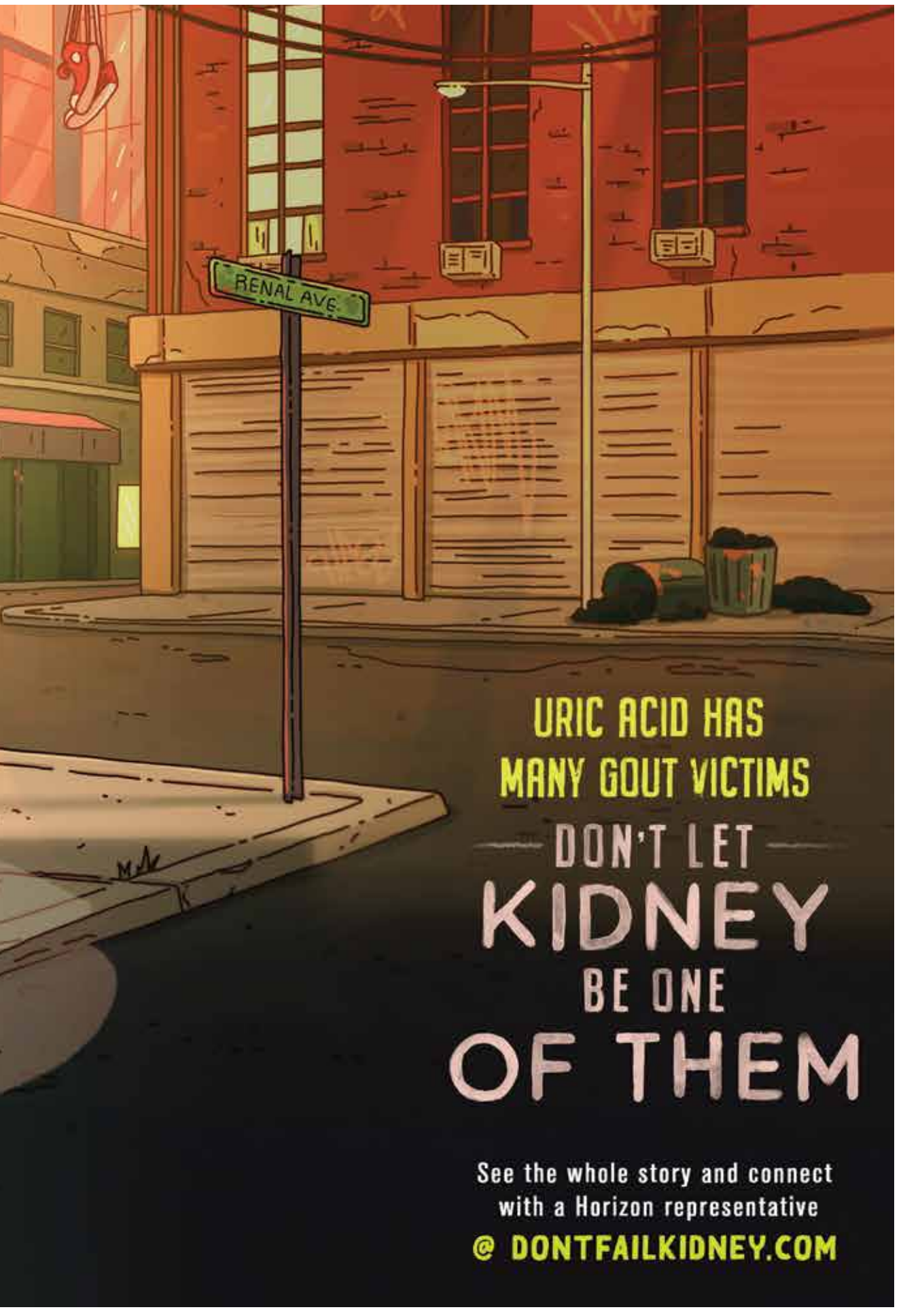


# Including People with Kidney Diseases in COVID-19 Trials: KHI Identifies Opportunities

People with kidney diseases should be included in COVID-19 clinical trials—especially vaccine candidates—as a crucial measure that increases "trust in the science and development process for the vaccine among kidney patients," according to a recent statement of the Kidney Health Initiative (KHI). Including people with kidney diseases and kidney failure, as well as those with undiagnosed reduced kidney function, will ensure the efficacy and safety profiles of any vaccine candidate will be understood in people with kidney diseases, the statement says.

The KHI statement builds on an earlier statement that encouraged inclusion of people with kidney diseases in all COVID-19 clinical trials. The follow-up statement identifies ways to increase enrollment of these populations. "We found a broad range of inclusion and exclusion criteria of people with kidney diseases after reviewing the published protocols of the vaccine candidates currently in phase 3 trials," said Raymond Harris, MD, FASN, co-chair of KHI and its COVID-19 response team. "It is important that we have data on this special population prior to widespread dissemination of a vaccine to ensure that those with kidney diseases who choose to be vaccinated can do so safely and obtain maximum preventive benefit."

People with kidney diseases are a large part of the general population, at 37 million in the US and 700 million worldwide, and have an increased risk for developing severe complications from infection by SARS-CoV-2, the virus responsible for COVID-19. Minority populations and those impacted by social determinants of health represent a significant and disproportionate percentage of the 15% of the US population with kidney diseases, "further contributing to the disparities observed with the distribution of COVID-19 infection rates," according to the KHI statement. "In addition, individuals with severe chronic kidney disease or kidney failure have an increased risk of exposure to the virus as they are disproportionately hospitalized or are in long-term care facilities."

US Food and Drug Administration guidance encourages the inclusion of racial and ethnic minorities most at risk for infection, as well as elderly patients and those with medical comorbidities in COVID-19 vaccine development (1). KHI notes that all these groups encompass people with kidney diseases and calls upon all sponsors and investigators involved in current or planned COVID-19 vaccine trials to include this population, especially in phase 3 trials. Nephrologists are urged to reach out to their clinical trial colleagues to identify and encourage eligible kidney patients to participate in these trials.

Patient organizations that are members of KHI will be including resources that inform and educate their members on how to participate in COVID-19 vaccine trials, in consultation with their nephrologist and care team, within their ongoing clinical trial campaigns. "Participation will maximize our knowledge and ultimately benefits any public health vaccination campaign for people with kidney diseases," KHI states. ■

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# Study Strengthens Case for Drug-Coated Balloons for Dysfunctional AV Fistulas

By Ruth Jessen Hickman

A recent study in the *New England Journal of Medicine* may shift the balance for clinicians who are considering the use of drug-coated balloons (DCBs) for treating dysfunctional dialysis arteriovenous (AV) fistulas (1). The improved rates of fistula patency and reassuring data on safety underscore the potential of this technology to improve patients' lives and reduce healthcare expenditures.

Percutaneous transluminal angioplasty with standard balloons is currently the recommended treatment for dysfunctional hemodialysis fistulas. A balloon is inserted into the dialysis shunt and inflated in a stenotic area to stretch the vessel and restore normal flow. Although highly effective at restoring immediate patency, this approach is prone to restenosis and recurrent dysfunction, with around 50% or more of patients needing repeat intervention within 6 months (1).

"Unfortunately, these patients on lifelong hemodialysis might at any time be told, 'Today is the day your dialysis access isn't working anymore; you have to go have another procedure on it,'" said Robert A. Lookstein, MD, professor of radiology and surgery at the Icahn School of Medicine at Mount Sinai in New York City and principal investigator on the study.

In contrast to the balloons used in standard angioplasty, DCBs are coated with a drug, typically the anti-proliferative agent paclitaxel (used in much smaller amounts compared with its applications in cancer chemotherapy). The drug elutes from the balloon into the narrowed area of the blood vessel during the procedure, helping prevent future restenosis.

Currently, such DCBs are commonly used to treat symptomatic femoropopliteal peripheral artery disease and help prevent future restenosis and reinterventions, and a large body of evidence now supports their use in that application. Yet a meta-analysis in 2018 of such devices raised concerns of higher mortality rates in patients receiving DCBs (2), resulting in the convergence of a Food and Drug Administration Safety Panel to examine the issue (3).

These safety concerns helped slow the adoption of such products for AV fistulas. Of note, a 2019 meta-analysis did not show any difference in safety between patients with AV fistula lesions treated with DCBs compared with those treated via standard balloons (4). The issue is complicated by the multiple DCBs available, which may or may not have identical effects.

Scott O. Trerotola, MD, is the Stanley Baum Professor of Radiology and professor of radiology in surgery at the University of Pennsylvania School of Medicine in Philadelphia, PA. He was the principal investigator of a 2018 study that examined a different DCB device, designed by Lutonix, in the management of dysfunctional AV fistulas (5). Although the team demonstrated equivalent safety between the DCBs and standard angioplasty (at 6 months and 2 years), the study did not meet its primary endpoint. However, it did have some positive findings, including improved patency at 9 months, significantly longer time to reintervention, and significantly fewer reinterventions at 2 years for those receiving DCBs.

"Until this new paper came out, there was this equipoise," Trerotola said. "We had some positive studies and some negative studies, coupled with that mortality question. Now you've got this compelling study with great results and really meaningful numbers. This puts the wind back in the sails of the DCBs in this application."

## Medtronic study

The prospective, patient-blinded, randomized trial enrolled 330 patients, 170 of whom received treatment via the DCB. Patients had mature, upper extremity AV fistulas with either new or (nonstented) restenotic lesions that were at least 50% blocked. The global trial included data from 29 international sites (1).

The study met its primary endpoint of improved patency of the target lesion at 6 months in those who received a DCB. "When the outcomes were specifically looked at with respect to the initial stenosis, 20% more patients were patent at 6 months that were treated with the DCB as compared to those treated with standard angioplasty," Lookstein said. That amounted to 82.2% (125 of 152) of patients who were patent at 7 months on the DCB vs. 59.5% (88 of 148) of those who received standard angioplasty.

Moreover, analysis of secondary endpoints demonstrated an almost 25% benefit in patency for the entire dialysis access for those patients treated with DCBs. "If you look at the number of repeat procedures needed to maintain function of the entire dialysis access at 6 months out, this was reduced by over 55%," Lookstein said.

Among the potential reasons for different trial outcomes, Lookstein noted that the Lutonix balloon contains a paclitaxel dose of 2 μg/mm$^2$, whereas the Medtronic balloon carries a dose of 3.5 μg/mm$^2$ (5). Differences in DCB inflation duration and thus drug exposure time may have played a role. The two devices also have different excipient characteristics. Trerotola also pointed out that with one-third of participants from Japan, the Medtronic study did not have exactly the same population, including a noticeably different ratio of upper-arm fistulas to forearm fistulas.

"At this point, there might or might not be a difference between the two devices," Trerotola said. He added that he would be interested to see a randomized trial of the two devices in this context to address the question directly.

## Remaining research questions

Many other research avenues remain to be explored for DCBs. Lookstein noted that Medtronic is planning to perform a postmarket registry. "It will prospectively evaluate the efficacy and safety of the technology in the use of AV grafts as well as in patients who have had previous stents placed in their dialysis fistulas." The team is also hoping to evaluate whether DCBs might play a role in addressing central venous stenoses, which are common in this population, due to previous hemodialysis catheter placement.

"I think the postmarket registry data will allow us to generate data sets that will help us determine which patients are ideally suited for this technology compared to others," Lookstein said. "We are optimistic that we are going to be able to expand the indication to a broader spectrum of the population who have end stage renal disease."

## Practical barriers

Lookstein noted that practically, it should be easy for specialists to integrate DCBs into clinical use for AV stenosis if their clinical judgment supports it. Most hospitals already have similar balloons on the shelf to address arterial blockages in the leg. "It would really just be an expansion of their current inventory to allow the technology to be brought in to treat patients with dialysis dysfunction."

However promising, it is unclear whether DCBs will now be used more commonly in this application. Although standard angioplasty is still the most common method of managing AV fistula stenoses, covered stents (also known as stent grafts) are sometimes used instead (6). Data from some randomized trials in AV fistulas have shown improved patency of the lesion and access circuit with stent grafts compared with standard balloon angioplasty (7). Partly because of this, reimbursement rates are higher for such stent grafts compared with standard angioplasty.

Both Trerotola and Lookstein pointed out that although stent grafts are effective for restoring short-term patency, they can eventually become restenotic and can make future surgical revision more difficult. Stents can fracture and embolize, erode through the skin, or become infected. In effect, by utilizing a stent graft instead of angioplasty with a DCB, one may be opting for short-term patency in exchange for longer-term issues.

"The big problem for the drug-coated balloons is that there is no payment for them," Trerotola said. Yet the use of DCBs might provide a huge savings to the healthcare system in terms of long-term improved dialysis access patency and a reduction in future procedures. Trerotola exhorts, "I hope this paper will be a burning message for [the Centers for Medicare & Medicaid Services] to do something about this reimbursement issue for clinicians."

"The reason that I am so enthusiastic about this technology is that it is a procedure that all vascular specialists understand and find easy to use," concluded Lookstein. "I think that it is a very simple, inexpensive technology that does not force the patient to have a permanent implant in their body that clearly benefits our patients with end stage renal disease."

