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NKF, ASN Recommend State Medicaid Changes to Allow Coverage of Scheduled Dialysis for Undocumented Patients

By Bridget M. Kuehn

It's a week-to-week challenge for Eric Wallace, MD, and his colleagues to treat patients with end stage kidney disease (ESKD) who are undocumented immigrants. Many are young people in their 20s and 30s who are working or in school; one recently was pregnant. They are not eligible for coverage under Medicare and cannot buy coverage through the Affordable Care Act on state exchanges. If they cannot buy private insurance, their only option for care is emergency dialysis, which is covered by the Emergency Medical Treatment and Active Labor Act (EMTALA).

"All of us are hoping and praying they make it to their next treatment," said Wallace, who as medical director of home dialysis at the University of Alabama at Birmingham frequently cares for undocumented Latinx patients. He worries that a patient may have an emergency between visits and wait too long to seek help. The situation is especially heart-breaking for Wallace, whose mother came to the United States from South America as an undocumented immigrant at 18 years old and later became a citizen.

"We are treating one set of human beings differently, and they are young and exactly like my mom when she came over," Wallace said. "You get patient and provider burnout because we are providing substandard care."

Emergency dialysis also contributes to worse outcomes for the estimated 5000 to 7000 undocumented patients with kidney failure in the United States (1) and is about 4 times more costly than scheduled dialysis (2). These costs are paid for by the hospital or state Medicaid programs. To reduce these burdens, at least 12 states have already expanded their Emergency Medicaid programs to cover scheduled outpatient dialysis for this vulnerable group of patients (3). In August 2021, the ASN signed on to a letter from the National Kidney Foundation (NKF) urging more state Medicaid directors to make this change as well as to cover home dialysis.

"The kidney care these individuals receive is inhumane, extraordinarily expensive, and largely ineffectual," the NKF

Continued on page 5

Does Nephrology Need *U.S. News & World Report* Rankings?

By T. Alp Ikizler and Beatrice Concepcion

Annually, *U.S. News & World Report* (*USNWR*) publishes a ranking of the best hospitals in the United States by adult specialties. According to the *USNWR* website, the aim of these rankings is to provide a tool for patients with life-threatening or rare conditions that would help them find skilled inpatient care at a hospital that excels in treating complex, high-risk cases (1). Hospitals are ranked from 1 to 50 in each specialty, and any hospital in the top 10% of all rated hospitals (but not ranked in the top 50) is given a "high performing" designation (1).

In addition to ranking hospitals by specialties, *USNWR* also rates hospitals on their performance of procedures and treatment of specific conditions. Hospitals are rated as high performing, average, or below average for each specific procedure and condition. Based on the cumulative performance in specialty rankings and procedures and conditions, the Best Hospitals Honor Roll recognizes the nation's top 20 hospitals. In 2020–2021, a hospital's overall score partly came from rankings of 12 "data-driven" specialties (including nephrology) comprising components for patient experience (patient surveys, 5%), discharge-to-home metric (7.5%), reputation

Continued on page 7

Inside

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Kerendia®
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In adult patients with CKD associated with T2D KERENDIA is indicated to reduce the risk of[1]:

- **Sustained eGFR decline**
- **End-stage kidney disease**

- **CV death**
- **Non-fatal MI**
- **Hospitalization for heart failure**

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

INDICATION:

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

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

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

MOST COMMON ADVERSE REACTIONS:

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

Visit KerendiaHCP.com for more information and to request samples from a representative

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS:

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

USE IN SPECIFIC POPULATIONS:

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

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

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

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

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

Kerendia is contraindicated in patients:

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

5 WARNINGS AND PRECAUTIONS

5.1 Hyperkalemia

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

Laboratory Test

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

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors and Inducers

Strong CYP3A4 Inhibitors

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

Moderate and Weak CYP3A4 Inhibitors

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

Strong and Moderate CYP3A4 Inducers

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

7.2 Drugs That Affect Serum Potassium

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

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

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

10 OVERDOSAGE

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

Manufactured for:

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Whippany, NJ 07981

Manufactured in Germany 6711200BS1A

NKF, ASN Recommend State Medicaid Changes

Continued from page 1

letter states. "Our organizations believe it is imperative that state policymakers act expeditiously to follow the lead of states like Arizona and Colorado and expand Emergency Medicaid for undocumented immigrants living in the United States."

"Gut wrenching"

When Oanh Nguyen, MD, assistant professor in the Division of Hospital Medicine at the University of California—San Francisco, started seeing patients as an intern at Parkland Hospital in Dallas, she was shocked to learn that patients with ESKD who were undocumented immigrants received emergency dialysis instead of scheduled dialysis. She had gone to medical school in California where the state's Medicaid program covers scheduled dialysis for this vulnerable population and described what she saw during her residency and later as a member of faculty as "gut-wrenching."

"These were good, honest, hardworking people just trying to support their families," Nguyen said. "They were just so grateful to be receiving any care, but it was hard to be face-to-face with them knowing that this is not the type of care they should be receiving."

As a resident at Indiana University in Indianapolis, Areeba Jawed, MBBS, assistant professor of medicine at Wayne State University in Detroit, saw the difference that scheduled dialysis can make for these patients. The safety net hospital she was interning at initially offered scheduled dialysis as charity care to undocumented immigrants, but a change in leadership led to the decision to switch to emergency dialysis. As a result of the policy change, she and her colleagues saw a decline in patients' health. One young man wanted to do his emergency dialysis on the weekends to continue working during the week to support his family. But like many patients on emergency dialysis, he lost residual kidney function over time.

"We saw him deteriorate to the point that he just couldn't survive without dialysis between Monday and Friday; he couldn't continue to work," she said. Jawed's experience is now backed by a growing evidence base showing emergency dialysis leads to poor outcomes and is less cost effective than scheduled dialysis for these patients.

When a change in national policies allowed some of Nguyen's patients who were undocumented to purchase private insurance in 2015, she used it as an opportunity to compare outcomes and costs for the patients who were able to begin scheduled dialysis covered by private insurance with those who remained on emergency dialysis (4). She found that the 1-year mortality rate for patients who remained on emergency dialysis was 17% compared with just 3% among the patients who switched to scheduled dialysis. The patients on scheduled dialysis had six fewer emergency department visits a month and spent 10 fewer days in the hospitals for every 6 months. This translated to $5700 less in healthcare costs per month, or about $70,000 per year for the scheduled dialysis patients.

A retrospective study led by Lilia Cervantes, MD, associate professor of hospital medicine at the University of Colorado School of Medicine, comparing outcomes among 211 undocumented patients who received scheduled dialysis in California or emergency dialysis in Texas or Colorado, found 14 times higher 5-year mortality among those receiving emergency dialysis (5). The patients receiving emergency dialysis also required 10 times more days of acute care than those receiving scheduled dialysis. Patients also report experiencing extreme physical and psychological distress, often feeling like they are drowning or can't breathe as they accumulate fluids between visits (6).

"Patients described death anxiety, feeling that they didn't know if they would live from week to week," Cervantes said. It can also have a devastating effect on families. A young mother named Hilda, who Cervantes cared for, with two school-aged children experienced three heart attacks causing distress for her children (7). Hilda eventually found a family to adopt her children and chose to end dialysis and pursue palliative care until she passed away.

Seeing these outcomes and feeling unable to provide better care cause moral distress for many clinicians. A survey of clinicians at a safety net hospital in Indianapolis, Indiana, found that almost three-quarters experienced distress over patients suffering because of inadequate dialysis (8). Another study of clinicians caring for these patients also reported high levels of moral distress, burnout, and frustration over this poor use of health resources (9).

"It puts physicians in a position where we feel helpless and inhumane," Wallace said.

Moving the needle

Hilda's case inspired Cervantes and her colleagues to study this issue and push for a change in Colorado's Medicaid policies. Colorado made the change to its policies in 2019, which is expected save the state $17 million a year (10). It also has led to dramatic improvements in patients' health and quality of life (6). She said support from national organizations like NKF and ASN for more states to make this change may help further "move the needle."

There was a clear consensus among the members of the ASN Quality Committee to support signing on to the letter, said the committee's chair, Scott Bieber, DO, a nephrologist at Kootenai Health in Coeur D'Alene, Idaho. Bieber, who has practiced in states with and without Medicaid coverage for scheduled dialysis, said there is a stark difference in the quality of care patients receive.

"[Scheduled dialysis] is the right thing to do to keep patients healthy," Bieber said.

The NKF-ASN letter also advocates for coverage of home dialysis. Wallace, who is also a member of the ASN Quality Committee and a Medical Director of Home Dialysis, said home dialysis in particular may help improve patients' quality of life by enabling them to continue with school or work. He called the letter "a first step" and said he'd like to go further to offer transplant as well. Bieber noted that many other committee members shared that sentiment.

"As the data illustrate, the manner in which undocumented people with kidney failure are treated is needlessly expensive," the letter states. "At a time when states' budgets are under enormous pressure, ensuring that undocumented people with kidney failure can access Emergency Medicaid is just common sense."

There are also potential cost savings for hospitals that may have to cover the costs of emergency dialysis. In her study, Nguyen estimated that switching all undocumented patients from emergency dialysis to scheduled dialysis would save Parkland Hospital $13 million a year. The study inspired the hospital to change its policy and work with outpatient dialysis providers to provide scheduled dialysis for undocumented patients, she said. Now, they are piloting home peritoneal dialysis, which may further reduce costs and improve patients' quality of life. Nguyen acknowledged there are challenges in reliably estimating potential cost savings. But she said evidence from California suggests that contrary to some opponents' fears, allowing coverage for scheduled dialysis does not lead to an influx of undocumented patients seeking dialysis.

"Scheduled dialysis should be the universal standard of care for everyone," she said. "There is really no reason to withhold that standard of care from an ethical or even an economical standpoint."

Additionally, offering scheduled outpatient dialysis allows hospitals to more effectively deploy their resources to serve their entire communities, Nguyen said. Jawed said this is particularly important now in the face of the pandemic. Requiring undocumented patients with kidney failure to come into the emergency department for dialysis increases their risk of becoming infected as well as adds to the burden of already overwhelmed clinicians and facilities running short on beds, said Jawed, who documented the disproportionate toll COVID-19 has taken on undocumented patients with ESKD in a recent *Kidney News* article (11). She noted that undocumented immigrants are often frontline workers and may live in crowded housing, increasing their risk of infection.

Jawed said that while physicians may not ultimately make the decision about what policies to enact, they have a role to play in shaping policies. She noted they can help by recognizing the contributions that undocumented immigrants make to our communities whether through the jobs they do or the taxes they pay. They can also make decision-makers aware of how policies are affecting patients, clinicians, and care systems.

"This is an area where not just nephrologists but all clinicians can really come together in solidarity and advocate for a very vulnerable or marginalized population," Cervantes said. ■

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Does Nephrology Need *U.S. News & World Report* Rankings?

Continued from page 1

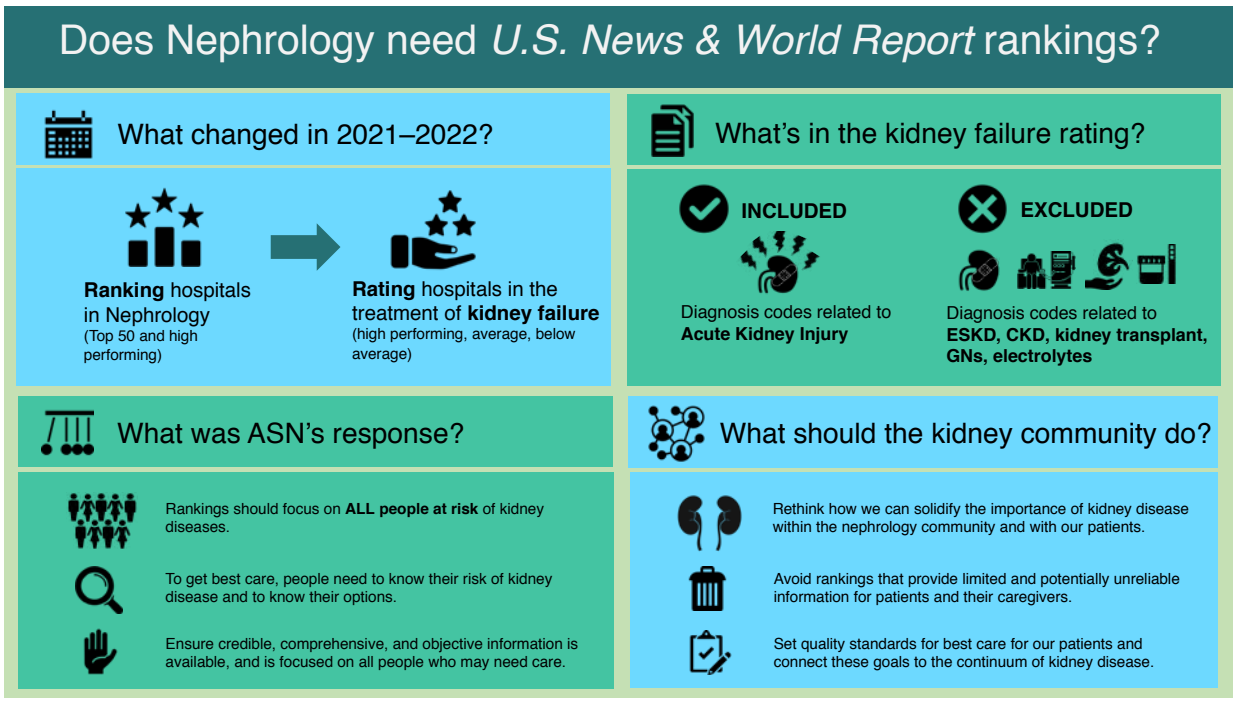
(27.5%), structure (capturing staffing and patient services, advanced technologies, external designations [e.g., nurse magnet], trauma center, intensivists, and volume, 30%), and 30-day mortality (30%). A document detailing the methodology for ranking hospitals and specialties can be found on the *USNWR* website (2).

What changed, and what is the relevance to nephrology?

In an unprecedented move, *USNWR* did not include nephrology among the 15 adult specialties listed in the 2021–2022 rankings. It is common for *USNWR* to make changes in its evaluation process on a yearly basis, but based on the communication by *USNWR* prior to its release, this was not an expected change, at least within the nephrology discipline. Instead of ranking nephrology as a specialty, as has been done in the past, a new "kidney failure" condition was included among 17 procedures and conditions that were rated (3). Although the rationale for this change is not explicit, the *USNWR* website notes that the kidney failure rating covers nearly all of the same hospital admissions as adult nephrology (1). It is important to note that despite rating hospitals in the treatment of conditions such as chronic obstructive pulmonary disease, congestive heart failure, or diabetes, the specialties of pulmonology and lung surgery, cardiology and heart surgery, and diabetes and endocrinology remain on the list of ranked specialties.

The relevance and utility of *USNWR* ratings and rankings have been long debated and are not the focus of this commentary. Nevertheless, it is important for the nephrology community to understand what these ratings and rankings represent. First and foremost, the clinical relevance of the *USNWR* kidney failure rating, the only grading for nephrology in 2021–2022, is limited to only a subset of patients with kidney disease, i.e., ones with acute kidney injury (AKI) (3). In other words, the care delivered by institutions for chronic kidney disease (CKD), end stage kidney disease (ESKD), and kidney transplantation is not included in the evaluation process. Although speculative, this change might be an attempt by *USNWR* to be consistent with its original premise of "a tool for patients with life-threatening or rare conditions that would help them find skilled inpatient care at a hospital that excels in treating complex, high-risk cases." AKI does indeed represent a high-risk and life-threating condition, but it constitutes only a small fraction of (hospitalized) patients with kidney disease (see below). Second, *USNWR* is a customer-oriented service allowing the clients (patients in this case) to explore and choose the product (the hospital in this case) to seek the best care. The ratings are based on the relevant information from the procedure and diagnosis codes. Accordingly, the rating system in place is more than adequate to provide an understanding of whether the hospital can manage a patient with AKI. On the other hand, it is of course debatable how much autonomy or opportunity a patient has when choosing a hospital in the setting of AKI because the condition is usually diagnosed after the index hospitalization, and the choice of kidney replacement therapy is usually straightforward once the patient is hospitalized. In rare circumstances, a patient requiring a complex dialysis procedure may be referred to a tertiary hospital due to the lack of services. Even in that case, the patient has minimal to no input because the options are limited to availability.

In terms of rankings, the previous years did include ESKD and CKD codes, reflecting a more thorough catchment of patients with kidney disease for data-driven nephrology rankings. Some of these conditions included glomerular diseases, gout and diabetes-related kidney disease, and kidney transplant status, although nephrology service covers much more than these select diagnoses, especially only when captured during a hospitalization. The rankings were also influenced by recognition of peers, i.e., how many nephrologists considered the hospital as one of the best. Notably, the selection of these peer groups was dependent on many questionable factors, such as being a part of a mailing list or membership to certain online applications. Finally, the hospital's operational resources and size played a significant role in the final rankings. In the end, it was not surprising to see some highly prestigious institutions dominate the top 10 for many years in a row, regardless of many factors that the nephrology community would consider a reflection of high-quality service.



What is the relevance of ASN's announcement in response to *USNWR*'s rankings?

As the leading entity representing physicians and healthcare workers involved in kidney disease, the American Society of Nephrology (ASN) released a statement when the news broke that nephrology was excluded from data-driven rankings by *USNWR*. In its statement, ASN highlights several important issues: the significantly limited relevance of these ratings in terms of patient population considered (2%), the importance of recognizing kidney disease that affects almost 1 out of 6 individuals in the United States, and an overview of how rankings and ratings are developed and their implications. In this document, targeted toward patients and their caregivers, ASN pledges to make sure credible and comprehensive information from experts is available to the public, to include all people who need care in these rankings, to avoid inappropriate use of rankings and ratings, and to urge legislation to oversee the objectiveness of these measurements. ASN also provides a short but very comprehensible overview of the rankings."

How does this impact the nephrology discipline, and what should the kidney community do?

The ASN leadership should be commended for responding to this unexpected change by *USNWR*. The basic knowledge and impetus provided by this document give us a reason to rethink how we can solidify the importance of kidney disease within the nephrology community as a whole and with our patients. In that sense, it may be a blessing in disguise that *USNWR* excluded nephrology from its rankings since rankings provide not only very limited information but also potentially unreliable information that could lead to misconception by patients and their caregivers. One of the most appealing aspects of nephrology as a discipline is its unparalleled breadth and depth of patient diversity, ranging from diseases that have a primary impact on kidney histology but normal kidney function to ones where there is no residual function, but patients are still able to live close to a normal life for long periods, unlike in any other solid organ failure. For individuals or institutions managing such a complex and multi-faceted patient population, a single ranking system not only would be unfair, but also unnecessary. It is more reasonable to set quality standards for the best care for our patients with the overall goal of providing optimal kidney disease management. In doing so, it is important to connect the quality goals to the continuum of kidney disease to avoid creating silos of clinical care. Nephrology has always been at the forefront of major advancements in healthcare that have significant, direct implications for patients, such as long-term dialytic therapies, solid organ transplantation, and bundled payment models. It is again nephrologists' responsibility to act, so as to not only participate in currently established quality standards by legislators but also to create and redefine standards that are most important to our patients and their caregivers. ■

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The authors report no conflicts of interest related to this article.

The Division of Nephrology and Hypertension at VUMC ranked 7th, 9th, and 10th in *USNWR* rankings over the past 3 years. The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of VUMC. Responsibility for the information and views expressed herein lies entirely with the authors.

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Maximizing the Educational Value of Tweetorials

By Amy A. Yau and Sayna Norouzi

Using Twitter is the great new foray of medical education. It is free and easily accessible, and information is available as short "bite-sized" tweets. Threading together multiple tweets to create a tweetorial is one popular method to reach and educate learners (1) (Figure 1). Beyond dissemination of knowledge, tweetorials are also seen as a tool to stimulate medical curiosity, which has the added benefits of encouraging independent study and critical thinking (2, 3). However, given the lack of definitive studies linking social media and educational outcomes, this begs the question of how to best maximize the educational value of tweetorials (4–6).

For creators, a few tips are provided, but it is important to plan a tweetorial just as you would a lecture (Table 1). First, identify your target audience. Next, pick a topic, and define learning objectives (Figure 2). More specialized topics will narrow your audience, but broader topics may lend to a lengthier tweetorial, which may be off-putting to readers (1). When crafting your tweetorial, the first one or two tweets are the hooks to draw in your reader. The following tweets, or at most pair of tweets, should guide your reader and answer objectives. Your final summary tweet helps reiterate important concepts. A strong summary tweet can also inspire readers to go back and read tweets that they may have initially glossed over (1).

Despite your best efforts, the vast majority of readers will not make it past the first or even second tweet (1). The best tweetorial is a read tweetorial. Keep your reader engaged by making it interactive. Use polls, and respond to questions and replies. Provide visuals such as images, tables, figures, and GIFs (Graphics Interchange Format). Provide links to source material, additional reading, blogs, and YouTube videos. If you cannot find an appropriate table or figure, then consider making your own. Consider supplementing your tweetorial with a homemade animation, video, or audio recording. This has the added benefit of catering to different learning styles and further increasing your educational reach and retention (7).

As a tweetorial consumer, maximize your learning by really taking time to read a tweetorial. Look at the images and figures. Open links; read cited material. Think about the content, and ask questions. We encourage readers to read replies to the original thread and "Quote Tweets." Use tweetorials as a springboard to supplement your current education, or dig deeper into a topic of interest.

Not every tweetorial will and should be the same. Just as educator styles vary, so will tweetorial styles. Remember to be engaging, and have fun! For more examples of tweetorials check out the Renal Fellow Network "Have a Nephrology Question? There Might Be a #Tweetorial for That!" post (https://www.renalfellow.org/have-a-question-there-might-be-a-tweetorial-for-that/)(8), and if you want to learn more about how to construct tweetorials, consider joining the Nephrology Social Media Collective. ■

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Drs. Yau and Norouzi are co-leaders with the Nephrology Social Media Collective Blog and Tweetorial Rotation.

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Figure 1. Example of a tweetorial

For more examples, please check out the Renal Fellow Network (8).

Figure 2. A taxonomy of educational objectives

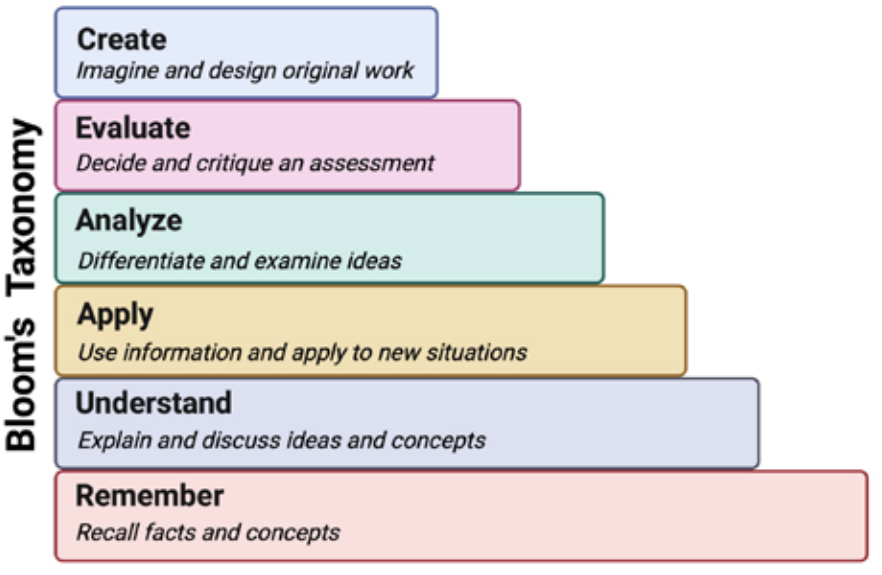
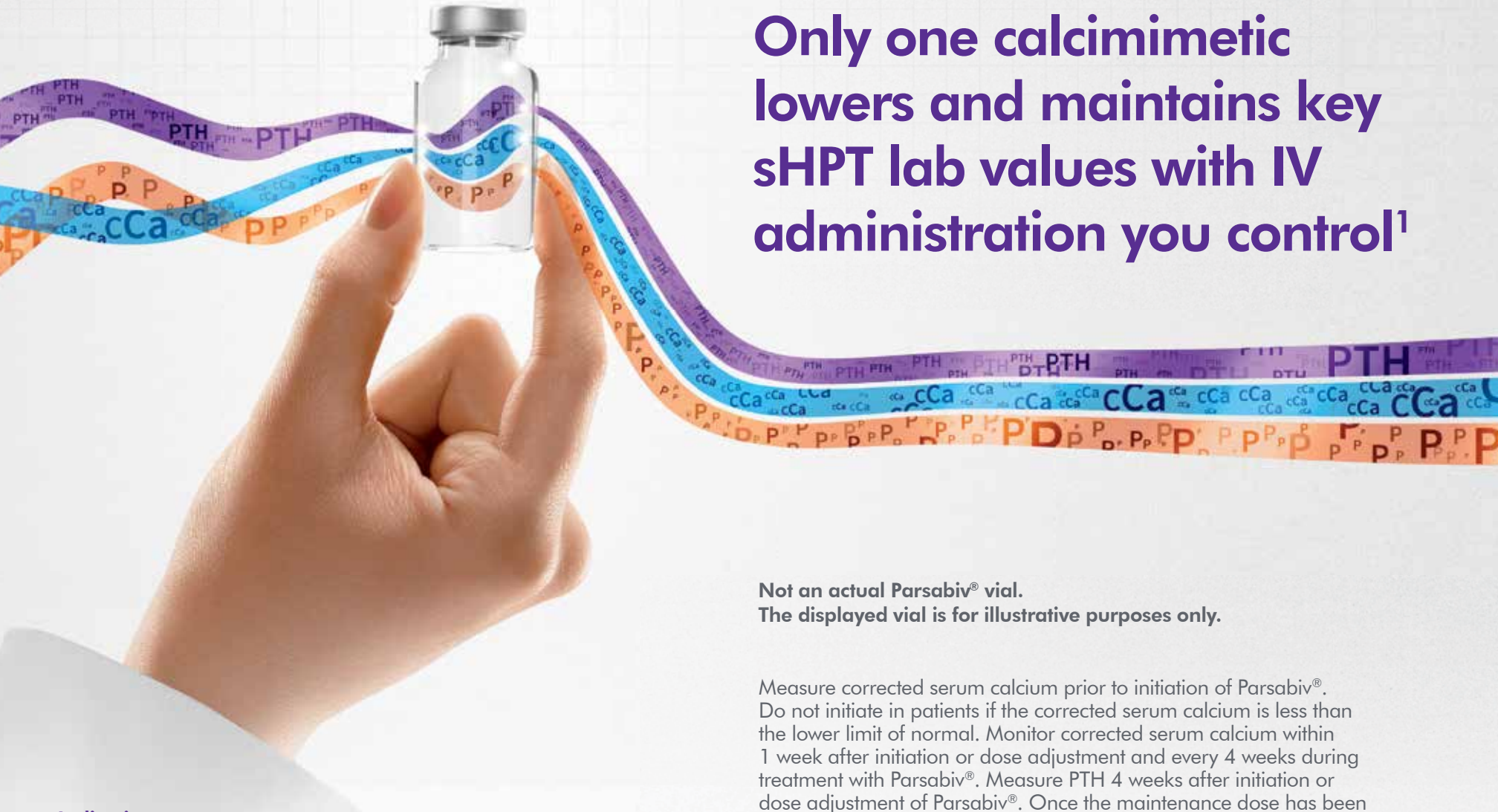