*Ruth Jessen Hickman, MD, is a freelance medical and science writer in Bloomington, IN.*

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**A1C reductions**
including weight loss, as add-on to metformin in adult patients like Pam*

***JARDIANCE is not indicated for weight loss or reduction of systolic blood pressure.[3]**

## Proven CV benefit

**38% RRR in CV death**
in adult patients with T2D and established CVD†
2.2% absolute risk reduction
HR=0.62 (95% CI: 0.49-0.77)

## Convenient once-daily dosing

**Can be taken with or without food in the morning**
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†Established CV disease consisted of peripheral artery disease, coronary artery disease, or a history of MI or stroke.[6]

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### JARDIANCE is taken with or without food in the morning

- No fasting requirements before or after dose

### No dose adjustment recommended when coadministered with commonly prescribed medications

- No dose adjustment needed in patients with eGFR ≥45 mL/min/1.73 $m^2$

- In patients with volume depletion, correcting this condition prior to initiation of JARDIANCE is recommended
- A lower dose of insulin or insulin secretagogues (eg, sulfonylureas) may be required to reduce the risk of hypoglycemia when JARDIANCE is used in combination with these agents
- JARDIANCE is contraindicated in patients with a history of serious hypersensitivity to empagliflozin or any of the excipients in JARDIANCE, severe renal impairment, end-stage renal disease, or dialysis

**Dosing in patients with renal impairment:**

- Glycemic efficacy of JARDIANCE is dependent on renal function, which should be assessed prior to initiation of JARDIANCE and periodically thereafter
- Should not be initiated if eGFR is <45 mL/min/1.73 $m^2$
- Should be discontinued if eGFR is persistently <45 mL/min/1.73 $m^2$
- Reduction in risk of CV death was consistently observed among patients, including those with eGFR <60 mL/min/1.73 $m^2$

**To learn about how JARDIANCE could give your patients the power to do more, visit JARDIANCE.com**

## INDICATIONS AND LIMITATIONS OF USE

JARDIANCE is indicated to reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus and established CV disease.

JARDIANCE is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

## IMPORTANT SAFETY INFORMATION

**CONTRAINDICATIONS:** History of serious hypersensitivity to empagliflozin or any of the excipients in JARDIANCE, severe renal impairment, end-stage renal disease, or dialysis.

## SELECT WARNINGS AND PRECAUTIONS

**Hypotension:** Empagliflozin causes intravascular volume contraction and symptomatic hypotension may occur. Before initiating JARDIANCE, assess and correct volume status in the elderly, and in patients with renal impairment, low systolic blood pressure, or on diuretics. Monitor for hypotension.

**Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. Patients who present with signs and symptoms of metabolic acidosis should be assessed for ketoacidosis, even if blood glucose levels are less than 250 mg/dL. If suspected, discontinue JARDIANCE, evaluate, and treat promptly. Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing JARDIANCE for at least 3 days prior to surgery.

**Please see additional Important Safety Information and Brief Summary of Prescribing Information on following pages.**

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**Acute Kidney Injury and Impairment in Renal Function:** Empagliflozin causes intravascular volume contraction and can cause renal impairment. Acute kidney injury requiring hospitalization and dialysis has been identified in patients taking SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age. Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury. Consider temporary discontinuation in settings of reduced oral intake or fluid losses. Monitor patients for signs and symptoms of acute kidney injury. If it occurs, discontinue JARDIANCE and treat promptly.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Before initiating JARDIANCE, evaluate renal function and monitor thereafter. More frequent monitoring is recommended in patients with eGFR <60 mL/min/1.73 $m^2$. Discontinue JARDIANCE in patients with a persistent eGFR <45 mL/min/1.73 $m^2$.

**Urosepsis and Pyelonephritis:** Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been identified in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate for signs and symptoms of urinary tract infections and treat promptly.

**Hypoglycemia: The use of JARDIANCE in combination with insulin or insulin secretagogues** can increase the risk of hypoglycemia. A lower dose of insulin or the insulin secretagogue may be required.

**Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Serious, life-threatening cases requiring urgent surgical intervention have occurred in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue JARDIANCE.

**Genital Mycotic Infections:** Empagliflozin increases the risk for genital mycotic infections, especially in patients with prior infections. Monitor and treat as appropriate.

**Hypersensitivity Reactions:** Serious hypersensitivity reactions have occurred with JARDIANCE (angioedema). If hypersensitivity reactions occur, discontinue JARDIANCE, treat promptly, and monitor until signs and symptoms resolve.

**Increased Low-Density Lipoprotein Cholesterol (LDL-C):** Monitor and treat as appropriate.

**MOST COMMON ADVERSE REACTIONS (≥5%):** Urinary tract infections and female genital mycotic infections.

**DRUG INTERACTIONS:** Coadministration with diuretics may enhance the potential for volume depletion.

## USE IN SPECIAL POPULATIONS

**Pregnancy:** JARDIANCE is not recommended, especially during the second and third trimesters.

**Lactation:** JARDIANCE is not recommended while breastfeeding.

**Geriatric Use:** JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment. Renal function should be assessed more frequently in elderly patients. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in patients ≥75 years treated with empagliflozin.

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# JARDIANCE® (empagliflozin) tablets, for oral use

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## BRIEF SUMMARY OF PRESCRIBING INFORMATION

## Please see package insert for full Prescribing Information.

**INDICATIONS AND USAGE:** JARDIANCE 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 cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. Limitations of Use: JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

**CONTRAINDICATIONS:** History of serious hypersensitivity reaction to empagliflozin or any of the excipients in JARDIANCE *[see Warnings and Precautions]*. Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations]*.

**WARNINGS AND PRECAUTIONS: Hypotension:** JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations]*. **Ketoacidosis:** Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including JARDIANCE. Fatal cases of ketoacidosis have been reported in patients taking JARDIANCE. JARDIANCE is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*. Patients treated with JARDIANCE 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 JARDIANCE may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE 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, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified. Before initiating JARDIANCE, 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 JARDIANCE for at least 3 days prior to surgery [*see Clinical Pharmacology*]. Consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE 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 JARDIANCE. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue JARDIANCE and seek medical attention immediately if signs and symptoms occur. **Acute Kidney Injury and Impairment in Renal Function:** JARDIANCE causes intravascular volume contraction *[see Warnings and Precautions]* and can cause renal impairment *[see Adverse Reactions]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including JARDIANCE; some reports involved patients younger than 65 years of age. Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing JARDIANCE in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment. JARDIANCE increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDIANCE *[see Adverse Reactions]*. Renal function should be evaluated prior to initiation of JARDIANCE and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 $m^2$. Use of JARDIANCE is not recommended when eGFR is persistently less than 45 mL/min/1.73 $m^2$ and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 $m^2$ *[see Dosage and Administration, Contraindications and Use in Specific Populations]*. **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 JARDIANCE. 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. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE. **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 JARDIANCE. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with JARDIANCE 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 JARDIANCE, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control. **Genital Mycotic Infections:** JARDIANCE increases the risk for genital mycotic infections *[see Adverse Reactions]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with JARDIANCE. If a hypersensitivity reaction occurs, discontinue JARDIANCE; treat promptly per standard of care, and monitor until signs and symptoms resolve. JARDIANCE is contraindicated in patients with a previous serious hypersensitivity reaction to empagliflozin or any of the excipients in JARDIANCE *[see Contraindications]*. **Increased Low-Density Lipoprotein Cholesterol (LDL-C):** Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions]*. Monitor and treat as appropriate.

**ADVERSE REACTIONS:** The following important adverse reactions are described below and elsewhere in the labeling: Hypotension *[see Warnings and Precautions]*; Ketoacidosis *[see Warnings and Precautions)]*; Acute Kidney Injury and Impairment in Renal Function *[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]*; Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions]*. **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. Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg: The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials. These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 $m^2$). Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline, occurred more commonly on JARDIANCE than on placebo and occurred in greater than or equal to 2% of patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg.

**Table 1: Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy**

| | Number (%) of Patients | | |
|---|---|---|---|
| | Placebo N=995 | JARDIANCE 10 mg N=999 | JARDIANCE 25 mg N=977 |
| Urinary tract infection[a] | 7.6% | 9.3% | 7.6% |
| Female genital mycotic infections[b] | 1.5% | 5.4% | 6.4% |
| Upper respiratory tract infection | 3.8% | 3.1% | 4.0% |
| Increased urination[c] | 1.0% | 3.4% | 3.2% |
| Dyslipidemia | 3.4% | 3.9% | 2.9% |
| Arthralgia | 2.2% | 2.4% | 2.3% |
| Male genital mycotic infections[d] | 0.4% | 3.1% | 1.6% |
| Nausea | 1.4% | 2.3% | 1.1% |

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis
[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).
[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia
[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. *Volume Depletion:* JARDIANCE causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. JARDIANCE may increase the risk of hypotension in patients at risk for volume contraction *[see Warnings and Precautions and Use in Specific Populations]*. *Increased Urination:* In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on JARDIANCE than on placebo (see Table 1). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. *Acute Impairment in Renal Function:* Treatment with JARDIANCE was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes. *[see Warnings and Precautions* and *Use in Specific Populations]*. In a long-term cardiovascular outcome trial, the acute impairment in renal function was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes play a role in the renal function changes observed with empagliflozin.

**Table 2: Changes from Baseline in Serum Creatinine and eGFR[a] in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study**

| | | Pool of 24-Week Placebo-Controlled Studies | | |
|---|---|---|---|---|
| | | Placebo | JARDIANCE 10 mg | JARDIANCE 25 mg |
| Baseline Mean | N | 825 | 830 | 822 |
| | Creatinine (mg/dL) | 0.84 | 0.85 | 0.85 |
| | eGFR (mL/min/1.73 $m^2$) | 87.3 | 87.1 | 87.8 |
| Week 12 Change | N | 771 | 797 | 783 |
| | Creatinine (mg/dL) | 0.00 | 0.02 | 0.01 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -1.3 | -1.4 |
| Week 24 Change | N | 708 | 769 | 754 |
| | Creatinine (mg/dL) | 0.00 | 0.01 | 0.01 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -0.6 | -1.4 |
| | | Moderate Renal Impairment[b] | | |
| | | Placebo | | JARDIANCE 25 mg |
| Baseline Mean | N | 187 | – | 187 |
| | Creatinine (mg/dL) | 1.49 | – | 1.46 |
| | eGFR (mL/min/1.73 $m^2$) | 44.3 | – | 45.4 |
| Week 12 Change | N | 176 | – | 179 |
| | Creatinine (mg/dL) | 0.01 | – | 0.12 |
| | eGFR (mL/min/1.73 $m^2$) | 0.1 | – | -3.8 |
| Week 24 Change | N | 170 | – | 171 |
| | Creatinine (mg/dL) | 0.01 | – | 0.10 |
| | eGFR (mL/min/1.73 $m^2$) | 0.2 | – | -3.2 |
| Week 52 Change | N | 164 | – | 162 |
| | Creatinine (mg/dL) | 0.02 | – | 0.11 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | – | -2.8 |
| Post-treatment Change[c] | N | 98 | – | 103 |
| | Creatinine (mg/dL) | 0.03 | – | 0.02 |
| | eGFR (mL/min/1.73 $m^2$) | 0.16 | – | 1.48 |

[a]Observed cases on treatment.
[b]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 $m^2$
[c]Approximately 3 weeks after end of treatment.

*Hypoglycemia:* The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when JARDIANCE was administered with insulin or sulfonylurea *[see Warnings and Precautions]*.

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**Table 3: Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo- Controlled Clinical Studies[c]**

| **Monotherapy (24 weeks)** | **Placebo (n=229)** | **JARDIANCE 10 mg (n=224)** | **JARDIANCE 25 mg (n=223)** |
|---|---|---|---|
| Overall (%) | 0.4% | 0.4% | 0.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Metformin (24 weeks)** | **Placebo + Metformin (n=206)** | **JARDIANCE 10 mg + Metformin (n=217)** | **JARDIANCE 25 mg + Metformin (n=214)** |
| Overall (%) | 0.5% | 1.8% | 1.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Metformin + Sulfonylurea (24 weeks)** | **Placebo (n=225)** | **JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)** | **JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)** |
| Overall (%) | 8.4% | 16.1% | 11.5% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Pioglitazone +/- Metformin (24 weeks)** | **Placebo (n=165)** | **JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)** | **JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)** |
| Overall (%) | 1.8% | 1.2% | 2.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Basal Insulin +/- Metformin (18 weeks[d])** | **Placebo (n=170)** | **JARDIANCE 10 mg (n=169)** | **JARDIANCE 25 mg (n=155)** |
| Overall (%) | 20.6% | 19.5% | 28.4% |
| Severe (%) | 0% | 0% | 1.3% |
| **Table 3 (cont'd)** | | | |
| **In Combination with MDI Insulin +/- Metformin (18 weeks[d])** | **Placebo (n=188)** | **JARDIANCE 10 mg (n=186)** | **JARDIANCE 25 mg (n=189)** |
| Overall (%) | 37.2% | 39.8% | 41.3% |
| Severe (%) | 0.5% | 0.5% | 0.5% |

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Treated set (patients who had received at least one dose of study drug)
[d]Insulin dose could not be adjusted during the initial 18 week treatment period

*Genital Mycotic Infections:* In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (see Table 1). Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%). *Urinary Tract Infections:* In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions and Use in Specific Populations]. Laboratory Tests:* Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. **Postmarketing Experience:** Additional adverse reactions have been identified during postapproval use of JARDIANCE. 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 *[see Warnings and Precautions]*; Urosepsis and pyelonephritis *[see Warnings and Precautions]*; Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions];* Angioedema *[see Warnings and Precautions]*; Skin reactions (e.g., rash, urticaria).

**DRUG INTERACTIONS: Diuretics:** Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions]*. **Insulin or Insulin Secretagogues:** Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions]*. **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, JARDIANCE is not recommended during the second and third trimesters of pregnancy. Limited data available with JARDIANCE in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*. In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. Empagliflozin was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg when administered during organogenesis *[see Data]*. The estimated background risk of major birth defects is 6-10% in women with pregestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >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, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. *Data:* Animal Data: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13 week drug-free recovery period. 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. In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose. In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose). **Lactation:** *Risk Summary:* There is no information regarding the presence of JARDIANCE in human milk, the effects of JARDIANCE on the breastfed infant or the effects on milk production. Empagliflozin 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, including the potential for empagliflozin to affect postnatal renal development, advise women that use of JARDIANCE is not recommended while breastfeeding. **Pediatric Use:** The safety and effectiveness of JARDIANCE in pediatric patients under 18 years of age have not been established. **Geriatric Use:** No JARDIANCE dosage change is recommended based on age. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished glycemic efficacy in elderly patients with renal impairment *[see Use in Specific Populations]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions and Adverse Reactions]*. **Renal Impairment:** The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 $m^2$, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 $m^2$ and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 $m^2$. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. In a large cardiovascular outcomes study, there were 1819 patients with eGFR below 60 mL/min/1.73 $m^2$. The cardiovascular death findings in this subgroup were consistent with the overall findings. The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Contraindications and Warnings and Precautions]*. **Hepatic Impairment:** JARDIANCE may be used in patients with hepatic impairment.

**OVERDOSAGE:** In the event of an overdose with JARDIANCE, contact the Poison Control Center. 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. Removal of empagliflozin by hemodialysis has not been studied.

Additional information can be found at www.hcp.jardiance.com



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# End-Stage Renal Disease Treatment Choices (ETC) Model Finalized

By Mallika Mendu and David White

In September 2020, the Centers for Medicare & Medicaid Services (CMS) and its Innovation Center (CMMI) finalized the End-Stage Renal Disease (ESRD) Treatment Choices (ETC) Model. This model will test changes to care for Americans with kidney disease within a 30%, randomized set of Medicare beneficiaries with ESRD. The stated goals are increasing patient choice, increasing utilization of home dialysis, and providing greater access to transplantation, options for which the American Society of Nephrology (ASN) has long advocated.

The government will use hospital referral regions (HRRs) to randomize participation. Within those selected HRRs, both dialysis units, "facility," and nephrologists, "managing clinicians," will be included. Nephrologists will be organized in the model at the nephrology practice level and identified based on their primary practice zip code. The model excludes ESRD patients with Medicare Advantage (MA), children, hospice and nursing facility and skilled nursing facility patients, acute kidney injury-D (AKI-D), and those with dementia. The model runs from January 21, 2021, through June 30, 2027.

The 80% combined home dialysis and preemptive transplant rate discussed in the proposed rule was not finalized. Also, after the first two years of the program, benchmarking specifics become vague. However, the model indicates that future rulemaking is likely, allowing for future changes.

ASN had strongly advocated for ways to aggregate at the HRR level to account for home dialysis–only facilities within a practice or company—particularly if an institution sends its home dialysis patients to such a provider. In the final rule, CMMI allows for aggregation of facilities owned by the same company in a selected HRR as well as nephrology practices in an HRR. CMMI, however, did not create a virtual relationship as ASN advocated to be used where, for example, an institution has an arrangement to send all its home patients to a provider not owned by the institution. ASN is investigating how to address this potential gap.

ASN has strongly urged CMMI to examine stronger methods to risk adjust for or accommodate issues such as housing insecurity, socioeconomic status, or social determinants of health. ASN is encouraged that in the final rule the Innovation Center supports examining methodology to address these vital issues that impact health equity through future rulemaking. The final rule did indicate openness on this issue: "We seek input from the public on how to construct a risk adjustment methodology for the home dialysis rate that could account for socioeconomic factors, like the one from the Hospital Readmissions Reduction Program, to inform any future rulemaking on this topic" (1). The rule also indicated CMMI "will assess use of homelessness Z-codes Z59.7–.9."

Scoring under the model is weighted to two-thirds home dialysis rate blended with a one-third transplant waitlist or living donor rate. The proposed rule had tied the transplant rate to actual transplantation rates, but the finalized rule uses a blended approach of transplant waitlisting for deceased donation with an actual living donor transplant rate.

The Home Dialysis Payment Adjustment (HDPA) remained the same as the proposed rate, with a 3% bonus in calendar year (CY) 2021, 2% in CY 2022, 1% in CY 2023, and penalty points reduced by 2% across the board. There was minor adjustment of the Performance Payment Adjustment (PPA).

"We were pleased to see that CMMI adopted many of ASN's recommendations to improve the model and ensure its success on behalf of patients," said ASN President Anupam Agarwal, MD, FASN. "The society stands ready to work with its members and kidney patient organizations to achieve high quality outcomes for kidney patients through this model. In the United States, only 12% of the total dialysis population use home dialysis despite the evidence of improved outcomes and quality of life. We can, and we will, do better."

Dr. Agarwal added, "Together, both the finalized ETC Model and the Kidney Care Choices Model represent substantive efforts to improve patient access and choice, by focusing upstream to slow the progression of kidney disease, encouraging access to and use of home dialysis, and increasing preemptive transplants and the overall transplant rate."

The ETC Model resulted from broader government efforts to realign kidney care payments to incent innovation, increased modality choices for patients, increased rates of kidney transplantation, and reduced rates of progression to kidney failure. The implementation period for the Kidney Care First (KCF) program has begun, and the program commences April 1, 2021.

At the same time CMS finalized the ETC rule, the Health Resources and Services Administration (HRSA) issued a final rule amending regulations implementing the National Organ Transplant Act of 1984 to remove financial barriers to organ donation by expanding the scope of reimbursable expenses incurred by living organ donors to include lost wages, and child- and elder-care expenses incurred by a caregiver.

*Mallika Mendu, MD, MBA, is Assistant Medical Director for Quality and Safety at Brigham and Women's Hospital in Boston. She is a practicing nephrologist, and part of the Partners Population Health Management Team. David White is regulatory and quality officer at ASN.*

**Reference**

1. 42 CFR Part 512 [CMS-5527-F] RIN 0938-AT89 Medicare Program; Specialty Care Models to Improve Quality of Care and Reduce Expenditures

STATE-OF-THE-ART LECTURE

# National Academy of Medicine President to Speak on Genome Editing

Victor J. Dzau, MD

The president of the National Academy of Medicine will present a state-of-the-art address entitled "Human Genome Editing: Responsible Pathway Forward." The address is scheduled for Thursday, Oct. 22.

Victor J. Dzau, MD, is also vice chair of the National Research Council. He is chancellor emeritus and James B. Duke Professor of Medicine at Duke University and the former CEO of the Duke University Health System. His previous positions include serving as chair of medicine at Harvard Medical School's Brigham and Women's Hospital and chair of the department of medicine at Stanford University.

Dr. Dzau is an internationally acclaimed scientist whose work has improved healthcare in the United States and globally. His seminal work in cardiovascular medicine and genetics laid the foundation for the development of the ACE inhibitors class of drugs to treat hypertension and heart failure. Dr. Dzau also pioneered gene therapy for vascular disease and was the first to introduce DNA decoy molecules to block transcriptions in humans in vivo. His groundbreaking research in cardiac regeneration led to the paracrine hypothesis of stem cell action and his recent strategy of direct cardiac reprogramming using microRNA. He maintains an active National Institutes of Health (NIH)-funded research laboratory.

Dr. Dzau has led efforts in innovation to improve health, including the development of the Duke Translational Medicine Institute, the Duke Global Health Institute, the Duke-National University of Singapore Graduate Medical School, and the Duke Institute for Health Innovation. He has served as a member of the advisory committee to the NIH director, chaired the NIH cardiovascular disease advisory committee, and currently chairs the NIH Cardiovascular Stem Cell Biology and Translational Consortia.

He chairs the international scientific advisory committee of the Qatar Genome Project, the scientific board of the cardiac center at the University of Toronto, and the scientific board of the cardiovascular institute at the University of Glasgow.

During his tenure at the National Academy of Medicine, Dr. Dzau has designed and led important initiatives, including the Commission on a Global Health Risk Framework for the Future, the Human Gene Editing Initiative, and Vital Directions for Health and Health Care.

His many honors include the Max Delbruck Medal from the Max Delbruck Center for Molecular Medicine in Berlin, the distinguished scientist award from the American Heart Association, the Henry G. Friesen International Prize in Health Research, and a public service medal from the president of Singapore. He has been elected to the National Academy of Medicine, American Academy of Arts and Sciences, European Academy of Sciences and Arts, and Academia Sinica.

He received his MD from McGill University in Montreal followed by an internship in internal medicine at Cornell University, a residency in pathology at Children's Hospital in Boston, a clinical fellowship in medicine at Harvard University, a postdoctoral research fellowship in physiology at Harvard University, and a fellowship in cardiology at Massachusetts General Hospital.

# Researcher to Address Tubular Cell Reprogramming

Katalin Susztak, MD, PhD

A leading researcher in genetics and genomics will deliver the Barry M. Brenner, MD, Endowed Lectureship on "Tubular Cell Metabolic Reprogramming in Renal Fibrogenesis" on Thursday, Oct. 22.

The speaker will be Katalin Susztak, MD, PhD, a professor of medicine in the division of renal electrolyte and hypertension and professor of genetics at the University of Pennsylvania.

"I think this is a really exciting time in science," Dr. Susztak said. "New technologies are emerging, which will really accelerate research progress, and I think we have fantastic new discoveries ahead of us in biology."

Dr. Susztak leads a team interested in understanding the pathophysiology of CKD development. She has made discoveries fundamental to defining critical genes, cell types, and mechanisms of CKD. She was instrumental in defining genetic and epigenetic transcriptional changes in diseased human kidneys. She identified novel kidney disease genes and demonstrated the contribution of Notch signaling and metabolic dysregulation in kidney disease development.

Her lab was the first to map the kidney epigenome and catalogue genotype-driven gene-expression variation in human kidneys. Integration of genome-wide association study, expression quantitative trait loci, and epigenome data has been essential to ranking disease-causing genes and variants.

Dr. Susztak generated the first unbiased, comprehensive kidney cell-type atlas using single-cell transcriptomics. She demonstrated that specific renal endophenotypes are linked and likely caused by the dysfunction of specific cell types.

In follow-up animal model studies, she conclusively demonstrated that MANBA, DAB2, DACH1, and APOL1 are new kidney disease risk genes. Her work established the role of proximal tubule cells, endolysosomal trafficking, metabolic pathways, and developmental pathways in kidney disease development.

Dr. Susztak's discoveries span genetics, genomics, epigenetics, molecular biology, physiology, and nephrology, and have enormous translational relevance and considerable therapeutic potential.

She serves on the editorial boards of *JASN, Disease Models and Mechanisms, Diabetes, PLOS ONE, Kidney International, American Journal of Physiology/Renal and Electrolyte Section, and Scientific Reports*.

Dr. Susztak received the Young Investigator Award of the American Society of Nephrology and American Heart Association. Her laboratory is supported by the National Institutes of Health, the American Diabetes Association, the Juvenile Diabetes Research Foundation, and private sources.

She received her medical and doctoral degrees from Semmelweis University Medical School in Budapest, Hungary. She completed her internship and residency in internal medicine as well as her nephrology fellowship at the Albert Einstein College of Medicine.

# Proteinuria Expert to Speak on Podocyte Drug Targeting

Mario Schiffer, MD, MBA

A researcher who has spent 20 years investigating proteinuria causes and treatments will deliver the Michelle P. Winn, MD, Endowed Lectureship on "Drug Targeting of the Podocyte Actin Cytoskeleton."

Mario Schiffer, MD, MBA, professor of medicine, director of the department of nephrology and hypertension, and head of the department of internal medicine at the University Hospital Erlangen in Germany will speak on Thursday, Oct. 22.

Dr. Schiffer began his research into proteinuria development as a postdoctoral fellow at the Albert Einstein College of Medicine in New York City. His research using mouse models led to his discovery of a novel pathway for apoptosis in podocytes and the characterization of several novel pathways for podocyte loss.

After four years of postdoctoral training, Dr. Schiffer returned to his native Germany, where he became an independent investigator with funding from the German Research Council. He expanded his research to investigate pathways in proteinuric human diseases such as diabetic glomerulosclerosis, membranous glomerulonephritis, and transplant glomerulopathy.

He developed an effective measure of proteinuria in zebrafish larvae that permitted the monitoring of proteinuria in mutant as well as in morphant zebrafish larvae. That approach enabled him to perform rapid screening of novel genes involved in proteinuria development and study novel potential treatment targets. He collaborated with several other researchers—including the lectureship's namesake, Dr. Michelle P. Winn—to produce a series of peer-reviewed publications about this novel method.

His main scientific goal is the identification of novel treatments for albuminuria. His high-throughput screening system to identify novel candidate genes involved in the pathogenesis of glomerular kidney diseases is being used by other researchers in the field worldwide. His zebrafish approach can be used to screen compounds and substances to treat early stages of proteinuric kidney disease.

In addition to his proteinuria research, Dr. Schiffer developed a strong clinical background in general nephrology, glomerular diseases, and transplant nephrology. This expertise was recognized in 2010 when he was awarded the Heisenberg Professorship for Transplant Nephrology. Among his many honors. Dr. Schiffer has received the Franz Volhard Award of the Germany Society of Nephrology, Hans U. Zollinger Award of the German Society of Nephrology, and Nils Alwall Award of the German Association for Clinical Nephrology.

He received his medical degree from the Free University of Berlin.

# CRRT Expert to Deliver Address on Electrolyte Abnormalities

Ashita Tolwani, MD, MSc

The title of the Burton D. Rose, MD, Endowed Lectureship will be "Managing Electrolyte Abnormalities on Continuous Renal Replacement Therapy (CRRT)." The speaker will be Ashita Tolwani, MD, MSc, professor of medicine at the University of Alabama at Birmingham (UAB). The lecture is scheduled for Thursday, Oct. 22.