Table 1. Tips for plannning a tweetorial

Identify your audience.
Pick a topic.
Define learning objectives.
Make it interactive with polls, responding to readers.
Provide visuals (consider making your own).
Consider the length (recommended optimal length of 10–15 tweets).
Give credit to others (always link to source material).
Provide links to supplementary educational resources (podcasts, videos, books, etc.).
Pin your tweetorial to your profile, or create a moment collating all of your tweetorials.



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

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

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

Indication

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

Limitations of Use:

Parsabiv® has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv® is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred.

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

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

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

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

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv® in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv®.

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

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

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

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

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

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

Parsabiv® (etelcalcetide) Injection for intravenous use

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

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Hypocalcemia

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

QT Interval Prolongation and Ventricular Arrhythmia

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

Seizures

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

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

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

Monitoring Serum Calcium and Patient Education

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

Management of Hypocalcemia

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

Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

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

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

Adynamic Bone

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

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

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

Description of Selected Adverse Reactions

Hypocalcemia

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

Hypophosphatemia

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

QTc Interval Prolongation Secondary to Hypocalcemia

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

Hypersensitivity

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

Immunogenicity

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Data

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

Pediatric Use

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

Geriatric Use

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

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

OVERDOSAGE

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

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Beyond Heart and Kidney Protection
Potential Uses of SGLT2 Inhibitors

By Jefferson L. Triozzi and L. Parker Gregg

Sodium-glucose cotransporter-2 (SGLT2) inhibitors demonstrate multiple effects beyond improving cardiovascular and kidney outcomes. Although much remains to be learned about the underlying mechanisms, early data suggest possible roles for SGLT2 inhibitors in the management of hypomagnesemia, nephrolithiasis, hyponatremia, anemia, cardiorenal syndrome, and in kidney transplant recipients (Figure 1).

SGLT2 inhibitors may increase magnesium reabsorption in the nephron (Figure 2). In clinical trials, SGLT2 inhibitors led to an approximate 0.04–0.1 mM (0.10–0.24 mg/dL) increase in serum magnesium level when compared to placebo (1). This observed effect was generally within the physiologic range for serum magnesium level, but one case series suggests that SGLT2 inhibitors may have greater effect and therapeutic potential for patients with refractory urinary magnesium wasting (2). By potentially impacting magnesium reabsorption in multiple segments of the nephron, SGLT2 inhibitors may be useful for managing medication-induced urinary magnesium wasting, such as decreased paracellular reabsorption in patients taking loop diuretics or transient receptor potential melastatin type 6 (TRPM6) downregulation in patients taking thiazide diuretics or calcineurin inhibitors.

However, studies have not shown similar effects on handling of urinary calcium, another divalent cation (3). This may be because decreased urinary phosphate excretion in response to SGLT2 inhibition stimulates parathyroid hormone secretion (4). Despite the lack of substantial impact on urinary calcium excretion, the combined effects of SGLT2 inhibitors on urine volume, urinary phosphate excretion, and uric acid homeostasis may decrease the risk of nephrolithiasis (4–6).

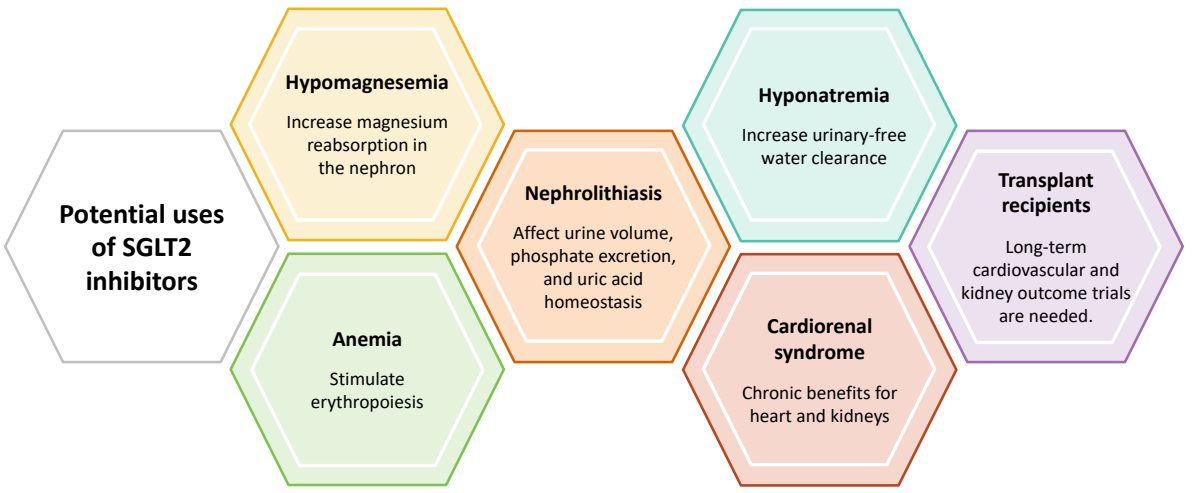
The osmotic diuresis generated by SGLT2 inhibitors increases water excretion and may have a role in the management of hyponatremia. Empagliflozin was shown to raise plasma sodium concentration faster than placebo over 4 days in individuals with the syndrome of inappropriate antidiuretic hormone (SIADH) (7). Studies including more prolonged intervention and longer-term follow-up are needed, as transient changes in urine volume due to SGLT2 inhibitor initiation may not produce sustained effects on net water balance (8).

Clinical trials have shown higher hematocrit concentrations with SGLT2 inhibitors compared to placebo and decreased need for iron supplementation, erythropoiesis-stimulating agents, or blood transfusions in those with concomitant diabetes and chronic kidney disease (9, 10). In patients with type 2 diabetes, hyperglycemia causes maladaptive changes in the kidney that alter hypoxia-inducible factor pathways and impair erythropoiesis (10). Although incompletely understood, SGLT2 inhibitors may stimulate erythropoiesis by decreasing glucose accumulation in the cortical interstitium and by altering oxygen tension in the cortex and outer medulla (10–12). Less is known about the therapeutic role of SGLT2 inhibitors for anemia in patients without diabetes.

Given the heart and kidney protective effects of SGLT2 inhibitors, these agents are currently recommended in patients with chronic cardiorenal syndromes. In patients with stable heart failure, natriuresis after initiation of an SGLT2 inhibitor led to decreased blood and plasma volume without the concomitant neurohormonal activation or hypokalemia typically seen after loop diuretic administration (13). Less is known about the use of these drugs in patients with acute cardiorenal syndromes. In rats, SGLT2 inhibition may protect against cardiorenal acute kidney injury by reducing oxidative stress in the kidney (14). In patients with diabetes mellitus, SGLT2 inhibitors were associated with a decreased risk of acute kidney injury compared to other glucose-lowering medications (15–17). Understanding these relationships for patients with cardiorenal physiology will require studies incorporating biomarkers of kidney injury other than glomerular filtration rate, which may reflect hemodynamic changes rather than true kidney injury (18). Existing evidence is insufficient to support SGLT2 inhibitor use in cases of acute cardiorenal syndromes.

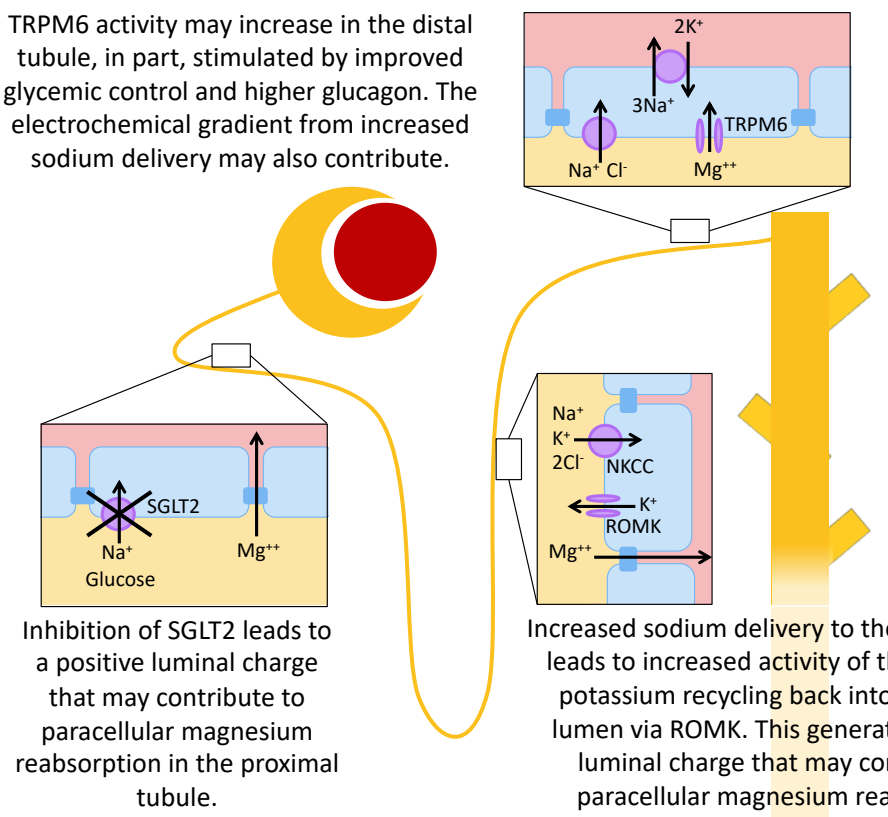
Although kidney transplant recipients were excluded from large SGLT2 inhibitor outcome trials, it is plausible that cardiovascular benefits could be extrapolated to this population in appropriate clinical contexts (19). One placebo-controlled randomized trial showed that empagliflozin lowered hemoglobin A1c by a median of –0.2% and body weight by a median of –2.5 kg in 44 kidney transplant recipients with posttransplant diabetes mellitus (20). Despite their immunosuppressed status, there was no increase in infections among patients receiving SGLT2 inhibitors, with three participants each in the

Figure 1. Potential clinical uses for SGLT2 inhibitors



Early data suggest several potential applications and proposed mechanisms for SGLT2 inhibitors beyond their well-known benefits for cardiovascular and kidney protection.

Figure 2. Proposed effects of SGLT2 inhibitors on magnesium handling in the nephron



Several mechanisms potentially contribute to increased reabsorption of magnesium in the nephron. NKCC, sodium-potassium-2 chloride cotransporter; ROMK, renal outer medullary potassium channel; SGLT2, sodium-glucose cotransporter-2; TRPM6, transient receptor potential melastatin type 6.

empagliflozin and placebo groups developing urinary tract infections and one participant in the empagliflozin arm with a genital yeast infection. Larger studies are needed to evaluate efficacy and safety of SGLT2 inhibitors in this population and to better understand how these drugs affect allograft perfusion in kidney transplant recipients with impaired autoregulatory mechanisms.

Evidence supporting these potential uses of SGLT2 inhibitors is in early stages. It remains to be determined whether such uses differ among individual SGLT2 inhibitors. More research is needed to assess the mechanisms, durability, and clinical implications of these effects. ■

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The authors report no conflicts of interest.