"My research focus is on the clinical aspects of CRRT in the treatment of acute kidney injury in the ICU and more specifically with the use of citrate anticoagulation," Dr. Tolwani said. "UAB has been a pioneering research institution in CRRT. We currently have 25 CRRT machines providing over 5000 patient-days of treatment a year. There is even a group in Australia that has named their anticoagulation protocol, 'The Modified Alabama Protocol,' based on the protocol that was developed at UAB."

Dr. Tolwani has performed extensive clinical outcomes research in AKI and CRRT, with a particular focus on citrate anticoagulation. She is the director of ICU nephrology at UAB and heads the CRRT program. She organizes an annual UAB CRRT academy for trainees, practicing physicians, and nurses from across the United States. She also teaches CRRT courses nationally and internationally.

Dr. Tolwani completed a combined nephrology and critical care fellowship. "Doing a combined fellowship allowed me the opportunity to handle a little bit of everything in internal medicine and still be able to do many procedures that attracted me to critical care in the first place," she said. "With this I have been able to find my academic niche in ICU nephrology that has allowed for many new career opportunities."

Dr. Tolwani directed the UAB nephrology fellowship program from 2002 to 2010 and is now associate program director.

She serves on the editorial boards of *CJASN* and *Kidney International Reports*. She is co-course director of the ASN critical care nephrology pre-course; is on the organizing committee of the Acute Kidney Injury and CRRT International Conference on Advances in Critical Care Nephrology; and is a workgroup member of the ASN initiative, AKI!Now: Promoting Excellence in the Prevention and Treatment of Acute Kidney Injury.

She received her medical degree from the UAB School of Medicine, where she also completed her internal medicine residency and nephrology fellowship. She became a faculty member in 1999. She also has a master's in epidemiology from the Harvard School of Public Health.

# Public Health Policy Expert to Discuss COVID-19

Nicole (Nicki) Lurie, MD, MSPH

Public health leader Nicole (Nicki) Lurie, MD, MSPH, will deliver the Christopher R. Blagg, MD, Endowed Lectureship on "Kidney Care and the COVID-19 Experience."

Dr. Lurie is a physician, professor of medicine, and public health official who is internationally renowned as a health services researcher and policy expert. Her long history in the health services research field has focused on access to and quality of care, managed care, mental health, prevention, public health infrastructure and preparedness, and health disparities.

She will discuss how the COVID-19 pandemic has reshaped America's emergency response infrastructure and changed kidney care in ways that are likely here to stay. Her talk will provide a big-picture view of the government response to COVID-19, how kidney patients were uniquely affected, and lessons for the kidney community in preparing for future pandemics. Her lecture will be part of a session on "Policy in a Post-COVID World."

Dr. Lurie served as the assistant secretary for preparedness and response at the U.S. Department of Health and Human Services during the Obama administration. In this role, she provided leadership in preventing, responding to, and recovering from public health emergencies and disasters.

A consultant to the World Bank and the Coalition for Epidemic Preparedness Initiatives, she has also served as medical advisor to the commissioner at the Minnesota department of health and as professor in the University of Minnesota schools of medicine and public health.

When at the RAND Corporation, her focus was on access to and quality of care, health equity, and population health. She has led several successful community-wide initiatives to improve the health of underserved populations.

She was senior editor of Health Services Research and served on editorial boards and as a reviewer for numerous journals. She served as president of the Society of General Internal Medicine and on the board of directors for Academy Health.

Dr. Lurie has received many awards, including the Association for Health Services' young investigator award, the American Federation of Clinical Research's Nellie Westerman Prize for Research in Ethics, and the University of Pennsylvania School of Medicine's distinguished alumni award.

Dr. Lurie attended medical school at the University of Pennsylvania and completed her residency and master's degree at the University of California, Los Angeles, where she was also a Robert Wood Johnson Foundation clinical scholar.

STATE-OF-THE-ART LECTURE

# Plenary to Address Physician Well-Being

Tait D. Shanafelt, MD

An international thought leader in the field of physician well-being and its implications for quality of care will deliver the state-of-the-art address "Reducing Physician Distress: Organizational Approaches to Improve Physician Well-Being" at a plenary on Friday, Oct. 23.

The speaker will be Tait D. Shanafelt, MD, who is the chief wellness officer, associate dean, and Jeanie and Stewart Ritchie Professor of Medicine at Stanford University. Dr. Shanafelt's pioneering studies in this area nearly 20 years ago have been credited with helping launch the field of organizational efforts to promote physician well-being.

He was the founding director of the Mayo Clinic program on physician well-being and served a three-year term as the president of the Mayo Clinic voting staff.

In 2017, he moved to Stanford, where he leads the WellMD Center. He is a member of the American College of Physicians Taskforce on Physician Well-being and the National Academy of Medicine Committee on System Approaches to Support Clinician Well-being. He has helped hundreds of organizations and their leaders work to improve burnout and promote professional fulfillment for physicians.

Dr. Shanafelt has published over 120 scientific manuscripts on this topic and he has served as a keynote speaker to the American Medical Association, Accreditation Council for Graduate Medical Education, Association of American Medical Colleges, and American Board of Internal Medicine. Dr. Shanafelt's studies in this area have been cited in CNN, *USA Today, U.S. News & World Report*, and *The New York Times*. In 2018, he was named by TIME Magazine as one of the 50 most influential people in healthcare.

In his clinical work, Dr. Shanafelt is a hematologist/oncologist focused on the care of patients with chronic lymphocytic leukemia. He is a member of the National Cancer Institute (NCI) Leukemia Steering Committee and is currently the principal investigator on three NCI grants. He has been the principal investigator on numerous clinical trials testing new treatments for patients with chronic lymphocytic leukemia. He has published more than 350 peer-reviewed manuscripts and commentaries in addition to more than 100 abstracts and book chapters in this area.

He is associate editor of the journal *Leukemia*.

Dr. Shanafelt received his MD from the University of Colorado Health Sciences, followed by an internship and residency in internal medicine at the University of Washington. He completed a fellowship in hematology and oncology at the Mayo Clinic.

# Personalized Medicine and Osteoporosis to Be Featured

Glenn M. Chertow, MD, MPH

A researcher with a broad portfolio will provide the "Rationale for Personalized Medicine Approaches to the Management of CKD-Associated Osteoporosis" in the Jack W. Coburn, MD, Endowed Lectureship on Friday, Oct. 23.

The speaker will be Glenn M. Chertow, MD, MPH, who is the Norman S. Coplon Satellite Healthcare Professor of Medicine and chief of the division of nephrology at Stanford University School of Medicine.

In addition to teaching, mentoring, and maintaining an active clinical practice, Dr. Chertow has carried out a robust clinical research program centered on clinical epidemiology, health-services research, decision science, and clinical trials in acute and chronic kidney disease. He has been the author or co-author of more than 500 peer-reviewed manuscripts shedding light on AKI, CKD, ESKD, and associated complications, including those related to bone and mineral metabolism, cardiovascular disease, and nutrition.

He has served in leadership roles for multiple clinical trials sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Heart, Lung, and Blood Institute; Veterans Administration; and industry. Recent projects for NIDDK include work on the Acute Renal Failure Trials Network Study, the U.S. Renal Data System Special Studies Center in Nutrition, the Chronic Renal Insufficiency Cohort Study, and the Frequent Hemodialysis Network Study.

Dr. Chertow has served in an advisory capacity to the Medicare Payment Advisory Committee and the National Quality Forum on issues related to the ESKD program as well as on National Institutes of Health study sections. He was vice chair and member of two workgroups for the Kidney Disease Outcomes Quality Initiative (K/DOQI). He has served ASN in many roles, including on the public policy board, on the quality metrics taskforce, and as associate editor of *JASN*. He is co-editor of *Brenner and Rector's The Kidney*.

He received the Belding H. Scribner Award from ASN, the National Torchbearer Award and Nephrologist of the Year Award from the American Kidney Fund, and the David M. Hume Memorial Award from the National Kidney Foundation. He has been elected to the Association of American Physicians, National Academy of Medicine, and American Society of Clinical Investigation.

Dr. Chertow received his medical degree from Harvard Medical School and his master of public health in epidemiology and biostatistics from the Harvard School of Public Health. He completed his residency in internal medicine and fellowship in nephrology at Brigham and Women's Hospital in Boston before joining the Harvard faculty, where he remained until 1998. He then joined the faculty at the University of California, San Francisco, where he served as director of clinical services in the division of nephrology. He was promoted through the academic ranks to full professor in the department of medicine and the department of epidemiology and biostatistics. He joined the Stanford faculty in 2007.

STATE-OF-THE-ART LECTURE

# Genome Pioneer to Describe Efforts to Curate Genome

Heidi Rehm, PhD

"Global Efforts to Curate the Genome" is the title of a state-of-the-art lecture scheduled for Sat., Oct. 24. The speaker will be Heidi Rehm, PhD, a human geneticist and genomic medicine researcher. She is medical director of the Clinical Research Sequencing Platform and an institute member at the Broad Institute in Cambridge, Mass.

She is also chief genomics officer in the department of medicine at Massachusetts General Hospital and a professor of pathology at Mass General, Brigham and Women's Hospital, and Harvard Medical School. A leader in defining standards for the interpretation of sequence variants, Rehm is a principal investigator for a major National Institutes of Health-funded effort called ClinGen (Clinical Genome Resource), which provides free, publicly accessible resources to support the interpretation of genes and variants.

Dr. Rehm also co-leads the Broad Center for Mendelian Genomics, which is focused on discovering novel rare disease genes, and co-leads the Matchmaker Exchange, which is aimed at gene discovery. A pioneer in open science and data sharing, she is working to extend these approaches through her role on the steering committee of the Global Alliance for Genomics and Health. Rehm is also a co-investigator of the BabySeq Project exploring the clinical use of genomic sequencing as an adjunct to newborn screening; principal investigator in the eMERGE consortium supporting genomic discovery and genomic medicine implementation; and a principal investigator on a project to develop the Informatics for Integrating Biology and the Bedside Center into a health innovation platform for clinical decision support.

In 2001, Dr. Rehm began building the Laboratory for Molecular Medicine within the Harvard-Partners Center for Genetics and Genomics. Now a part of Partners HealthCare Personalized Medicine, the laboratory focuses on the rapid translation of new genetic discoveries into clinical tests and brings novel technologies and software systems into clinical use to support the integration of genetics into medicine. The laboratory, which Rehm directed until 2018, has been a leader in translational medicine and offers exome and genome sequencing services for both clinical diagnostics and genomic medicine research projects.

Dr. Rehm is involved in defining standards for the use of next-generation sequencing in clinical diagnostics and the interpretation of sequence variants through her committee roles at the American College of Medical Genetics and Genomics. She serves as a council member of the Human Genome Organization, Human Genome Variation Society, and Human Variome Project. Among her honors, she has received the Brigham and Women's Hospital Physician Recognition Award for Clinical Innovation and the *Boston Business Journal's* 40 Under 40 Award for Civic Leadership. She was a member of teams that won the 2012 CLARITY Challenge run by Boston Children's Hospital and the 2013 *Bio-IT World* editors' prize for the GeneInsight software system.

Dr. Rehm earned her MS in biomedical science from Harvard Medical School and her PhD in genetics from Harvard University. She completed her postdoctoral training in neurobiology and a fellowship in clinical molecular genetics at Harvard Medical School.

# Internationally Known Researcher to Speak on Vascular Resistance

Friedrich (Fred) C. Luft, MD

The intriguing title of the Robert W. Schrier, MD, Endowed Lectureship is "How the Unknown Unknowns Cause the Increased Peripheral Vascular Resistance." The speaker, Friedrich (Fred) C. Luft, MD, said he "will report on a single project that spans more than 25 years of clinical and basic research" that demonstrates "how ignorance drives science."

Internationally recognized for his research in nephrology, hypertension, physiology, and genetics, Dr. Luft is a professor at the Max-Delbrück Center for Molecular Medicine, Charité Medical Faculty, in Berlin, Germany. The lecture is scheduled for Sat., Oct. 24.

The Luft Lab has long focused on the molecular genetics of hypertension and brachydactyly, two closely linked phenotypes in a family discovered more than 15 years ago. "Hypertension and the organ damage that ensue from it are tremendously challenging topics for research because they arise through an interaction between many genes and environmental factors," according to the lab's website. "This project began as a classic search for a mutation in a gene and has led us to new insights into one of the most interesting current themes in science: the epigenetic regulation of the genome. While trying to explain the brachydactyly phenotype, we discovered a series of very complex cis- and trans-regulatory epigenetic phenomena; they may serve as a model system to explore important open questions about genome architecture and regulation."

Dr. Luft was born in Berlin but grew up in Texas and New Mexico. He graduated from Jefferson Medical College, Philadelphia, in 1968. He spent two years in the U.S. Army, followed by 20 years at Indiana University, Indianapolis, where he completed house-staff training, a chief residency, and a nephrology fellowship. He served on the faculty in internal medicine, nephrology, and critical care medicine. His research focus was hypertension and cardiovascular disease.

Dr. Luft returned to Germany in 1989, first to the University of Erlangen and then to Berlin in 1992.

In Berlin, Dr. Luft chaired an academic department of internal medicine/nephrology that was associated with the newly founded Max-Delbrück Center for Molecular Medicine (MDC). In addition to his clinical duties, his research focused on molecular genetics of cardiovascular disease. In 2010, he was released from administrative clinical duties but continued as director of the Experimental and Clinical Research Center, the interface between the basic science MDC and the Charité Medical Faculty. He also served as adjunct professor at the University of Iowa from 2005 to 2012 and at Vanderbilt University from 2013 to 2018. He was appointed senior professor at the Charité in 2018.

Dr. Luft was awarded the research excellence in hypertension award by the American Heart Association. He is a member of the German National Academy of the Sciences.