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Laboratory Evaluation of Acute Kidney Injury

By Yumeng Wen and Chirag R. Parikh

Acute kidney injury (AKI) is common in hospitalized patients and is associated with long-term risks of chronic kidney disease (CKD) and end stage kidney disease (ESKD). An abrupt increase in serum creatinine (SCr) over 48–72 hours is the key finding in the diagnosis of AKI, as recommended by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline (1). Despite advances in biomarkers of AKI, over- and under-diagnosis remain challenges in the evaluation of AKI. In patients with CKD, the false positive rate of AKI diagnosis can occur in 30.5% of patients, possibly due to a lack of appreciation of the analytic variability of SCr (2,3).

Most laboratories in the US use one of two types of SCr assays: Jaffe alkaline picrate or enzymatic methodology (3). The coefficient of variation of these assays ranges from 2.7% to 5.3%, according to the College of American Pathologists 2019 survey, which means some small variation is expected when comparing results across different labs and among serial measurements in a single patient. Also, biological variability of SCr is estimated to be approximately 4.5% in individuals with and without CKD (3–5). Taken together, for most US laboratories using enzymatic or Jaffe methods, a change in SCr from baseline by less than 20% is within the range of normal lab variation and is unlikely to represent significant change in glomerular filtration rate (GFR) (3). Conversely, in critically ill patients, elderly patients, and those with a rapid change in volume status, SCr may not increase by 0.3 mg/dL until significant decline in GFR has developed (6). Therefore, a recent report proposed a revised threshold of SCr change to diagnose AKI: an increase of SCr by 0.2 mg/dL or of 20% from baseline, whichever is higher (3). Further studies are needed to compare the performance of these proposed AKI criteria against the current KDIGO definition.

In addition to SCr, urine microscopy is often used in the evaluation of AKI. The presence of cellular casts, dysmorphic red blood cells, and certain crystals is highly informative in differentiating the etiology of AKI. In patients with suspected acute tubular injury, a validated scoring system that includes the number of casts and renal tubular epithelial cells has been shown to predict AKI severity (7). Automated systems have been increasingly incorporated into routine urinalysis to assess for the presence of casts and crystals. However, these systems are less likely to detect many important pathologic features, such as dysmorphic red blood cells, renal tubular epithelial cells, granular casts, and crystals, when compared to nephrologists' manual review (8). Therefore, while these automated systems do have diagnostic value, clinicians should not rely solely on them to diagnose diseases such as acute tubular injury, glomerulonephritis, and crystal nephropathy. Furthermore, the art of manual urine microscopy review is a valuable skill that should continue to be emphasized in nephrology fellowship training (9).

There are several common tests that, despite their widespread use, offer limited or no value in the diagnosis of AKI. Urine sodium and fractional excretion of sodium (FENa) are not useful in differentiating prerenal azotemia from intrinsic AKI, since the former can be easily diagnosed by assessing fluid responsiveness. This is because urine sodium and FENa can be low in diseases when the kidney is sodium avid and are influenced by dietary sodium intake. A study once commonly performed when interstitial nephritis was suspected was urine eosinophils. This study has been shown not to be useful in differentiating acute interstitial nephritis from other causes of AKI and thus has widely been abandoned (10).

Fortunately, many novel biomarkers are on the verge of clinical application to dissect the phenotype and prognosis of AKI and differentiate parenchymal kidney injury from hemodynamic changes. These biomarkers could be used to predict the progression of AKI and predict AKI to CKD transition and may help to guide AKI management, as delineated in our recent review (11). In the ASSESS-AKI (Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury) study, the increase in urine albumin and urine chitinase 3-like protein (YKL-40) and the decrease in uromodulin at 3 months after AKI hospitalization were found to be independently associated with developing CKD or CKD progression (12, 13). Insulin-like growth factor-binding protein-7 (IGFBP-7) and tissue inhibitor of metalloproteinase 2 (TIMP-2) have been found to predict AKI in critically ill patients, and intervention based on urinary TIMP-2 * IGFBP-7 > 0.3 after cardiac surgery was shown to reduce AKI incidence in one pilot trial (14, 15). Although urine albumin measurement is heading toward standardization, many biomarkers, including TIMP-2 and IGFBP-7, are measured by various commercially available immunoassay platforms (16). Establishing the proper reference interval, determining the analytical variability across measurement platforms, and understanding biological variability across patient populations by close collaboration with laboratorians are crucial for the effective clinical implementation of these novel biomarkers.

There have been many advances in our approaches to diagnose AKI since the KDIGO AKI definition was published in 2012 (Table 1). Clinicians, researchers, and laboratory scientists must continue to work together to fill in the remaining gaps in our understanding of these testing strategies. ■

Table 1. Considerations in laboratory evaluation of acute kidney injury

Laboratory tests	Current and potential use	Considerations in laboratory evaluation	Cost
Serum creatinine	Cornerstone in the diagnosis and management of AKI	· Biological variability · Analytic variability across labs and assays · Potential delayed diagnosis in patients with low serum creatinine	$
Urine sediment	Identify AKI etiologies (prerenal, acute tubular injury, acute interstitial nephritis, glomerulopathies, etc.).	· Automated urine sediment evaluation provides poor sensitivity in detecting certain pathologic features. · Manual review is considered the gold standard in detecting pathologic features and should continue to be emphasized in fellowship training.	$ (manual) $$ (automated)
Novel biomarkers	· Early diagnosis and guide management of AKI · Potential to differentiate hemodynamic AKI from acute tubular injury · Potentially predict AKI to CKD transition	· Lack of established reference Interval · Lack of evaluation of biological and analytic variability	$$$

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†14.5% vs 9.2% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.61 (95% CI: 0.51–0.72); *P*<0.0001.[1,3]
‡6.8% vs 4.7% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.69 (95% CI: 0.53–0.88); *P*=0.0035.[1,3]

Study design: DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter clinical trial of 4304 adults with eGFR 25-75 mL/min/1.73 m^2, and UACR 200-5000 mg/g, with or without T2D, randomly assigned to receive FARXIGA (10 mg once daily) or placebo for a median follow-up of 2.4 years.[3]

INDICATIONS AND LIMITATIONS OF USE for FARXIGA® (dapagliflozin)

FARXIGA 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 hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular (CV) disease or multiple CV risk factors
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction
- to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression

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

FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

IMPORTANT SAFETY INFORMATION

Contraindications

- Prior serious hypersensitivity reaction to FARXIGA
- Patients on dialysis

Warnings and Precautions

- **Ketoacidosis in Diabetes Mellitus** has been reported in patients with type 1 and type 2 diabetes receiving FARXIGA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Some cases were fatal. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue FARXIGA, evaluate and treat promptly. Before initiating FARXIGA, consider risk factors for ketoacidosis. Patients on FARXIGA may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis
- **Volume Depletion:** FARXIGA can cause intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Acute kidney injury requiring hospitalization and dialysis has been reported in patients with type 2 diabetes receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in these patients, assess volume status and renal function. After initiating therapy, monitor for signs and symptoms of hypotension and renal function
- **Urosepsis and Pyelonephritis:** SGLT2 inhibitors increase the risk for urinary tract infections (UTIs) and serious UTIs have been reported with FARXIGA. Evaluate for signs and symptoms of UTIs and treat promptly
- **Hypoglycemia:** FARXIGA can increase the risk of hypoglycemia when coadministered with insulin and insulin secretagogues. Consider lowering the dose of these agents when coadministered with FARXIGA
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Rare but serious, life-threatening cases have been reported in patients with diabetes mellitus receiving SGLT2 inhibitors including FARXIGA. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Assess patients presenting with pain or tenderness, erythema, swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue FARXIGA
- **Genital Mycotic Infections:** FARXIGA increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Monitor and treat appropriately

Adverse Reactions

In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with FARXIGA 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

Use in Specific Populations

- **Pregnancy:** Advise females of potential risk to a fetus especially during the second and third trimesters
- **Lactation:** FARXIGA is not recommended when breastfeeding

DOSING

To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control.

For all other indications, the recommended dose is 10 mg orally once daily.

Please see Brief Summary of Prescribing Information on adjacent pages.

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

CI=confidence interval; CKD=chronic kidney disease; DAPA-CKD=Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; eGFR=estimated glomerular filtration rate; FDA=Food and Drug Administration; HR=hazard ratio; NYHA=New York Heart Association; SGLT2i=sodium-glucose cotransporter 2 inhibitor; RRR=relative risk reduction; T2D=type 2 diabetes; UACR=urine albumin-to-creatinine ratio.

References: 1. FARXIGA® (dapagliflozin) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** FARXIGA granted Breakthrough Therapy Designation in US for chronic kidney disease [press release]. Published October 2, 2020. Accessed March 17, 2021. https://www.astrazeneca-us.com/media/press-releases/2020/farxiga-granted-breakthrough-therapy-designation-in-us-for-chronic-kidney-disease.html **3.** Heerspink HJL et al. *N Engl J Med.* 2020;383(15):1436-1446.

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Initial U.S Approval: 2014

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INDICATIONS AND USAGE

FARXIGA (dapagliflozin) 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 hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.
- FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

DOSAGE AND ADMINISTRATION

Prior to Initiation of FARXIGA

Assess renal function prior to initiation of FARXIGA therapy and then as clinically indicated *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Assess volume status and, if necessary, correct volume depletion prior to initiation of FARXIGA *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6) in the full Prescribing Information]*.

Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to FARXIGA, such as anaphylactic reactions or angioedema *[see Adverse Reactions (6.1) in the full Prescribing Information]*.
- Patients on dialysis *[see Use in Specific Populations (8.6) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Ketoacidosis in Patients with Diabetes Mellitus

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including FARXIGA *[see Adverse Reactions (6.1) in the full Prescribing Information]*. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking FARXIGA. FARXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1) in the full Prescribing Information]*.

Patients treated with FARXIGA 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 FARXIGA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, FARXIGA should be discontinued, the 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 the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating FARXIGA, 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 FARXIGA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in the full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing FARXIGA 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 FARXIGA. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue FARXIGA and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

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

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including FARXIGA. 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 (6) in the full Prescribing Information]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with FARXIGA.

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 FARXIGA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with FARXIGA 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 FARXIGA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

FARXIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor and treat appropriately.

ADVERSE REACTIONS

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

- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Volume Depletion *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6) in the 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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

FARXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of FARXIGA was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

Pool of 12 Placebo-Controlled Studies for FARXIGA 5 and 10 mg for Glycemic Control

The data in Table 1 is derived from 12 glycemic control placebo-controlled studies in patients with type 2 diabetes mellitus ranging from 12 to 24 weeks. In 4 studies FARXIGA was used as monotherapy, and in 8 studies FARXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14.1) in the full Prescribing Information]*.

These data reflect exposure of 2338 patients to FARXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FARXIGA 5 mg (N=1145), or FARXIGA 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 2 shows common adverse reactions associated with the use of FARXIGA. These adverse reactions were not present at baseline, occurred more commonly on FARXIGA than on placebo, and occurred in at least 2% of patients treated with either FARXIGA 5 mg or FARXIGA 10 mg.

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA (cont'd)

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, FARXIGA 5 mg=581, FARXIGA 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, FARXIGA 5 mg=564, FARXIGA 10 mg=595).

Pool of 13 Placebo-Controlled Studies for FARXIGA 10 mg for Glycemic Control

FARXIGA 10 mg was also evaluated in a larger glycemic control placebo-controlled study pool in patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with FARXIGA 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

FARXIGA causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3 *[see Warnings and Precautions (5.2)]*.

Table 3: Adverse Reactions Related to Volume Depletion* in Clinical Studies in Patients with Type 2 Diabetes Mellitus with FARXIGA

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies		DECLARE Study	
	Placebo	FARXIGA 5 mg	FARXIGA 10 mg	Placebo	FARXIGA 10 mg	Placebo	FARXIGA 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/ 1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Hypoglycemia

The frequency of hypoglycemia by study in patients with type 2 diabetes mellitus *[see Clinical Studies (14.1) in the full Prescribing Information]* is shown in Table 4. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.4) in the full Prescribing Information]*.

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Monotherapy (24 weeks)	**N=75**	**N=64**	**N=70**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=137**	**N=135**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**-**	**N=109**
Severe [n (%)]	0	-	0
Glucose <54 mg/dL [n (%)]	3 (2.8)	-	7 (6.4)

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus (cont'd)

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=141**	**N=140**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	1 (0.7)	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**–**	**N=225**
Severe [n (%)]	0	–	1 (0.4)
Glucose <54 mg/dL [n (%)]	1 (0.4)	–	1 (0.4)
Add-on to Insulin with or without other OADs‡ (24 weeks)	**N=197**	**N=212**	**N=196**
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose <54 mg/dL [n (%)]	43 (21.8)	55 (25.9)	45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose <54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with FARXIGA and 83 (1.0%) out of 8569 patients treated with placebo.

Genital Mycotic Infections

In the glycemic control trials, genital mycotic infections were more frequent with FARXIGA treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on FARXIGA 5 mg, and 4.8% on FARXIGA 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with FARXIGA 10 mg. Infections were more frequently reported in females than in males (see Table 1). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, FARXIGA 5 mg, and FARXIGA 10 mg, respectively). In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, serious genital mycotic infections were reported in <0.1% of patients treated with FARXIGA and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with FARXIGA and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with FARXIGA treatment. In glycemic control studies, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of FARXIGA-treated patients. If hypersensitivity reactions occur, discontinue use of FARXIGA; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis in Patients with Diabetes Mellitus

In the DECLARE study *[see Warnings and Precautions (5.1) and Clinical Studies (14.2) in the full Prescribing Information]*, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the FARXIGA-treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including FARXIGA causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.2) in the full Prescribing Information]*. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with FARXIGA.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit values were observed in FARXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were –0.33% in the placebo group and 2.30% in the FARXIGA 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FARXIGA 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in FARXIGA-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and FARXIGA 10 mg groups, respectively. In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in FARXIGA-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of FARXIGA 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the FARXIGA and exenatide-extended release treatment groups *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

DAPA-CKD Chronic Kidney Disease Study

No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease.

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of FARXIGA in patients with diabetes mellitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

DRUG INTERACTIONS

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, FARXIGA is not recommended during the second and third trimesters of pregnancy.

Limited data with FARXIGA in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 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 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats *(see Data)*. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. 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 breastfed infants, advise women that use of FARXIGA is not recommended while breastfeeding.

Data

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use

Safety and effectiveness of FARXIGA in pediatric patients under 18 years of age have not been established.

Geriatric Use

No FARXIGA dosage change is recommended based on age.

A total of 1424 (24%) of the 5936 FARXIGA-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of FARXIGA in improving glycemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1) in the full Prescribing Information]*.

In both the DAPA-HF and DAPA-CKD studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

Renal Impairment

FARXIGA was evaluated in 4304 patients with chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m^2) in the DAPA-CKD study. FARXIGA was also evaluated in 1926 patients with an eGFR of 30 to 60 mL/min/1.73 m^2 in the DAPA-HF study. The safety profile of FARXIGA across eGFR subgroups in these studies was consistent with the known safety profile *[see Adverse Reactions (6.1) and Clinical Studies (14.3 and 14.4) in the full Prescribing Information]*.

FARXIGA was evaluated in two glycemic control studies that included patients with type 2 diabetes mellitus with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2 *[see Clinical Studies (14.1) in the full Prescribing Information]*, and an eGFR of 30 to less than 60 mL/min/1.73 m^2, respectively). Patients with diabetes and renal impairment using FARXIGA may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, 13 patients receiving FARXIGA experienced bone fractures compared to none receiving placebo. Use of FARXIGA for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

Efficacy and safety studies with FARXIGA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2. FARXIGA is contraindicated in patients on dialysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program for FARXIGA.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

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ASN *Kidney News* Commentary

Transition of Care after Allograft Failure

By Itunu Owoyemi

Transplantation remains the best treatment modality for kidney failure. Despite the significant improvement in immunosuppression and reduction in acute rejection rates, allograft failure with return to dialysis is common (1). Infection and cardiovascular disease are the two major causes of mortality after returning to dialysis (2). It is important to carefully optimize immunosuppression management due to the need to balance the risk of infection and mortality with continuation on dialysis versus the chronic inflammatory state and increased sensitization to allograft major histocompatibility complex (MHC) antigens with discontinuation of immunosuppression (3).

The American Society of Transplantation-Kidney Pancreas Community of Practice (AST-KPCOP) established a work group to study Kidney Recipients with Allograft Failure, Transition of Kidney Care (KRAFT). AST-KPCOP conducted a survey among adult transplant providers covering 49% of transplant centers across the United States. The survey was performed to evaluate current practices that highlighted the need to standardize immunosuppression management after graft failure as well as effective transition of care in clinical practice (4). Only 22% of the respondents mentioned that a majority of their patients with failing allografts were relisted for another kidney transplant before starting dialysis. Most of the respondents reported their decision to wean off immunosuppression was most importantly based on the availability of a living donor, followed by risk of infection, risk of sensitization, frailty, and side effects of the medications. The most common approach for tapering immunosuppression was to initially discontinue the antimetabolite (such as mycophenolate mofetil or azathioprine). The survey also showed that 25% of the respondents would use urine volume/residual kidney function as a guide for weaning immunosuppression. Whereas a paucity of data exists for tapering immunosuppression based on urine volume, survival benefit has been demonstrated in recipients who remained on immunosuppression with residual kidney function (5). Most of the respondents referred patients for nephrectomy when there were persistent signs and symptoms of rejection.

The survey highlighted the varying care of the failing transplant and the need to have high value and collaborative care in clinical practices. The KRAFT study group later proposed a comprehensive shared-care model for improved collaboration between transplant providers and general nephrologists to improve clinical outcomes with management of the failing allograft outlined in the *American Journal of Transplantation* (6). ■

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Dr. Owoyemi reports no conflicts of interest related to the article content, including outside honoraria or consultancy arrangements.

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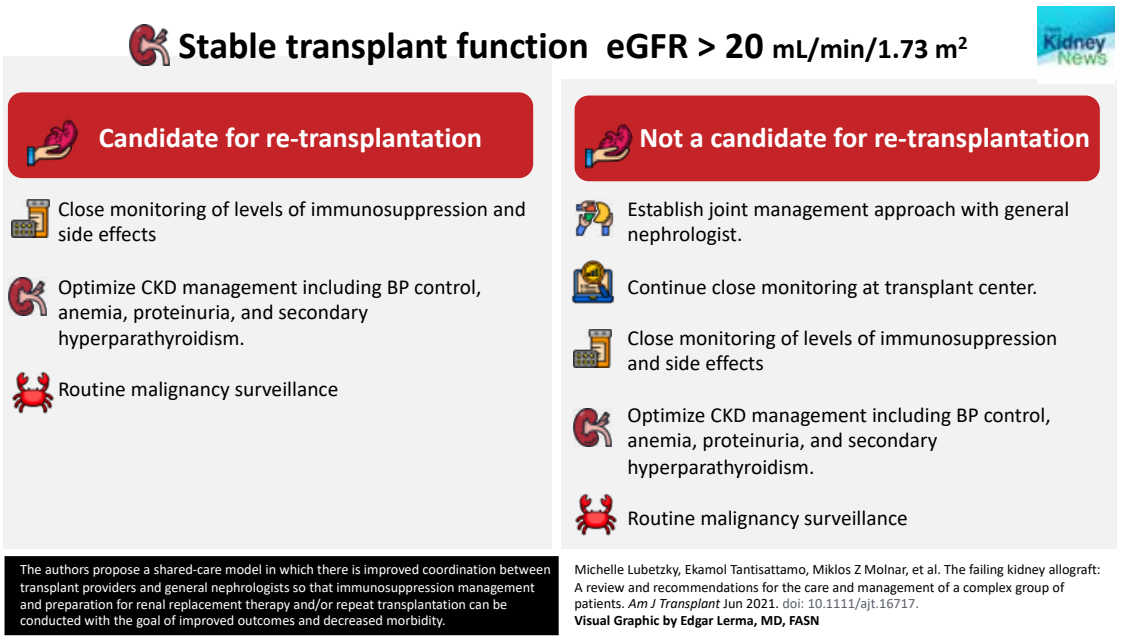

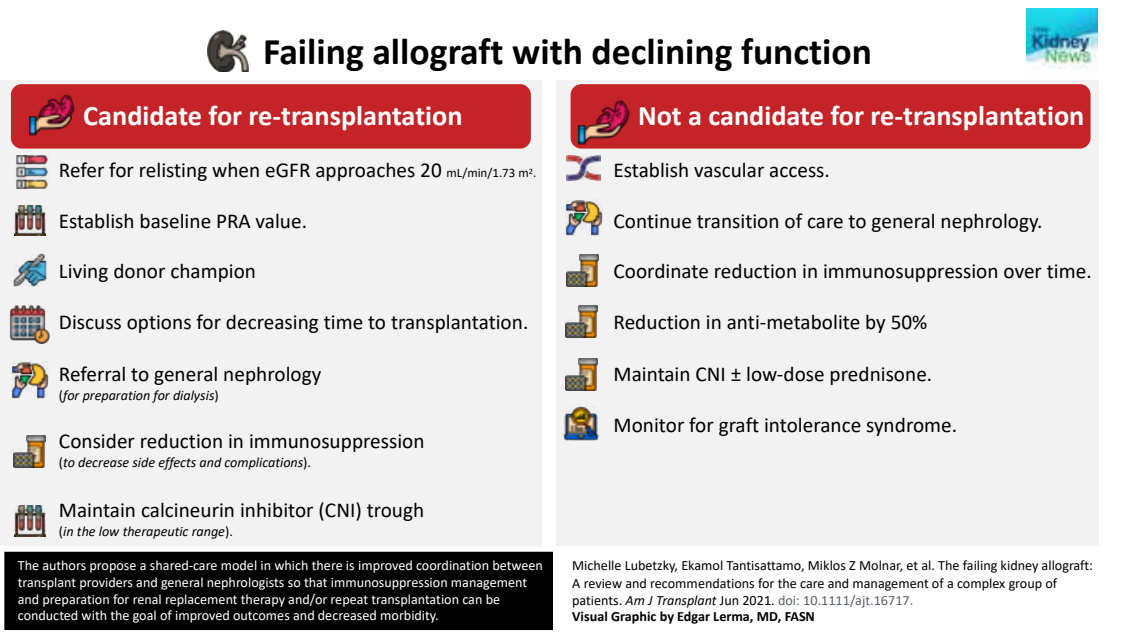

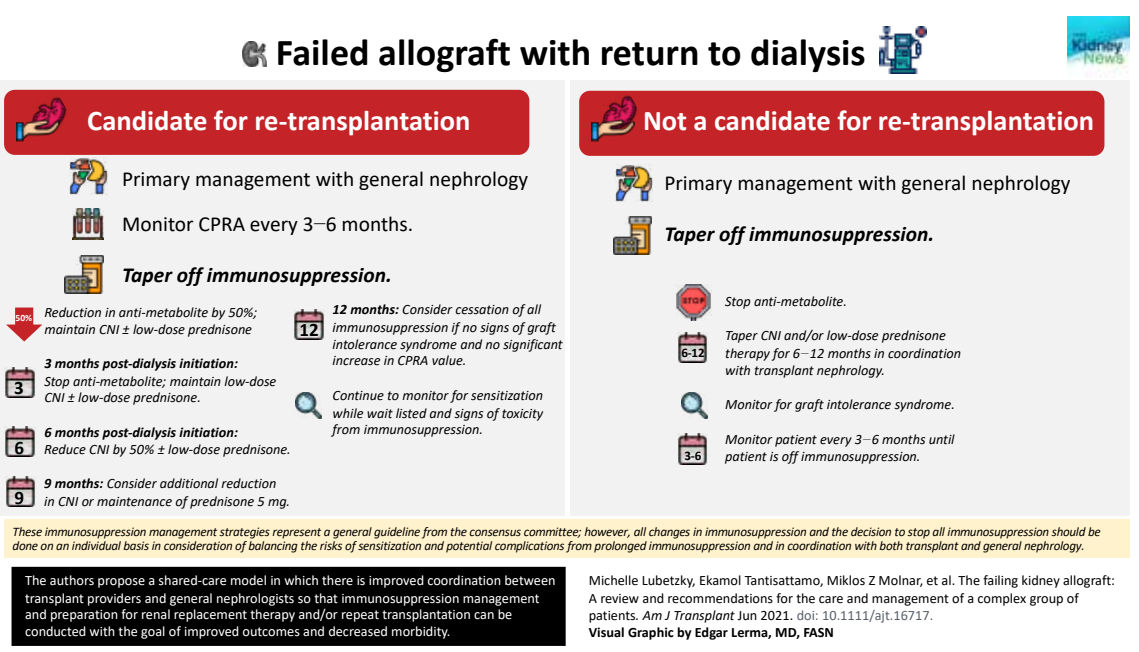

The RVU Does Have Value but Also a Cost

By Mitchell H. Rosner and Charles R. Manley

We cringe when we hear about how many relative value units (RVUs) we have produced. There is no doubt that being a clinician is defined by much more than our RVUs. Nephrologists care for the most complex patients, and many elements of this care are not easily captured by the RVU system (1, 2). It is no wonder that RVUs have become a "four-letter word" for clinicians.

Relative value scales date back to the 1950s and were designed to establish prices that state and federal governments would pay for physician services on the basis of relative value of time and intensity of physician work and resource costs. The Centers for Medicare & Medicaid Services (CMS) is responsible for updating RVUs, and CMS relies on advice and recommendations from the American Medical Association/Specialty Society Relative Value Scale Update Committee (2). RVUs are broken down into three components as shown in Figure 1.