STATE-OF-THE-ART LECTURE

# Early RNA Investigator to Share Journey of Discovery

Joan A. Steitz, PhD

A researcher who has devoted her career to investigating RNA will give a state-of-the-art lecture, "RNA Biology and Medicine: A Journey of Unexpected Discovery," on Sunday, Oct. 25. The speaker, Joan A. Steitz, PhD, is Sterling Professor of Molecular Biophysics and Biochemistry at Yale University and an investigator at the Howard Hughes Medical Institute.

Perhaps her biggest breakthrough came in 1979, when Dr. Steitz and her colleagues described a group of cellular particles called small nuclear ribonucleoproteins (snRNPs), a breakthrough in understanding how RNA is spliced. Subsequently, her laboratory defined the structures and functions of other noncoding RNPs, such as those that guide the modification of ribosomal RNAs and microRNAs, as well as several produced by transforming herpes viruses.

She was publishing significant findings as early as 1967, when her doctoral thesis with mentor James Watson examined the test-tube assembly of an RNA bacteriophage (antibacterial virus) known as R17.

Dr. Steitz spent the next three years in postdoctoral studies at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, where she used early methods for determining the biochemical sequence of RNA to study how ribosomes know where to initiate protein synthesis on bacterial mRNAs. In 1970, she was appointed assistant professor of molecular biophysics and biochemistry at Yale, becoming full professor in 1978. She established a laboratory at Yale dedicated to the study of RNA structure and function.

She is an editor of the *Proceedings of the National Academy of Sciences*, associate editor of *RNA*, associate editor of the *Journal of Cell Biology*, and a member of the editorial boards of *Genes and Development* and *Molecular Cell*.

Her many honors include the U.S. Steel Foundation Award in Molecular Biology, National Medal of Science; Federation of American Societies for Experimental Biology Excellence in Science Award, RNA Society Lifetime Achievement Award, Gairdner Foundation International Award, Pearl Meister Greengard Prize, the grand medal from the French Academy of Sciences, American Society of Biochemistry and Molecular Biology Herbert Tabor Award, American Chemical Society Biopolymers Murray Goodman Memorial Prize, Jonathan Kraft Prize for Excellence in Cancer Research, and Lasker-Koshland Special Achievement Award in Medical Science of the Albert and Mary Lasker Foundation.

Dr. Steitz is a member of the American Academy of Arts and Sciences, American Philosophical Society, National Academy of Sciences, and Institute of Medicine. She received her doctorate in biochemistry and molecular biology from Harvard University.

# Lectureship to Focus on Patient Safety Metrics in Dialysis

Allison Tong, PhD, MPH

The title of the Celeste Castillo Lee Memorial Lectureship will be "Developing Actionable Patient Safety Outcome Metrics for Dialysis." Scheduled for Sunday, Oct. 25, the speaker will be Allison Tong, PhD, MPH, a principal research fellow and professor at the Sydney School of Public Health, the University of Sydney in Australia.

Dr. Tong has extensive experience in patient-centered outcomes research in chronic disease, particularly CKD. Her work focuses on patient involvement in research, including in the context of research priority setting, the development of core outcomes for research, and in the co-production of clinical trials. She co-founded and is on the Executive Committee of the global Standardized Outcomes in Nephrology (SONG) Initiative, which aims to establish consensus-based core outcomes across the spectrum of CKD. She established the Patient-Centered Research Network (PACER), which aims to facilitate knowledge exchange, cross-disciplinary collaboration, patient involvement, and innovation in conducting patient-centered outcomes research.

She is associate editor of *CJASN*, the *American Journal of Transplantation, American Journal of Kidney Disease, Transplantation, BMC Medical Research Methodology, BMJ Open, Nephrology,* and *Research for All*, and is a reviewer for more than a dozen journals.

Among her many activities, she chairs the patient-reported outcomes working group of the European Society of Transplantation and is a member of the patient engagement work group of the International Society of Nephrology Advancing Clinical Trials, the patient-reported outcome measures group of the Australian and New Zealand Dialysis and Transplant Registry, the scientific program and education committee of the Transplantation Society of Australia and New Zealand, and the transplant working group of the Australian Kidney Trials Network.

She has received an award for outstanding mid-career research from the University of Sydney, the Ian McKenzie Award for Outstanding Contribution to Transplantation from the Transplantation Society of Australia and New Zealand, the Kidney Health Australia Prize for the Best Presentation in the Field of Clinical Research, and the Young Investigators Award from the Children's Hospital at Westmead.

She received a PhD and MPH from the school of public health at the University of Sydney, and master of management in community management from the University of Technology in Australia. She was the recipient of a career development fellowship from the Australian National Health and Medical Research Council.

# Lifetime Achievement Awards

**ASN will bestow Life Achievement Awards, Midcareer Awards, President's Medals, and the Young Investigator Award during the 2020 ASN Business Meeting on Sunday, October 25.**

## John P. Peters Award to Honor Ravi Thadhani

Ravi I. Thadhani, MD, MPH

ASN will recognize the wide-ranging contributions of Ravi I. Thadhani, MD, MPH, with the presentation of the John P. Peters Award. The Peters Award is given for outstanding contributions to improving the lives of patients and furthering the understanding of the kidneys in health and disease.

Dr. Thadhani is the chief academic officer at Partners Healthcare, dean for academic programs at Harvard Medical School, and a physician at Massachusetts General Hospital. He is the former head of the division of nephrology at Massachusetts General.

Dr. Thadhani has two major areas of research interest: medical complications of pregnancy and dialysis mortality. His pregnancy-related studies have centered on human studies in the area of angiogenic factors and preeclampsia. In dialysis, his team has conducted studies examining the effect of vitamin D in the survival of chronic hemodialysis patients.

His main focus in the study of kidney diseases is the cardiovascular and infectious consequences of defective vitamin D signaling in individuals with kidney failure. His team has performed several hypothesis-generating observational studies suggesting that therapy with activated vitamin D sterols is associated with improved survival among patients with kidney failure. These studies included thousands of dialysis patients and have been confirmed by more than 25 independent investigators worldwide. National and international guidelines have taken note of these studies, and clinical practices have implemented their findings. He has collaborated with basic scientists to move these hypotheses forward and is currently performing randomized trials to formally test these hypotheses in humans.

His research has led to the publication of more than 250 peer-reviewed articles, eight book chapters, and many review articles and invited commentaries. Dr. Thadhani has also mentored several fellows and junior faculty members, who have developed strong track records of publications and faculty appointments at leading institutions around the country.

He has served ASN in a variety of capacities, including as a member of the annual meeting program committee. For the National Kidney Foundation, he has chaired the clinical research committee and served on the annual meeting planning committee.

He has been on the editorial boards of *JASN, Kidney International, and Nephrology Dialysis Transplantation*. He was associate editor of the *American Journal of Kidney Diseases* and has been a guest editor of *JASN*.

Dr. Thadhani received his medical degree from the University of Pennsylvania and his MPH from the Harvard School of Public Health. He completed his internship, residency, and nephrology fellowship at Massachusetts General Hospital.

## ASN to Bestow Belding H. Scribner Award on Josef Coresh

Josef Coresh, MD, PhD

The Belding H. Scribner Award will be tendered to Josef Coresh, MD, PhD, for his career-long contributions to the practice of nephrology. Dr. Coresh is the George W. Comstock Professor of Epidemiology, Biostatistics, and Medicine at the Johns Hopkins University Bloomberg School of Public Health. He also directs the cardiovascular epidemiology training program and the George W. Comstock Center for Public Health Research and Prevention.

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. Coresh has made significant contributions in patient care, research, and service to professional organizations.

His greatest contributions to the kidney realm are his epidemiologic studies in support of clinical practice guidelines for CKD definition and classification. Dr. Coresh served as vice chair for the workgroup for the 2002 National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) clinical practice guidelines, which developed the definition and classification of CKD that have been adopted internationally. He was part of the team that published the equations used for estimating kidney function globally. The methods he developed for the estimation of U.S. prevalence of CKD have become the standard for public health agencies in the United States and around the world.

For the 2009 Kidney Disease Improving Global Outcomes (KDIGO) 2009 conference on the definition, classification, and prognosis of CKD, he led more than 40 cohorts in the meta-analysis that led to consensus for revision of the CKD classification. This effort led to his founding of the Chronic Kidney Disease Prognosis Consortium (CKD-PC). CKD-PC now consists of more than 80 participating cohorts with data on kidney disease measures and outcomes on more than 10 million participants globally and is renowned for its fundamental contributions to our understanding of the burden of kidney disease and to improving patient care. CKD-PC research has informed clinical practice guidelines, regulatory agencies, and CKD prevention policies.

Dr. Coresh has co-authored more than 800 research articles that have been cited over 100,000 times covering a very broad range of topics. He leads the Atherosclerosis Risk in Communities (ARIC) study at Johns Hopkins, which is a cohort of 16,000 participants followed since 1988. Among other awards, he received the top scientific award of NKF.

He received a combined MD and PhD degree in epidemiology as well as a master's in biostatistics from Johns Hopkins University, where he has spent his career.

## Young Investigator Recognized for Contributions in Mechanism-Based Therapies

Anna Greka, MD, PhD, MHS

The Donald W. Seldin Young Investigator Award will be presented to Anna Greka, MD, PhD, MHS, who will speak on "From Genes to Medicines: The Arc of Discovery for Kidney Diseases" on Saturday, Oct. 24.

Dr. Greka is an associate professor at Harvard Medical School; an associate physician in the renal division at Brigham and Women's Hospital; and the founding director of Kidney-NExT (Center for Kidney Disease and Novel Experimental Therapeutics). She is also a member of the Broad Institute of the Massachusetts Institute of Technology and Harvard, where she directs the Kidney Disease Initiative.

She has made seminal contributions to nephrology and kidney diseases, and is responsible for the development of some of the first mechanism-based therapies for kidney diseases.

Her lab studies mechanisms of cell survival and metabolic regulation, with an emphasis on calcium signaling and transient receptor potential (TRP) ion channel biology. This work has led to important insights relevant to kidney function. For instance, applying this expertise to the study of kidney podocytes, the laboratory recently identified a specific TRPC5 channel blocker as the first mechanism-based therapeutic strategy for focal segmental glomerulosclerosis.

She has also made important discoveries in podocyte biology on the role of cellular regulators such as Nck, CTFC, and BRAF, illuminating actionable pathways for the development of podocyte-protective therapies. She has brought several technological innovations to the field, including single-cell genomics and human kidney organoids derived from induced pluripotent stem cells. She recently published a ground-breaking study on a novel mechanism for the development of toxic proteinopathies that affect the kidneys and other tissues that could be countered with an innovative therapeutic.

As the founding director of Kidney-NExT, Dr. Greka has made a significant contribution by organizing five internationally recognized symposia focused on kidney therapeutics. She also serves as co-chair of the Kidney Human Cell Atlas Consortium, an international effort to develop a comprehensive atlas of each cell type in the human kidney in both health and disease.

She maintains a clinical practice that receives referrals of patients from across the country with difficult-to-treat glomerular disorders and other rare kidney diseases.

Dr. Greka has been recognized with several honors, including an award for pioneering research and a young physician-scientist award from the American Society of Clinical Investigation, a U.S. Presidential Early Career Award for Scientists and Engineers, and a research scholar award from ASN.

She received her MD and PhD in neurobiology from Harvard Medical School.

# CRRT Expert Will Receive the Robert G. Narins Award

Ashita Tolwani, MD, MSc

Ashita Tolwani, MD, MSc, will receive the Robert G. Narins Award for her many efforts in education and training of the next generation of nephrologists. Dr. Tolwani is professor of medicine at the University of Alabama at Birmingham (UAB).

Dr. Tolwani directed the UAB nephrology fellowship program from 2002 to 2010 and continues as associate program director. In that capacity, she co-directed workshops on curriculum development and assisted in developing the curriculum and teaching tools portion of the ASN website. She wrote the nephrology fellowship manual now available on the website.

A nationally known expert on continuous renal replacement therapy (CRRT) in the treatment of acute kidney injury in the ICU, she has lectured on this topic and general ICU nephrology at the ASN Board Review Course & Update every year since 2010. She founded and directs the UAB CRRT Academy, a two-day course offered annually since 2007 that is the only national CRRT training course that features hands-on training with simulation mannequins. Many nephrology fellowship programs require their fellows to take this course.

Dr. Tolwani has given educational lectures on acute kidney injury and CRRT at academic institutions throughout the United States and at national and international conferences. She has presented CRRT workshops and tutorials at international conferences in South Africa, Belgium, Italy, India, and Malaysia.

She has won virtually every award for teaching given in the UAB medical school and department of medicine, including the President's Award for Teaching Excellence. UAB medical students have nominated her for their top teaching award every year since 2007, and she has won several times.

Dr. Tolwani is co-course director of the ASN critical care nephrology early program; on the organizing committee of the Acute Kidney Injury and CRRT International Conference on Advances in Critical Care Nephrology; and a workgroup member of the ASN initiative, AKI!Now: Promoting Excellence in the Prevention and Treatment of Acute Kidney Injury. She serves on the editorial boards of *CJASN* and *Kidney International Reports*.

Dr. Tolwani received her medical degree from the UAB School of Medicine where she also did her internal medicine residency and nephrology fellowship. She became a faculty member in 1999. She also has a master's in epidemiology from the Harvard School of Public Health.

# Nobel Laureate Ratcliffe to Receive Homer W. Smith Award

Sir Peter J. Ratcliffe

Nobel Prize winner Sir Peter John Ratcliffe will present the Homer W. Smith Award lecture on Friday, Oct. 23. This award recognizes outstanding contributions to understanding how kidneys function in normal and diseased states. He will speak on "Understanding Cellular Oxygen-Sensing Mechanisms: Implications for Medicine."