Despite the system being designed to determine reimbursement and compensation, RVUs are the de facto national standard for measuring productivity. A work RVU approximates the amount of work required to perform a service, thus providing a quantitative measure for tracking productivity beyond counting numbers of patients seen and procedures performed. There are clear flaws in the RVU system, most notably its failure to capture the effort outside of patient encounters required to provide high-quality care, as well as issues in stifling the growth of value-based care models. One of the greatest problems with this system is its use in benchmarking productivity. The RVU system itself has value that is well validated (3).

There are three commonly used benchmarking services: Clinical Practice Solutions Center (CPSC; Vizient), SullivanCotter, and Medical Group Management Association (MGMA). All attempt to describe the distribution of RVU productivity levels (given as percentiles). There are variations among these services that include nuances for regional variations, academic versus private practice, as well as subspecialty care. It is commonplace for a clinician to be told, for example, that his or her productivity target is the 55th percentile or 6500 RVUs.

CPSC benchmarks are derived using the CMS payment rule directly from encounter-specific billing data, and the MGMA and SullivanCotter benchmarks are derived using self-reported data. All benchmarks emanate from small samples ranging from approximately 180 to 300 physicians. These are woefully small surveys and subject to reporting bias. Factors that are not clearly accounted for in these benchmarking data include: 1) normalization to amount of clinical activity; 2) use of fellows or residents to enhance productivity in academic settings (some benchmarks have an academic subcategory); 3) use of physician extenders; 4) normalization to the amount of dialysis care provided, which is valued at a higher level than clinic work (some benchmarking groups include a dialysis component, and some do not); and 5) actual mix of clinical activity. For example, subspecialties within nephrology participate in extensive work that has no RVU value and is not captured in current benchmarking. This might include traveling to a remote dialysis center, care coordination meetings for patients with end-stage kidney disease (ESKD), or transplant-related meetings such as donor and recipient selection meetings. In addition, many benchmarking services do not include specific percentiles of productivity for transplant physicians or interventional nephrologists.

The end result of over-reliance on flawed benchmarking data is that clinicians are not appropriately evaluated for their efforts, feel disrespected, suffer burnout, and ultimately feel like they are chasing numbers rather than focused on high-value, cost-conscious care. The issue is not the RVU system but how RVU benchmarking has been translated into inflexible productivity targets.

A potential solution to the issue of inadequate benchmarking is for organizations such as the American Society of Nephrology (ASN) to contribute to producing granular, accurate, and actionable data to measure our work and ensure we are appropriately compensated for our efforts.

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Mitchell H. Rosner discloses that he is a member of the *CJASN* Editorial Board and serves on the Data Safety Monitoring Board for Clinical Trials supported by Reata, Travere, and AstraZeneca. Charles R. Manley has nothing to disclose.

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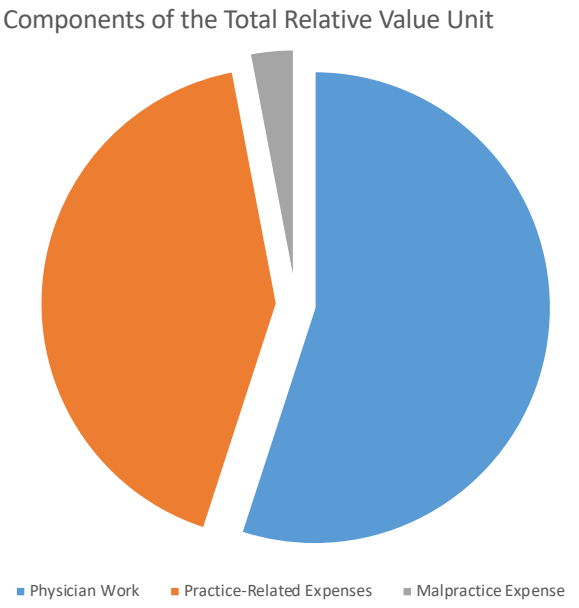
Figure 1. The three components of RVUs



Nephrologists' Value Exceeds RVU Calculations

By Timothy A. Pflederer

In their article "The RVU Does Have Value but Also a Cost," authors Rosner and Manley note that the relative value unit (RVU) system for determining physician work and reimbursement has merit, but it does not fully account for non-encounter-based work that supports patient care.

The Renal Physicians Association (RPA) concurs with this assessment. Furthermore, although this shortfall admittedly affects all physicians, specialties, and practice settings, nephrology is uniquely poised to be adversely affected by virtue of the patient population for which it provides care. Activities that support high-quality patient care but are not reflected in Current Procedural Terminology (CPT) code-specific RVUs include but are not limited to the following: 1) team leadership and running team-based care models; 2) travel to remote locations required for dialysis-dependent patients; 3) membership and participation in committees (such as for quality improvement); and 4) administrative time spent in private or academic practice management. Moreover, nephrologists serve as key liaisons among patients, dialysis organizations, hospitals, and academic institutions.

Certain activities should not be included, such as time spent on dialysis, facility medical director responsibilities (separately reimbursed), and those activities not part of the face-to-face patient encounter but for which Medicare is now assigning work value (e.g., care management), a move that reflects recognition of the concept that comprehensive patient care may require work not captured by the RVU as currently defined. In fact, effective use of the care management code families (chronic care management, transitional care management, or principal care management), in addition to participation in value-based payment models in the kidney arena, may provide a pathway to accounting and receiving compensation for activities that historically have fallen outside of a specific reimbursable physician service.

Given these advancements, the time seems ripe for a reexamination of how the RVU methodology is utilized. In both private practice and academia, there is great variability with regard to how this work is valued and credited, and as noted by Rosner and Manley, the RVU has become a measure of productivity used by many institutions to determine compensation. We agree that commonly used benchmarking surveys do not capture the essence of the work done by a nephrologist and join the call for the national specialty societies for nephrology (RPA and the American Society of Nephrology) to lead efforts to clarify the scope of the problem and identify the non-patient encounter activities where value has not been recognized. Understanding the degree of value associated with these activities and the volume or frequency at which those activities occur would enhance applicability across geographies and practice settings.

Existing structures could inform the data-gathering process, notably the RPA Nephrology Practice Business Benchmarking Survey, which has been conducted biannually by RPA for over 20 years. This initiative compiles data from nephrology practices nationwide on diverse data points, such as physician compensation, use of advanced practitioners, total income per full-time employee in nephrology practices, and integration of clinical research, among many others. A survey of patient care activities occurring outside of patient encounters, based on the RPA Benchmarking data, would be of tremendous benefit to the nephrology community and provide a more realistic basis upon which to apply productivity targets. This would provide nephrology practices, regardless of setting, with benchmarks and points of comparison through which value for currently uncompensated work could be ascertained. RPA welcomes the opportunity to participate in such an endeavor.

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The Rise, Fall, and New Rise of Home Hemodialysis

By Sindhura Talluri and Sadichhya Lohani

The rise

Hemodialysis became a reality in 1960 with the development of Belding Scribner's Teflon arteriovenous shunt (1). Yukihiko Nosé started home hemodialysis (HHD) in Japan in 1961 (2). Shortly thereafter, in 1964, Scribner developed a hemodialysis machine that was used in a young patient at home (Figure 1), marking the beginning of HHD in the United States (1, 3–5). Subsequently, John Merrill and Stanley Shaldon developed HHD programs in Boston and London, respectively, which quickly spread to France and Italy. In 1967, with the direction of the Seattle Artificial Kidney Center Unit Board, all new patients were started on HHD, and patients using in-center hemodialysis were transitioned to HHD, leading to the establishment of a HHD training center in Seattle (1, 4). HHD rose to be the preferred modality into the 1970s, as HHD became safer compared to the former years and more cost effective compared to the limited in-center hemodialysis.

The fall

In 1972 when HHD accounted for 50% of all patients using dialysis in the United States, an addendum to the Social Security Amendment Act H.R.1 (section 2991) led to Medicare assuming responsibility for the payment for maintenance dialysis, establishing nearly universal coverage, which turned out to be favorable for the development of for-profit dialysis centers. This led to fiscal bias against HHD, as funding was preferably directed toward in-center hemodialysis, disincentivizing the growth of HHD (1–6). The complexity of training and support—complications without direct physician supervision—further contributed to the decline of HHD. With the growth of kidney transplant, the highly motivated patients using HHD became more likely to get transplantation (7). Peritoneal dialysis also emerged as a lucrative modality after the development of the Tenckhoff peritoneal catheter in 1968 (8).

By the 1980s, only 4.6% of patients with end stage kidney disease (ESKD) were on HHD in the United States. This further declined to 0.58% by 2005 (9). Reimbursement policies in Europe also strongly favored for-profit in-center-based care, reducing interest in HHD (6). Only Australia, New Zealand, and Turkey continued to report significant use of HHD (around 11%–13%) in the early 2000s (7). Despite the similar legislation around dialysis coverage in both countries, Australia continued to flourish on HHD as opposed to the United States (6). At the end of 2017, ~18% of all patients using dialysis in Australia and 47% in New Zealand remained at home for hemodialysis (10).

The new rise—a promising future

After decades of decline, as studies demonstrated improved mortality outcome, blood pressure control, functional status with frequent hemodialysis, as well as cost effectiveness, the interest in HHD is rising again (Figure 2). HHD machines became safer, more efficient, and easier to operate as the NxStage machine received clearance for this purpose in 2005. Technologies have reassured physicians and patients of safe HHD monitoring (4).

In 2020, the Centers for Medicare & Medicaid Services (CMS) announced the End-Stage Renal Disease (ESRD) Treatment Choices Model for ESRD Medicare beneficiaries. The home dialysis payment-adjustment model provides bonus payments for HHD for 3 years. Providers can use this to invest in home therapies and performance payment adjustment based on HHD increased accountability. Medicare started paying for a monthly comprehensive tele-visit in 2019, which removed any geographic limitations. In the past decade, HHD has seen a threefold increase from 0.4% to 1.5% (6) and is expected to increase with the new initiatives and as the ESKD population grows out of proportion to the existing in-center hemodialysis resources.

This enthusiasm for HHD is increasing worldwide. Incentive models like those used in Australia for HHD programs (4, 7), if modeled across the globe, could lead to significant increases in HHD usage. Moreover, the availability of newer technologies and improved patient education portends a very bright future for the further rise in HHD worldwide in the next decade. ■

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The authors report no conflicts of interest or financial disclosures.

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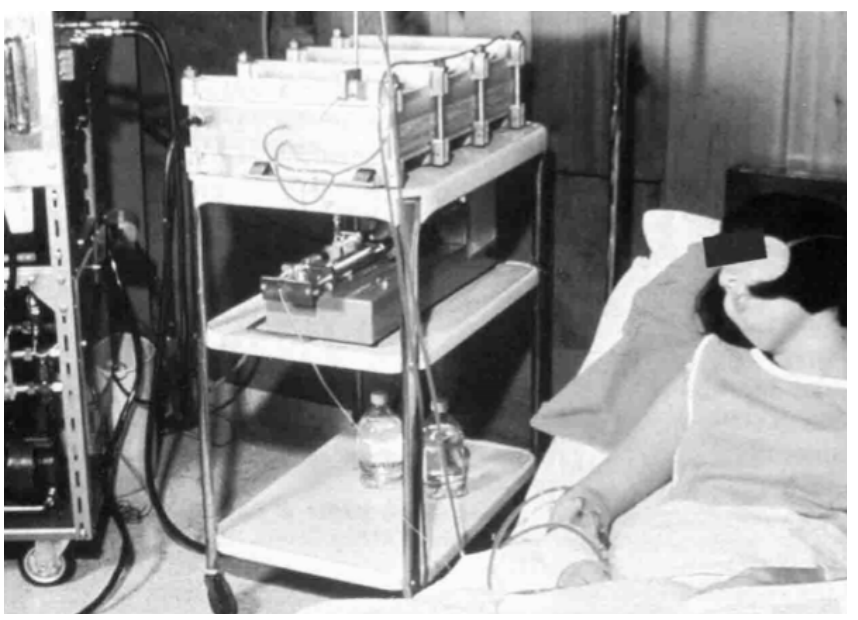
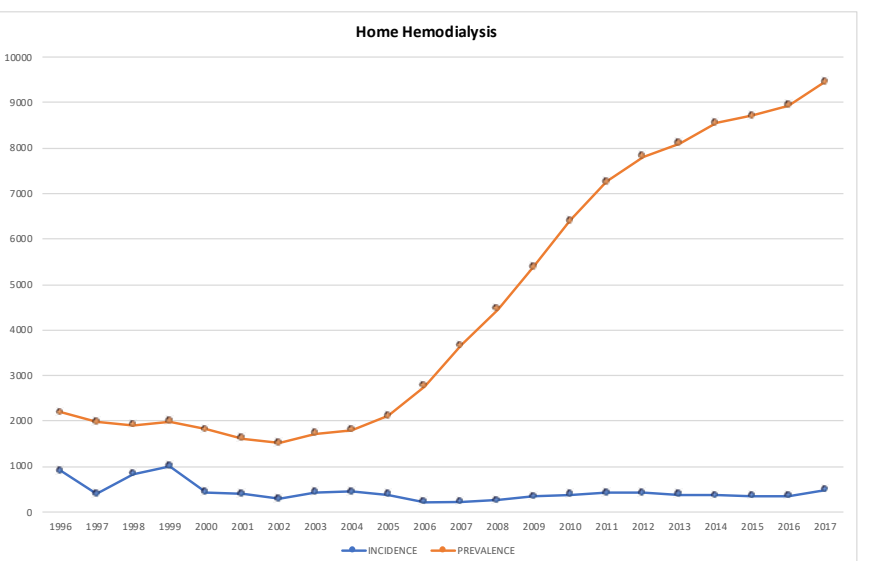
Figure 1. The first home hemodialysis patient



The first home hemodialysis patient in Seattle, WA, 1964, who did not meet criteria for hemodialysis in-center. Reprinted with permission from Elsevier (1).

Figure 2. Trends of ESKD patients on home hemodialysis



Graph showing trends in incidence and prevalence of home hemodialysis patients from 1996 to 2017. Although the prevalence of home hemodialysis has increased, the incidence has declined and plateaued (11). The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

Campaign Aims to Expand Home Dialysis

Several healthcare organizations have joined forces to launch Innovate Kidney Care, a campaign to improve patient options to receive home dialysis training and support. The organizations include Anthem, Inc.; Cricket Health; CVS Kidney Care; Home Dialyzors United; Intermountain Healthcare; the National Kidney Foundation; Outset Medical, Inc.; Strive Health; as well as ASN.

As part of its efforts, Innovate Kidney Care plans to advocate for the Centers for Medicare & Medicaid Services (CMS) to modernize its end-stage renal disease Conditions for Coverage and related guidance to achieve the quadruple aim of better patient outcomes, improved patient and provider experience, and lower costs of care. Among the group's goals are the following:

- removing barriers to home dialysis training and support;
- differentiating regulations to expand home dialysis training and support and improving transitions of care;
- alleviating the clinical burden of administrative tasks to focus on patient outcomes, empowerment, and safety; and
- allowing for home dialysis training and support to be delivered in a variety of healthcare settings.

With improvements in technology, as well as new service models aiming to create more convenient, flexible options for patients as to when, where, and how they receive dialysis, "We could be right at the cusp of a new dawn for home dialysis," said Leslie Trigg, MBA, Chief Executive Officer of Outset Medical.

Some elements of CMS' regulations stem from a decade or so ago and "don't quite match" today's environment, Trigg said. "We were interested in joining because we believed in the power that some modernization of regulations could have in creating this tipping point for home dialysis."

The Conditions for Coverage were designed for an era in which all patients would dialyze in a clinic, she said. "That's 1.0 dialysis. 2.0 dialysis is flexibility, convenience, and choice."

One aim would be to allow service providers to more easily offer transitional care units designed to transition patients to home dialysis. Currently, providers offering this service must adhere to the same regulatory requirements of a conventional dialysis clinic even though their mission is different, Trigg said. There also is a lack of clarity in the regulations around who can help train patients to transition to home dialysis—a dialysis nurse or a technician or nurse practitioner working under the direction of a dialysis nurse. A better explanation of this could help, especially during the nation's current shortage of dialysis nurses, Trigg said.

Furthermore, nephrologists currently do not receive the same payments for supporting dialysis patients at home versus the clinic, Trigg said. "It seems pretty good common sense that their workload is certainly at least equivalent when supporting patients at home versus in-center. We feel that it's important for nephrologists to have pay equity between the center and home."

The campaign's goals aligned for Intermountain Healthcare, which about 2 years ago developed a value-based kidney care program focused on early identification and management of individuals with chronic kidney disease, said Ray Morales, MPA, the health system's Assistant Vice President of Kidney Services. The company has a home-first policy for patients needing dialysis.

"This collaboration really fits well within our mission and the program we've built to look at empowering the patients with the right information at the right time," Morales said. "It also modernizes existing policies and regulations to help support advancements in home dialysis therapies and allows for support around self-care dialysis."

The campaign's work also fits for the National Kidney Foundation, said Miriam Godwin, the organization's Director of Health Policy.

"What patients want…is a system that's really designed around how people with kidney failure want to live, rather than having people try to fit their lives around dialysis," she said. "It's a really exciting time in kidney care to try and do things differently, and we're really honored and pleased to be part of that innovation."

The group plans to produce a white paper describing its position, Godwin said. For more information, see https://www.innovatekidneycare.com/.

Perspective

Are Weekly Dialysis Visits the Best Use of Nephrologists' Time?

By Arshia Ghaffari, Quinn Lougheide, and Lin Wang

As nephrologists, we are perpetually searching for more time in our workdays. Oftentimes, we find ourselves juggling among inpatient, clinic, dialysis unit, and administrative duties, all within the same day. This begs the question: Can nephrologists be more efficient while still providing high-quality patient-centered care?

In the current fee-for-service Medicare payment model, dialysis patients are mandated to have a comprehensive nephrologist evaluation at least once monthly (1). Hemodialysis (HD) patients can be seen up to an additional three times with increasing levels of reimbursement. This encourages an increased number of visits, irrespective of medical necessity. While some have argued that an increased number of visits may improve patient outcomes, multiple studies have found that there was no significant difference in mortality among patients with more provider visits per month compared with those patients with fewer provider visits (2–6). As a result, the increased documentation time and "window time" contribute to physician burnout and fatigue with no tangible benefit to patients.

Although change is difficult, we need to implement ways to deliver care that makes a difference for our patients by providing the right treatment at the right time—without increasing the stress on ourselves. The pandemic-era loosening of restrictions in the use of telehealth services in dialysis has been a natural experiment that demonstrated we can deliver certain aspects of care to patients without the need to be at chairside (7). Moreover, new Centers for Medicare & Medicaid Services (CMS)-proposed payment models, such as the Kidney Care First (KCF) and the Comprehensive Kidney Care Contracting (CKCC), provide capitated payments adjusted for outcomes and utilization rather than rote fee for service. While the rollout of these initiatives is likely to initially involve a small percentage of nephrology practices, future expansion of these quality-based incentives can potentially entice nephrology practices to focus more on patient outcomes rather than number of patient visits.

Although change is difficult, we need to implement ways to deliver care that makes a difference for our patients by providing the right treatment at the right time.

To plan for upcoming payment model changes and deliver efficient patient-centered care, the nephrology industry needs to better utilize technology and data in new care-delivery models. This aspirational concept will require a three-pronged approach (Figure 1): 1) utilizing predictive analytic patient care models; 2) implementing communication platforms to allow seamless patient and care-team interactions; and 3) changing nephrologists from single-patient providers to population health providers.

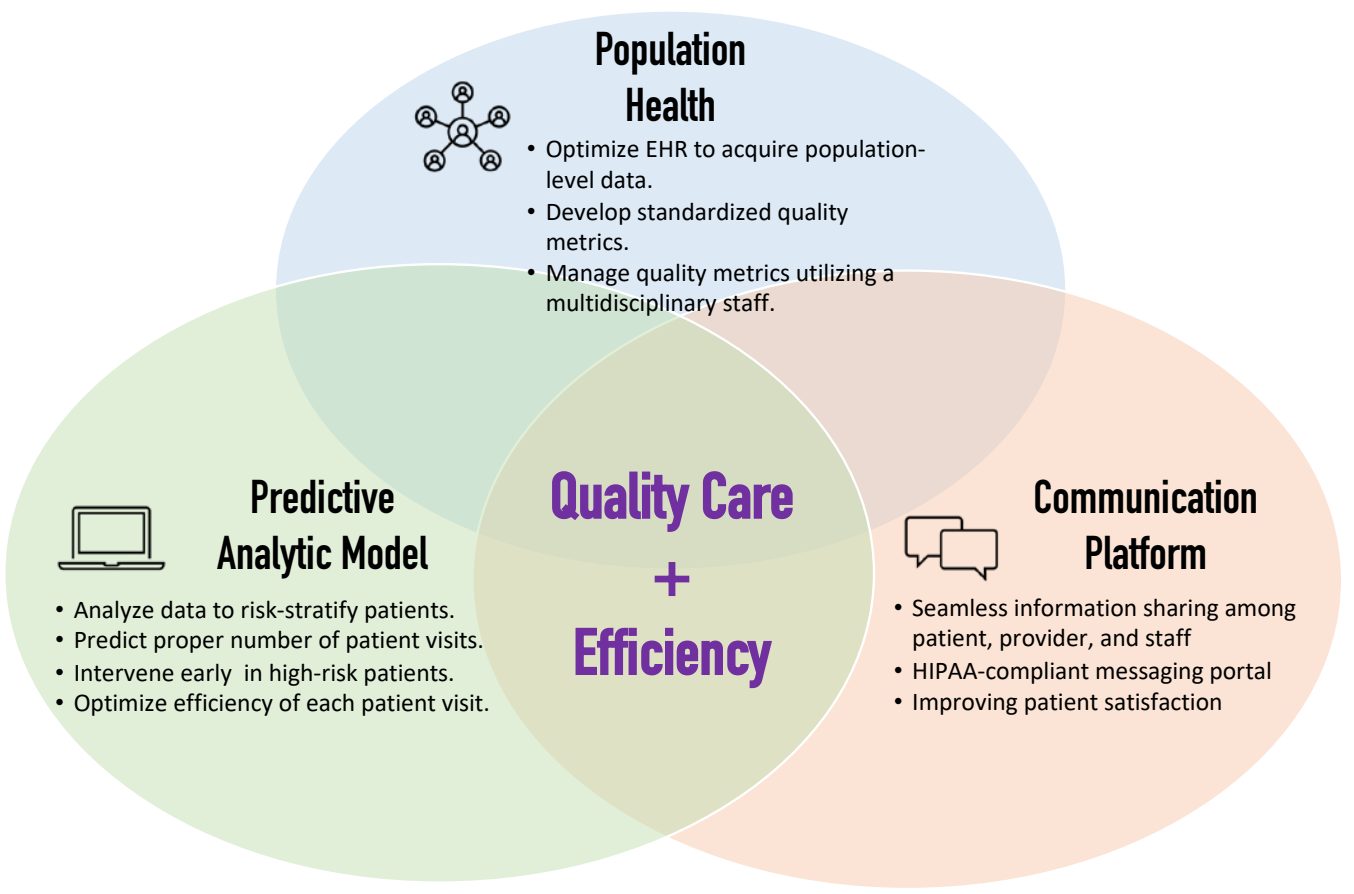
Predictive analytics refers to predicting future outcomes based on historical data. Multiple studies exist to determine what patient characteristics invoke worse outcomes (8–11). Some have suggested reduced hospitalizations when early interventions are invoked in high-risk patients, although more studies are required. When utilizing such models, lower-risk groups would receive a required baseline level of care, whereas the higher-risk groups would have an increased number of provider and dialysis staff visits (dietitian, social worker, nurse) with a goal of improving outcomes.

With a decreasing number of touchpoints between the physician and patient, the system needs to allow patients and chairside providers (nurses, techs) a way to relay information to the nephrologist without causing repeated disruption to the nephrologist's multiple day-to-day duties. A Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant communication portal would allow patients and dialysis staff to communicate seamlessly with the nephrologist to address issues that come up between visits.

Lastly, while nephrologists still must care for individual patients, given the relative shortage of nephrologists compared to a growing number of patients, nephrologists need to implement population health into their practices. That entails configuring electronic medical records to allow for population-level data on specific quality metrics. Utilizing a multidisciplinary approach to care, the nephrologist would then work with the care team to address specific quality metrics (12, 13).

This systematic change will require a culture shift of expectations by dialysis providers, patients, and nephrologists in the way care is delivered. Although there are some potential downsides to this approach (weakened patient-physician relationship, more screen time), each patient interaction will be better focused on the patient's issues and quality metrics that are aimed at improving patient outcomes. Moreover, it could potentially lower the cost of care delivery by focusing resources on where they are needed most. ■

Figure 1. Improving nephrologists' efficiency and quality of patient care



EHR, electronic health record; HIPAA, Health Insurance Portability and Accountability Act of 1996.

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SARS-CoV-2 Vaccinations in Transplant Recipients
The More the Better?

By Vinay Nair and Mersema Abate

Routine administration of inactivated, age-appropriate vaccines is recommended for organ transplant recipients. As with response to other vaccinations (1), antibody response to SARS-CoV-2 vaccine is diminished in transplant recipients (2). Moreover, these individuals face worse outcomes following COVID-19 infection (3).