Professor Ratcliffe is director of clinical research at the Francis Crick Institute in London as well as director of the Target Discovery Institute and distinguished scholar of the Ludwig Institute of Cancer Research at Oxford University.

After studying the physiology of renal circulation, Professor Ratcliffe became interested in the regulation of the hematopoietic growth factor erythropoietin, which is produced by the kidneys in response to reduced blood oxygen availability. In 1990, with funding as a Wellcome Trust senior fellow, he set up the hypoxia biology laboratory in the Weatherall Institute of Molecular Medicine in Oxford.

This work led to the unexpected discovery that the oxygen-sensing process underlying the regulation of erythropoietin production in the kidneys and liver operates across essentially all animal cells, irrespective of the production of erythropoietin, and that it directs a broad range of other cellular and systemic responses to hypoxia. These responses include altered energy metabolism, angiogenesis, and cell survival and differentiation decisions.

The laboratory went on to elucidate the mechanism of "oxygen sensing," an unprecedented mode of signal transduction mediated by the oxygen-dependent catalysis of prolyl and asparaginyl hydroxylation at specific sites within the key transcription factor, HIF (hypoxia-inducible factor). Prolyl hydroxylation marks HIF-alpha polypeptides for destruction by the von Hippel-Lindau ubiquitin E3 ligase. Asparaginyl hydroxylation blocks the recruitment of co-activators. In hypoxia these processes are suppressed, allowing HIF-alpha to escape destruction and assemble an active transcriptional complex with its dimerization partner HIF-beta.

His current research aims to understand the roles of signaling through protein hydroxylation and related oxidations. The work is focused both on the operation of the HIF hydroxylases themselves and on related enzymes that catalyze hydroxylations on other proteins. It aims to link these biochemical pathways to physiological control and to the pathophysiology of human diseases including cancer and ischemic vascular disease.

Professor Ratcliffe won the Nobel Prize in Physiology or Medicine in 2019. Among his many other honors, he was elected to the Fellowship of the Royal Society and to the Academy of Medical Sciences. His work on oxygen sensing has been recognized with the Louis-Jeantet Prize in Medicine, the Canada Gairdner International Award, and the Lasker Award for Basic Biomedical Research. He was knighted for services to medicine.

Professor Ratcliffe trained in medicine at Cambridge University and St. Bartholomew's Hospital in London before moving to Oxford to specialize in renal medicine. In 2004, he was appointed Nuffield Professor of Clinical Medicine at the University of Oxford, where he also served as head of the department of clinical medicine.

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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 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.

### Holly J. Kramer, MD, MPH

Dr. Kramer is professor of public health sciences and medicine in the division of nephrology and hypertension at Loyola University Chicago as well as being a clinical nephrologist. She is also the associate director for research at the Hines VA Medical Center.

Dr. Kramer's term as president of the National Kidney Foundation ended in October 2020. She has been a vice chair of the foundation's Kidney Disease Quality and Outcomes program since 2009.

Her research focuses on the intersections among kidney disease, nutrition, cardiovascular disease, and health disparities. She has done extensive research on obesity and kidney disease and on genetic variants for kidney disease. She is a co-investigator for the Multi-Ethnic Study of Atherosclerosis.

Along with research, advocacy remains a major focus in her career as she pushes for increased research funding to find better therapies for kidney disease prevention and treatment and to foster the development of young investigators.

Dr. Kramer completed medical school at Indiana University. She was chief resident during her internal medicine residency at Emory University and completed a nephrology fellowship at the Massachusetts General Hospital/Brigham and Women's Hospital.

She joined Loyola in 2002, where she became co-director of the clinical research methods and epidemiology program in 2005, developing several courses for the program. She became the program director for the master's in public health program in 2009.

### Kathleen D. Liu, MD, PhD, FASN

Dr. Liu is professor of medicine and anesthesia in the divisions of nephrology and critical care medicine as well as medical director of the apheresis/hemodialysis unit and medical intensive care unit at the University of California, San Francisco.

She teaches medical students, residents, and fellows and has written core curriculum articles on acute kidney injury and critical care nephrology for the *American Journal of Kidney Disease*.

Dr. Liu's research has focused on acute kidney injury, acute respiratory distress syndrome, and critical care nephrology. She is a member of the National Institutes of Health acute lung injury clinical trials network and is involved in a clinical trial of mesenchymal stem cells for the treatment of trauma-associated acute respiratory distress syndrome funded by the U.S. Department of Defense. She is currently performing research focused on the pathways that mediate the relationship between acute kidney injury and subsequent cardiovascular disease in patients enrolled in the National Institute of Diabetes and Digestive and Kidney Diseases-sponsored ASSESS-AKI (Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury) Study as well as studies of optimal strategies for renal recovery in patients with AKI that requires dialysis.

Dr. Liu completed an MD/PhD program at the University of California, San Francisco. She then trained in internal medicine at Brigham and Women's Hospital in Boston and in nephrology/critical care at the University of California, San Francisco. She joined the faculty at the University of California, San Francisco, in 2006.

## 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.

### Sofia B. Ahmed, MD, MS

Dr. Ahmed is a professor at the Cumming School of Medicine at the University of Calgary and the vice chair for research in the department of medicine. As a nephrologist and clinician-scientist, she is one of Canada's leading experts on sex and gender differences in human kidney and cardiovascular outcomes.

Dr. Ahmed's research interests are in the study of how women and men differ in terms of progression and complications of kidney disease, and how factors such as sleep apnea and nutrition play a role. She is an Alberta Innovates Health Solutions Investigator and is leading projects supported by the Kidney Foundation of Canada and the Heart and Stroke Foundation of Canada.

Dr. Ahmed is an advisory board member for the Institute of Gender and Health of the Canadian Institutes of Health Research (CIHR), the education chair for the Organization for the Study of Sex Differences, and is the sex and gender champion of the CIHR-funded Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD), a patient-oriented kidney research network.

She completed her MD and internal medicine residency at the University of Toronto and a renal fellowship at Brigham and Women's and Massachusetts General Hospital. She also completed a master's in medical sciences at Harvard University.

### Thu H. Le, MD

Dr. Le is the John J. Kuiper Distinguished Professor of Medicine and chief of nephrology at the University of Rochester.

As a physician-scientist, she is dedicated to patient care, research, and teaching. Her research focuses on kidney mechanisms and genetic determinants of susceptibility to hypertension and kidney disease progression. She has made seminal contributions in the understanding of how the *GSTM1* gene influences kidney disease progression in animals and humans, illustrating gene-gene and gene-environment interactions, and illuminating how the TMEM27 gene regulates blood pressure.

In addition to publishing in leading journals, she has authored book chapters on the renin-angiotensin-aldosterone systems in Seldin and Giebisch's *The Kidney: Physiology and Pathophysiology*. She has served on study sections for the American Heart Association, National Kidney Foundation, and National Institutes of Health.

Dr. Le has demonstrated a strong commitment to mentoring. She was the associate program director for the NIH T32 kidney disease and inflammation training program at the University of Virginia for 8 years. She has mentored seven junior faculty and 15 trainees including graduate students, nephrology fellows, and postdoctoral fellows. She has received multiple awards for excellence in teaching and clinical training, including the attending of the year in nephrology at UVA, a UVA department of medicine excellence in mentorship award, and the Castle Connolly Exceptional Women in Medicine Award.

A native of Vietnam, she earned her medical degree from George Washington University and completed her internal medicine and nephrology training at Duke University Medical Center. She was on the faculty at Duke from 2000 to 2009. She joined the UVA division of nephrology as associate professor in 2009, where she was awarded the Harrison Distinguished Endowed Chair in 2013 and promoted to Harrison Distinguished Professor of Medicine in 2017. She was recruited by the University of Rochester in 2018.

# 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.

### Derek M. Fine, MD

Dr. Fine is an associate professor of medicine at the Johns Hopkins University School of Medicine. He is the clinical director of the division of nephrology, having served as the Fellowship Program Director prior to his current role.

His area of clinical expertise includes glomerular diseases, particularly lupus nephritis and HIV-related kidney disease.

Dr. Fine's research has focused on optimizing renal outcomes in patients with kidney diseases, particularly those related to HIV and systemic lupus erythematosus. He has published many original research articles and reviews related to these areas.

He also published broadly on the natural history and clinical outcomes in HIV-infected individuals with kidney diseases in the era of highly active antiretroviral therapy. In addition, he has been a co-investigator on several National Institutes of Health grants and principal investigator on grants from the National Kidney Foundation Maryland Chapter.

His other research interests include the study of rhabdomyolysis and safety and outcomes of kidney biopsy.

He is a member of the Miller Coulson Academy of Clinic Excellence at Johns Hopkins and was named the 2018 Physician of the Year at Johns Hopkins Hospital.

Dr. Fine received his MD from Johns Hopkins, where he also completed his residency in internal medicine and fellowship in nephrology.

### Vandana Dua Niyyar, MD, FASN

Dr. Niyyar is professor of medicine in the division of nephrology at Emory University.

Her main clinical interest is in end stage kidney disease, with specific expertise in dealing with vascular access for hemodialysis patients. She is proficient in dialysis access procedures and in kidney ultrasonography, and is active in promoting multidisciplinary collaboration in research and education in the field of vascular access.

Dr. Niyyar serves the field in a variety of leadership roles, including as president-elect of the American Society of Diagnostic and Interventional Nephrology (ASDIN), and recently graduated as a fellow of the Woodruff Leadership Academy. She has represented ASN internationally through ASN Highlights and is a member of the ASN Continuous Professional Development Committee and the Kidney Week 2020 Reimagined Task Force. She is a co-author of the recent NephSAP Interventional Nephrology Update and has participated in workgroups including a vascular access task force, an interventional nephrology advisory group, and the Kidney Health Initiative.

Dr. Niyyar has taught at numerous training workshops regionally, nationally, and internationally. She co-chaired the ASDIN 2018 and 2019 scientific meetings, the 2018 and 2019 ASN and ASDIN ultrasound workshops and the 2019 National Kidney Foundation hands-on course. She has authored numerous manuscripts and is a regular reviewer for several nephrology journals.

After receiving her medical degree in India, she completed her internal medicine residency at the University of Louisville and her nephrology fellowship at Emory University.

# 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.

### Nisha Bansal, MD, FASN

Dr. Bansal is the Arthur Stach Family Endowed Professor in the division of nephrology at the University of Washington. She is also an investigator in the Kidney Research Institute, the associate director of the fellowship program, and the director of the kidney-heart service at UW.

Dr. Bansal's work has had a significant impact on clinical practice, policy, and the care of patients with kidney disease. Her research has advanced the understanding and treatment of cardiovascular disease among the high-risk population of patients with chronic kidney disease, for whom cardiovascular disease remains the leading cause of morbidity and mortality. Her research focuses on clinical, patient-oriented studies to understand the pathophysiology, diagnosis, and treatment of hypertension, cardiac arrythmias, and heart failure in patients with chronic kidney disease.

She has published extensively in top journals and her work has been cited in clinical practice guidelines and at national meetings. She has also played an important role in mentoring locally and nationally through multiple leadership positions.

She has been an active contributor to ASN, including her recent appointment as an associate editor for Kidney360.

Dr. Bansal received her medical degree from the University of Connecticut and her master's degree in clinical research from the University of California, San Francisco. She completed her internship and residency in internal medicine at Tufts Medical Center, followed by a nephrology fellowship at UCSF. Dr. Bansal was an assistant professor at UCSF prior to joining the University of Washington in 2013.

### Lesley Inker, MD

Dr. Inker is an associate professor at Tufts University School of Medicine as well as an attending physician in nephrology and medical director of the kidney and blood pressure center at Tufts Medical Center.

Dr. Inker's primary research interests are in kidney function measurement and estimation, alternative endpoints for clinical trials of kidney disease progression, and epidemiology and outcomes related to chronic kidney disease. She is an investigator on several trials of kidney disease progression.

She was the co-principal investigator of the Chronic Kidney Disease Epidemiology Collaboration. This effort pooled individual patient data to address central questions in the epidemiology of CKD and led to development of improved glomerular filtration rate estimation equations. She is currently investigating novel filtration markers, including low molecular weight proteins, beta trace protein, and beta-2-microglobulin.

Dr. Inker has led or collaborated in several research studies to evaluate kidney function in special populations, including HIV-positive patients, elderly patients, patients with severe liver disease, and patients with cancer. She is an investigator in the National Institute of Diabetes and Digestive and Kidney Diseases' effort to discover new markers for CKD.

Dr. Inker is also interested in research and policy related to implementation of CKD guidelines. She is the inaugural chair of the steering committee for the National Kidney Foundation patient network, which is the first national kidney disease patient registry. She also serves on the NKF scientific advisory board and co-chairs the clinical oversight committee of the Kidney Early Education Program. She is a member of the National Kidney Disease Education Program of the National Institutes of Health.

Dr. Inker received her MD from McMaster School of Medicine, in Hamilton, Ontario, and completed an internal medicine residency there. She completed clinical nephrology and research nephrology fellowships at the University of British Columbia. She received an MS in clinical research from Tufts.

### Shuta Ishibe, MD

Dr. Ishibe is associate professor of medicine in nephrology, director of the undergraduate summer research program for nephrology, and director of the research fellowship at Yale School of Medicine.

He is interested in defining the mechanism of proteinuria by studying podocytes. His team identified a network of proteins that human genetic studies have implicated to be causal for nephrotic syndrome.

Dr. Ishibe's laboratory identified the critical role of the clathrin-coated endocytic processes and cell matrix regulation in the podocytes in maintaining a functioning glomerular filtration barrier. The researchers used animal models with genetic knockout of genes implicated for endocytosis and cell matrix regulation to provide a framework to understand how slit-diaphragm proteins and receptors are recycled in the podocytes and how key focal adhesion proteins link integrins to actin. Further study of these knockout mice—which develop severe proteinuria, kidney failure, and foot process effacement—has allowed the researchers to identify potential targets for therapeutic interventions that may have human applicability to mitigate the progression of proteinuria-induced chronic kidney disease.

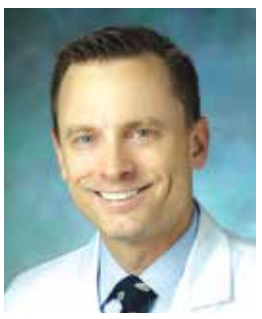
For ASN, he serves as an associate editor of Kidney360 and a reviewer for Kidney Week Abstracts and was a Kidney Week program committee member. He serves as a reviewer for a variety of journals.

Dr. Ishibe received his MD from the University of Texas Southwestern Medical School and completed an internship and residency at Parkland Memorial Hospital in Dallas.

# 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.



### John Sperati, MD

Dr. Sperati is associate professor of medicine in the division of nephrology at the Johns Hopkins University School of Medicine. He directs the nephrology fellowship training program, and previously was associate program director of the medical residency training program for 7 years. He has directly mentored more than 200 residents, fellows, and graduate students in the past 11 years.

Dr. Sperati has focused his clinical and educational efforts on thrombotic microangiopathies, hypertension, and fibromuscular dysplasia. He has lectured widely at national meetings and international institutions, in addition to helping to create care pathways and professional guidelines in the United States and abroad.

He has served the National Kidney Foundation as a member of its spring clinical meetings planning committee and its education committee. He is on the editorial board of *Advances in Chronic Kidney Disease and a section editor of Current Hypertension Reports*. He is a member of the American Board of Internal Medicine exam task force for nephrology. He developed an education seminar for large national and international companies that cultivates executive leadership using medical scenarios grounded in the Socratic method.

Dr. Sperati has received funding for clinical trials research in glomerular disease from the National Institutes of Health and industry.

He received his MD from the Pennsylvania State University College of Medicine and a master's in clinical epidemiology from the Johns Hopkins Bloomberg School of Public Health. He completed an internal medicine residency and nephrology fellowship at Johns Hopkins.

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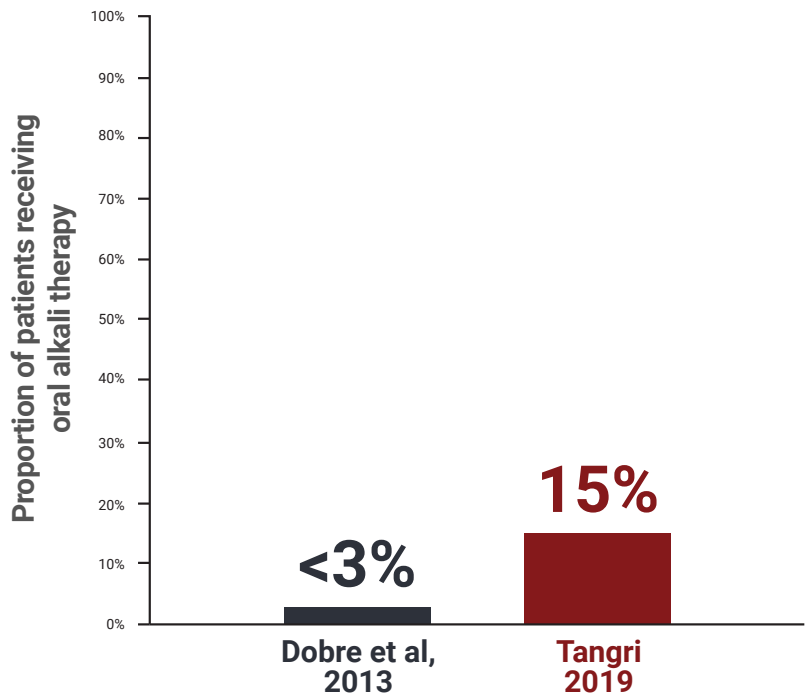
  - Less than 3% of the cohort were treated with oral alkali therapy[2]

**PATIENTS TREATED FOR METABOLIC ACIDOSIS**[1,2]

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**References: 1.** Tangri N. Metabolic acidosis is underdiagnosed and undertreated in patients with chronic kidney disease. Poster presented at: American Society of Nephrology Kidney Week 2019; November 5-10, 2019; Washington, DC. **2.** Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2013;62(4):670-678.



TRICIDA

# President's Medal Winners

## DRAWN FROM CDC AND ASN

Gisela Deuter, RN, MS

Priti R. Patel, MD

Two leaders from very diverse backgrounds will receive president's medals this year—Gisela Deuter, RN, MS, a former ASN staff member, and Priti R. Patel, MD, of the U.S. Centers for Disease Control and Prevention.

ASN awards the ASN President's Medal to individuals who have helped advance ASN's mission to lead the fight against kidney disease by educating health professionals, sharing new knowledge, advancing research, and advocating the highest quality care for patients.

Ms. Deuter provided outstanding and innovative leadership as a member of the ASN staff for 20 years. Her expertise and dedication enabled the society to develop, launch, and build the Nephrology Self-Assessment Program (nephSAP), now one of the premier educational programs in nephrology. The program has allowed kidney health professionals to extend their knowledge and enhance their ability to provide cutting-edge care.

Ms. Deuter also helped launch ASN Renal Weekends (now called ASN Highlights), expand educational offerings at ASN Kidney Week, and ensure ASN's accreditation as a provider of continuing medical education credits by the Accreditation Council for Continuing Medical Education.

Ms. Deuter received her nursing degree from Temple University, where she became a staff nurse at the university's inpatient dialysis unit, assistant nurse supervisor of the dialysis unit, renal research coordinator, and then nursing coordinator for continuous ambulatory peritoneal dialysis. In 1990, she moved from Philadelphia to Detroit to become the administrator of the nephrology and hypertension division at Henry Ford Hospital. While there, she added a master's degree in science administration from Central Michigan University. She joined the ASN staff in 2001 and retired in June 2020.

Dr. Patel was the dialysis activity leader in the Division of Healthcare Quality Promotion at the CDC and is a Captain in the U.S. Public Health Service. In this role, she has led the CDC's dialysis patient safety program, including infection prevention, surveillance, and outbreak response activities, for close to 15 years. She has supervised the response to many outbreaks of infections and other adverse events in dialysis centers, has overseen the National Healthcare Safety Network's Dialysis Event surveillance system, which tracks infection events among patients in over 6800 participating hemodialysis facilities, and worked closely with the Centers for Medicare & Medicaid Services to strengthen infection prevention elements of end stage renal disease quality and safety programs.

Dr. Patel co-led an initiative to reduce bloodstream infections among dialysis patients. Her team demonstrated that these infections could be prevented through adherence to a set of catheter care and infection prevention practices, which led to participating facilities lowering their rates of infection.

In 2016, Dr. Patel helped to launch the CDC's Making Dialysis Safer for Patients Coalition and served as the coalition's medical director. Through this coalition, the CDC developed partnerships with more than 90 kidney community, public health, and patient safety organizations committed to preventing hemodialysis-associated infections. Dr. Patel has also served as a CDC representative to ASN's Nephrologists Transforming Dialysis Safety Project Committee.

Dr. Patel has authored more than 80 peer-reviewed journal articles, book chapters, and other scientific publications. She contributed to the Department of Health and Human Services National Action Plan to Prevent Healthcare-Associated Infections in ESRD facilities and the Association for Professionals in Infection Control and Epidemiology (APIC) Guide to the Elimination of Infections in Hemodialysis.

She received a patient engagement and advocacy award from the American Association of Kidney Patients for her contributions to improving the lives of kidney patients.

Dr. Patel received her MPH degree from the Columbia University School of Public Health and attended medical school at Howard University. She completed her internal medicine residency at the University of Pennsylvania, and then served as an epidemic intelligence service officer in the Division of Viral Hepatitis at the CDC. She completed a preventive medicine residency at the CDC and was assigned to the Maryland Department of Health and Mental Hygiene. ■

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## Partial Nephrectomy in Patients with Severe CKD: Outcomes and Risk Factors

Some groups of patients with clinically localized kidney tumors and severe chronic kidney disease (CKD) are at high risk of adverse outcomes after partial nephrectomy (PN), according to a study in *The Journal of Urology*.

The retrospective study included 62 patients with clinically localized kidney tumors (T1-T2/N0M0) and stage 4 CKD who underwent PN at the Cleveland Clinic between 1999 and 2015. The patients were 44 men and 18 women, median age 67 years. Comorbid diseases were common, including hypertension in 94% of patients, cardiovascular disease in 53%, and diabetes in 32%. Median estimated glomerular filtration rate (eGFR) was 23 mL/min/1.73 $m^2$. Follow-up data were used to analyze factors associated with time to progression to end stage kidney disease (ESKD).

The surgical approach was open in nearly three-fourths of patients. Sixteen percent were found to have benign tumors; 37% had grade 3/4 tumors and 11% had pT3a disease. Adverse outcomes occurred in 24% of patients: 3% died within 90 days, 14% had Clavien grade IIIb or higher complications, and 12% had positive surgical margins.

Median time to ESKD was 27 months overall but differed substantially according to baseline kidney function: 58 months for patients with baseline eGFR greater than 25 mL/min/1.73 $m^2$ versus 14 months with eGFR less than 20 mL/min/1.73 $m^2$. The effect of preoperative eGFR remained significant on multivariable analysis: hazard ratio (HR) 2.59 at 20 to 25 mL/min/1.73 $m^2$ and 5.03 at less than 20 mL/min/1.73 $m^2$. Other independent risk factors were African American race, HR 2.55, and minimally invasive surgical approach, HR 2.05.

For oncologic patients with CKD, PN is preferred over radical nephrectomy, if possible. However, when severe CKD is present, the morbidity associated with PN may not be justified—particularly if it leads to rapid progression to ESKD.

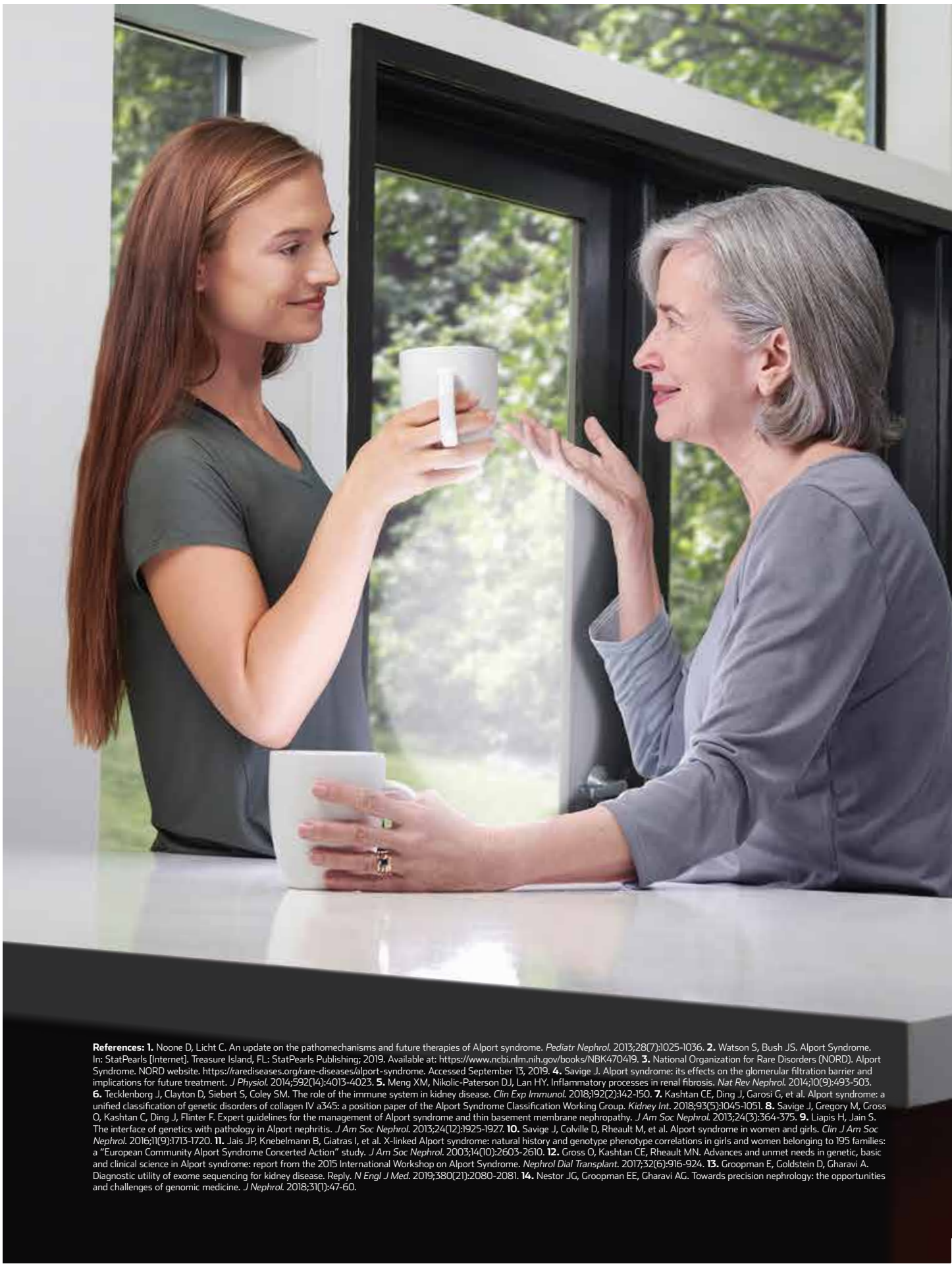
The new findings show a substantial risk of adverse outcomes after PN in patients with stage 4 CKD. "Renal mass biopsy should be strongly considered to improve oncologic risk stratification and patient selection," the researchers write. They suggest that alternate strategies may need to be considered for patients with risk factors including very low baseline eGFR, African American race, or high-complexity PN [Palacios DA, Li et al. Partial nephrectomy for patients with severe chronic kidney disease—is it worthwhile? *J Urol 2020; 204:434–441. doi: 10.1097/JU.0000000000001021].* ■

## Disparities in Predialysis Nephrology Care Persist, Study Finds

Recent years have brought little progress toward reducing disparities in access to predialysis nephrology care among racial/ethnic minority patients in the United States, concludes a study in *JAMA Network Open*.

The study included data on more than 1 million adults who initiated maintenance dialysis between 2005 and 2015, drawn from the US Renal Data System. The patients were 57.2% male; mean age was 62.4 years. Race/ethnicity was white in 54.6% of patients, Black in 27.8%, Hispanic in 14.0%, and Asian in 3.6%. Multivariable logistic regression analyses were performed to analyze trends in racial/ethnic disparities in receipt of at least 1 year of nephrology specialty care before the start of dialysis.

Overall, 31.1% of patients received at least 1 year of predialysis nephrology care. For all racial/ethnic groups, unadjusted rates of predialysis nephrology care increased between 2005–07 and 2014–15: from 30.1%



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to 39.5% for white, 24.5% to 32.5% for Black, 21.2% to 28.3% for Hispanic, and 26.1% to 37.1% for Asian patients.

On adjusted analysis, racial/ethnic minorities remained less likely to receive specialty care in the year before dialysis, compared to white patients. In 2005–2007, odds ratios (ORs) were 0.82 for Black, 0.67 for Hispanic, and 0.84 for Asian patients. These odds were little changed in 2014–2015: OR 0.76 for Black, 0.61 for Hispanic, and 0.90 for Asian patients. Exploratory mediation analyses suggested that racial/ethnic differences in health insurance type were more strongly associated with small reductions in racial/ethnic disparities, compared to other factors.

Among patients with end stage kidney disease, survival is significantly better for those receiving nephrology care before initiating dialysis. Increasing the percentage of patients who are treated by a nephrologist for at least 12 months before starting dialysis is a key part of Healthy People 2020 objectives for chronic kidney disease (CKD).

The new study provides evidence that racial/ethnic disparities in predialysis nephrology care have persisted over the past decade and suggests the need for national strategies targeting differences in access to specialist care for CKD. They conclude: "Potential strategies may include national efforts to enhance collaborations between primary care providers and nephrologists, particularly for members of racial/ethnic minority groups" [Purnell TS, et al. National trends in the association of race and ethnicity with predialysis nephrology care in the United States from 2005 to 2015. *JAMA Netw].*



# Outset Medical Goes Public

Outset Medical, based in San Jose, CA, went public on the Nasdaq exchange on Sept. 17, 2020, with a $241.7 million initial public offering (IPO). The IPO made quite a splash on the market. Nasdaq tweeted: "OM [Nasdaq trading symbol for Outset Medical] has the highest raise in 2020 of healthcare equipment and technology companies."

In a year in which hospitals have been battered by the COVID-19 pandemic, Outset Medical was ready with a product not only needed in healthcare settings, but also in homes. The company raised $125 million earlier in 2020 to make its product commercially viable, FierceBiotech reports. On March 31, the company received US Food and Drug Administration approval to use the system in patients' homes. The first patient was trained and used the system at home on July 13 in New Jersey.

The portable, four-wheel dialyzer Tablo unit is simple to operate. It requires an electrical outlet and tap water to make the dialysate and includes a wireless cloud connection for monitoring data. The system contrasts with other systems that require separate equipment for purifying water and generating dialysate.

The future remains to be written, but Seeking Alpha, an investment website, says Outset Medical's Tablo could spread widely into homes, which would quadruple its market presence.

"Basically, in a time period of just 1 to 2 years, Outset Medical has grasped a $50 million run rate in a market segment pegged at $2.2 billion, as home sales were cleared just a quarter ago," Seeking Alpha's Value Investor column states. "If the company can see the same adoption in the home care market, it might be a $200–$300 million business in a year or two."

Outset Medical was a winner of the 2019 KidneyX Redesign Dialysis competition. The KidneyX competition is a partnership between ASN and the US Department of Health and Human Services to support innovative strategies for tackling kidney diseases.

**KidneyCure congratulates the talented group of individuals awarded grants in 2020.**

With support from ASN members, industry partners, and nephrology leaders, KidneyCure (the ASN Foundation) provides approximately $3,000,000 annually to young researchers, fellows, and nephrology educators who are changing the future of kidney care. By providing financial security and protected research time, foundation grants encourage investigators to take innovative approaches to understanding the full spectrum of kidney diseases, from prevention to transplantation, that will soon lead to cures.

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# Transition to Independence Grants Program

The program invests $100,000 annually for two years to foster independent research careers and ensure a pipeline of innovative research in the field of nephrology. The Transition to Independence Grants Program is supported by contributions provided by ASN, Akebia Therapeutics, Inc., Amgen, and individual donors.

### Carl W. Gottschalk Research Scholar Grant Recipients

**Mark R. Hanudel, MD, MS, FASN***
*The Pathological Effects of Fibroblast Growth Factor 23 Fragments*

**Sho Morioka, PhD**
*Boosting Apoptotic Cell Removal During Acute Kidney Injury*

**Sanjeev Noel, PhD**
*T Cell TIGIT/CD226 Co-signaling in Acute Kidney Injury and Repair*

**Jin Wei, PhD**
*Role of Macula Densa RXFP1 in Gestational Hypertension*

**Ting Yang, MD, PhD**
*Renal Epithelial Actions of the Prostaglandin EP4 Receptor in Blood Pressure Control*

**Jie Zhang, PhD**
*A New Mechanism for the Sex Differences in Diabetic Glomerular Hyperfiltration and Kidney Injury*

### Joseph V. Bonventre Research Scholar Grant

**Sian Piret, PhD**
*Transcriptional Regulation of Proximal Tubular Amino Acid Metabolism in AKI*

### John Merrill Grant in Transplantation

**Liwei Jiang, PhD**
*Microengineering Third Party Off-shelf-biological Skin Construct for Burn Patient*

### Norman Siegel Research Scholar Grant

**Amar J. Majmundar, MD, PhD**
*Dissecting the Molecular Pathogenesis of NOS1AP and TRIM8 Mutations in Monogenic SRNS/FSGS*

# Ben J. Lipps Research Fellowship Program

Funding ten new research projects annually, the program distributes $50,000 for two years to conduct original, meritorious research. The Ben J. Lipps Research Fellowship Program is fully endowed by contributions provided by Fresenius Medical Care, ASN, the American Renal Patient Care Foundation, Inc., Amgen, Baxter, and the PKD Foundation.

### Ben J. Lipps Research Fellows

**Michael D. Donnan, MD***
*Defining the Role of Vascular Endothelial Growth Factor 3 (VEGFR3) in the Fenestrated Microvascular Beds of the Kidney*

**Seolhyun Lee, MD***
*Improved Removal of Protein-Bound Solutes During Hemodialysis by Partial Regeneration of the Dialysate*

**Kyle McCracken, MD, PhD***
*Characterization and Manipulation of Proximal Tubule Development in Kidney Organoids*

**Yuvaram Reddy, MBBS**
*Novel Methods to Inform Health Care Policy in Home Dialysis*

**Joshua S. Waitzman, MD, PhD**
*Structure and Molecular Mechanism of ApoL1*

### Sharon Anderson Research Fellow

**Mohammad Kazem Fallahzadeh Abarghouei, MD***
*Identifying Opportunities for Improved Cardiovascular Care Delivery Among Kidney Transplant Recipients*

### Joseph A. Carlucci Research Fellow

**Ankit B. Patel, MD, PhD**
*Derivation of Collecting Duct Principal Cells from Induced Pluripotent Stem Cells by Direct Programming via Transcription Factor Expression*

### Jared J. Grantham Research Fellow

**Qinzhe Wang, MS, PhD**
*Cryo-EM Structures of Polycystic Kidney Disease Proteins*

### Donald E. Wesson Research Fellow

**Russell S. Whelan, MD, PhD***
*Dissecting Shigatoxin-mediated Endothelial Injury in Engineered Renal Microvasculature*

### KidneyCure Research Fellow

**Irene Chernova, MD, PhD***
*The Role of Na-K-ATPase in the Pathogenesis of Lupus Nephritis*

# William and Sandra Bennett Clinical Scholars Program

Funded annually, the program provides $50,000 for two years to a nephrology educator to conduct a project to advance all facets of nephrology education and teaching.

**Samira S. Farouk, MD, MS, FASN**
*Implementation and Assessment of a Mobile-Optimized, Simulation-Based Nephrology Teaching Tool for Undergraduate Medical Education*

# ASN Pre-Doctoral Fellowship Program

The ASN Pre-Doctoral Fellowship Program provides funding to early career-stage PhD students to conduct original research projects and make contributions to the understanding of kidney biology and disease.

**Mariia Alibekova, BS**
*Elucidating the Role of Cell Microenvironment and Cell Differentiation Decisions in Kidney Organoid Heterogeneity Towards Better Models of Kidney Development and Disease*

**Alexander Flannery, PharmD***
*Alternative Renin Angiotensin |Aldosterone System (RAAS) Activation and RAAS Therapeutics in Septic-Shock Associated Acute Kidney Injury*

**Tessa Huffstater, BS, M.Eng.***
*Inhibition of Cadherin-11 in Acute Kidney Injury and Chronic Kidney Disease*

**Yan Xie, MPH***
*Comparative Effectiveness of Newer and Older Antihyperglycemic Medications on Chronic Kidney Disease*

# ASN-Harold Amos Medical Faculty Development Program

The ASN-Harold Amos Medical Faculty Development Program aims to increase diversity among future leaders in nephrology by supporting the research and career development of a kidney scholar and future health care leader from a historically disadvantaged background.

**Jason A. Watts, MD, PhD**
*Regulatory Mechanism of RNA Polymerase Pausing Affects Gene Expression in the Kidney*

** Kidney Week 2020 oral and/or poster abstract presenter*

# Classified



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

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

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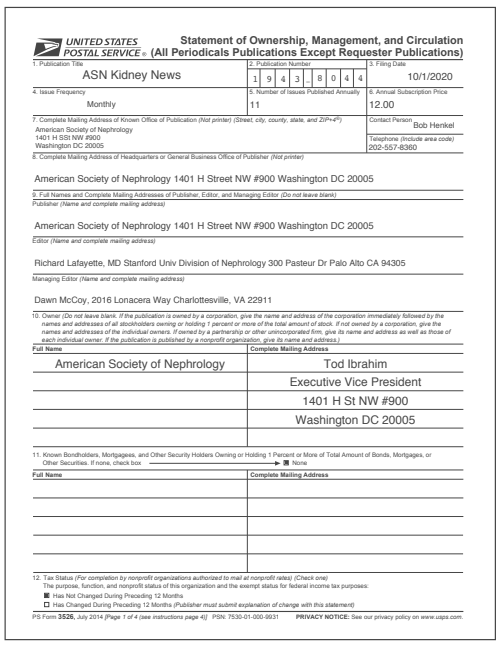

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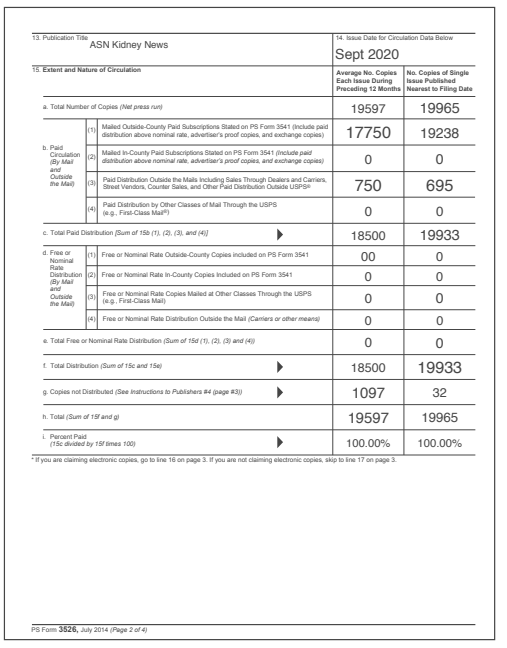

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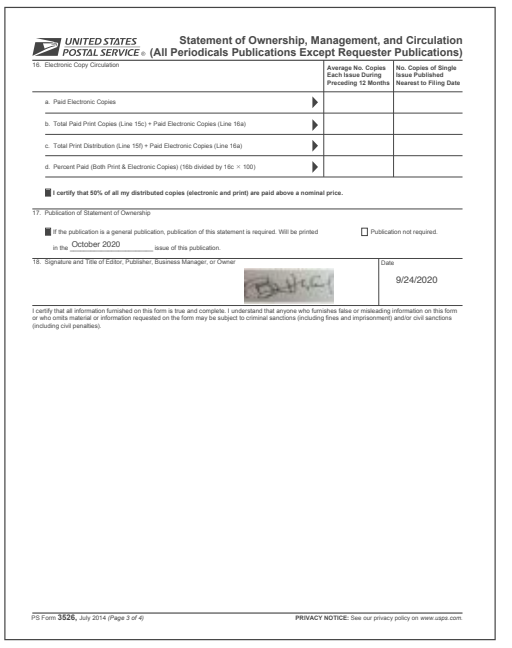

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