A Correspondence in the *New England Journal of Medicine* by Hall et al. found a booster dose of mRNA-1273 vaccine 2 months after the standard 2-dose series improved both antibody and T-cell immunity to SARS-CoV-2 in organ transplant recipients (4). At month 4, patients who received three doses of vaccine had a threefold increase in positive antibody response, higher viral neutralization, and SARS-CoV-2-specific T-cells. Two retrospective studies from France (5) and the US (6) demonstrate similar findings (Table 1), and an NIH-funded study (clinicaltrials.gov NCT04C969263) is underway. Subsequently, the FDA authorized booster mRNA vaccination for transplant recipients. Although a major milestone, there are several questions that need to be answered: What antibody titer is required to prevent COVID-19? How do neutralizing antibodies translate to the more commonly available spike protein antibody assay? How effective is cellular immunity in the prevention of COVID-19? If antibody response improves after each subsequent dose, should non-responders be given a fourth dose?

As transplant nephrologists, it is our duty to protect our patients from severe illness associated with COVID-19. The manuscript by Hall et al. (4) is a step toward this goal. However, larger studies are still needed that will look at hard endpoints, such as hospitalization and mortality due to COVID-19. ■

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The authors report no conflicts of interest associated with the work.

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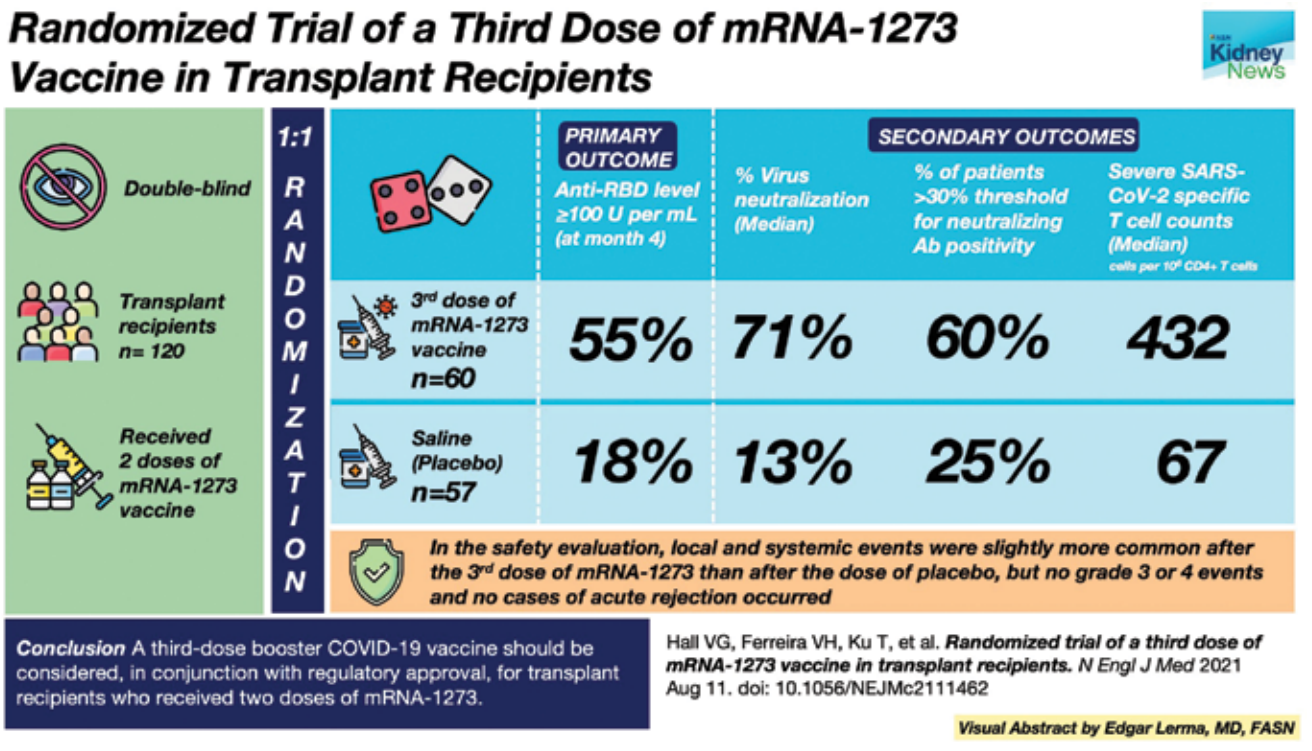
Table 1. Results of studies about SARS-CoV-2 vaccines in transplant recipients

Study	n	Design	Vaccine	Positive anti-SARS-CoV-2 antibody response	
				Two doses	Three doses
Hall et al., Canada	117	Randomized clinical trial	Moderna	18%*	55%*
Kamar et al., France	101	Retrospective cohort	Pfizer	40%**	68%**
Werbel et al., USA	30	Retrospective cohort	Initial 2 doses Moderna or Pfizer, 3rd dose Moderna, Pfizer, or Janssen	20%***	47%***

*Anti-receptor-binding domain (RBD) antibody ≥ 100 U/mL.
**Total anti-SARS-CoV-2 spike protein antibodies (IgG, IgM, IgA) signal-to-cutoff ratio >1.1.
***Anti-SARS-CoV-2 spike protein antibodies (EUROIMMUNE) IgG ≥ 1.1 arbitrary units, or anti-RBD (Roche) pan-Ig ≥ 0.8 U/mL. Includes any level of positive antibody.



What's in a Name, and Who's the Audience? "Kidney" vs. "Renal"

By Eric Seaborg

A broad consensus exists that patients understand the word "kidney" better than "renal." Thanks to that consensus, moves like the one for ASN to change its annual meeting from Renal Week to Kidney Week in 2011 to make its subject matter more understandable to the general public have been welcomed.

But the recent word usage proposals from a Kidney Disease: Improving Global Outcomes (KDIGO) meeting have proven more controversial. In June 2019, KDIGO convened a consensus conference in Amsterdam with the goal of standardizing and refining the English-language nomenclature to describe kidney function and disease. The "executive summary and glossary" of the meeting was published concurrently in 23 journals, a list that was wide ranging enough to include the *European Heart Journal* (1) and *American Journal of Transplantation* (2).

Although the stated aim was to present a "glossary," one short phrase has generated backlash and debate: "Use the term 'kidney' rather than 'renal' to describe kidney function and kidney disease."

As part of the pushback, a group of 27 leaders in nephrology, including several from the patient-advocate side, published a "point of view" in the *Journal of Nephrology*, "Nomenclature in nephrology: Preserving 'renal' and 'nephro' in the glossary of kidney health and disease" (3). The authors said: "'Renal' and 'nephro' should not be removed from scientific and technical writings. Instead, the terms can coexist and be used in their relevant contexts."

The KDIGO guidelines do not call for removing "renal" and "nephro" from scientific and technical writings, according to Andrew Levey, MD, the lead author of a report that appeared in *Kidney International* (*KI*) (4), as well as the widely published executive summary: "The KDIGO consensus conference did NOT recommend that 'kidney' should be used instead of 'renal' or 'nephro' in as many uses as possible. The recommendation applies for general terms related to kidney function and disease, not to specific anatomic structures, physiologic processes, or names of diseases (nor to names of clinical services or professional societies)."

Despite this interpretation, the statement—"use the term 'kidney' rather than 'renal' to describe kidney function and kidney disease"—does not contain any caveats about applying only to "general terms," and some authors have complained that the policy is being implemented much more broadly than Levey's statement would have it.

Ask the editors

To clarify some of this debate, *Kidney News* contacted the editors of four respected nephrology journals to ask how they are implementing the KDIGO guidelines. The editors all participated in the KDIGO consensus conference.

They agree that even journals have some aspects that are more patient facing than others—such as abstracts and summaries—in which they are more likely to favor "kidney." But they also said they are not trying to remove "renal" from scientific and technical writings.

The editors of the ASN-published journals, *Journal of the American Society of Nephrology* (*JASN*) and *Clinical Journal of the American Society of Nephrology* (*CJASN*), have taken somewhat different approaches, which ASN Executive Vice President Tod Ibrahim said is attributable to the "editorial firewall" between the publisher and the editors: "The editors of *JASN*, *CJASN*, *Kidney360*, and *Kidney News* have the authority to decide which terms to use in each publication, not ASN."

JASN

JASN Editor-in-Chief Josephine Briggs, MD, said: "*JASN* is taking what I would call a light-touch approach to these issues. In the main text of the paper, we view this as a matter of author's choice. There are many settings where authors elect to use renal, and we do not feel it is essential to remove this word from our vocabulary. The critical issue is the context in which it is being used, and that is what I mean by a light touch."

JASN does tend to favor "kidney" in the areas more likely to be read by lay audiences: "The significance statement is a brief summary of the highlights in the paper. The internet is increasing the extent to which people look at the scientific literature, and that was part of our notion of adding significance statements to our papers. We try to use 'kidney' wherever it seems to be appropriate in outward-facing statements likely to be read by the general-public.... In these parts of the papers, we primarily use the term 'kidney' unless there is a strong reason to use 'renal.'"

CJASN

CJASN Editor-in-Chief Rajnish Mehrotra, MD, FASN, said the use of "renal" "depends upon the context in which it is being used. The editors review every paper and determine the appropriate nomenclature to be used. It is not something that has been so front and center and important to us that we have a written policy."

"Our approach of not going down the path of 'required nomenclature' is author friendly. One of the biggest complaints authors have is that each journal has its own unique formatting requirement. And if their paper is unsuccessful in one journal, authors can spend hours just reformatting to the requirements of the next journal. [For the articles we accept], we take it upon ourselves to guide the authors, rather than ask authors to take it on. We want rigor, and an important component of rigor is to be consistent in how information is presented in the journal. 'Renal' vs. 'kidney' is a very small part of the bigger whole of rigor such that [the] material [that] appears in the pages of *CJASN* is consistent from article to article, from issue to issue over the years," Mehrotra said.

"We value patients accessing our content," he added. "Three years ago, we started an article type that is called 'the patient's voice,' where we invite a patient to review an article that we have published and provide a commentary on what that article means to [him or her] and the journey [he or she has] had with [his or her] illness."

ASN supports the journals by issuing press releases to publicize the articles the editors deem the most newsworthy, and the press releases use lay-friendly language.

KI and *American Journal of Kidney Diseases (AJKD)*

Two other journal editors described similar approaches to the KDIGO recommendations.

Pat Morrissey, executive managing editor of *KI*, said in an email: "The policy at *KI* is to use 'kidney' instead of 'renal,' per KDIGO guidelines. However, this does not mean that the word 'renal' is banned from use, but rather that the word 'kidney' is preferred in most cases. 'Renal' is very appropriate in some situations, but we simply agree with and encourage the use of 'kidney' when possible."

"As a rule, our *KI* copyeditors insert a general query into the author proofs asking authors to use the word 'kidney' when describing kidney function, where applicable. The copyeditors do not make any changes to the proofs themselves in this respect. The query is only added as a suggestion to the authors," she said.

"That being said, we do try to incorporate 'kidney' vs. 'renal' in the abstract since the idea of the KDIGO guidelines is to make nomenclature more understandable for the general reader, and the abstract might more likely be read by a broader audience," Morrissey said.

Nijsje Dorman, PhD, managing editor of *AJKD*, said: "Like the 23 other journals that co-published the executive summary, we at *AJKD* endorse the spirit and sentiments of the KDIGO effort to enhance the precision and patient centeredness of the language used in nephrology. That said, we appreciate that subtleties and nuances are inherent in communication, and while we make an effort to incorporate the KDIGO glossary in our editing process, authors have the opportunity to review these suggestions at proof, and we do not dictate or overrule authors' word choice. From this collabora-

tive process of editing, we hope to make AJKD's content accessible to the broadest swath of readers possible."

General journals

Outside of the kidney space, more generalized journals are aware of the KDIGO recommendations but do not seem to be changing their policies as yet. The editors at the *New England Journal of Medicine* (*NEJM*) noted that they are aware of the KDIGO recommendations and the "changing trends in nomenclature within the field of nephrology favoring language that is 'patient centered, precise, and consistent.' However, as there is not consensus across the field on this matter, we strive for clarity throughout each individual *NEJM* article without dictating one term over another."

(The *Journal of the American Medical Association* [*JAMA*] editorial office said, "We have no comment" in response to a query from *Kidney News* on its policy.)

The KDIGO guidelines are for English usage, and the debate is clearly an English language-centered issue. The French word for kidney is "rein," and the Spanish word is "riñon," so speakers of these languages have no problem with "renal."

"You talk to the non-English-speaking world—Spanish, French, and that is a huge part of the world—and they will tell you that they look at this whole issue in puzzlement, saying, 'Why are you doing this? Renal makes so much more sense for us,'" said Swapnil Hiremath, MD, MPH, associate professor of medicine at the University of Ottawa in Canada and co-host of the NephJC podcast, Freely Filtered.

It is also noteworthy that despite the focus on the "kidney" vs. "renal" recommendation, the main thrust of the KDIGO guidelines was to provide a glossary on more technical terms. For example, the "key takeaways" included general items such as "avoid the use of 'AKI' as a synonym for 'AKD.'" The more technical recommendations sought to clarify nomenclature such as: "Avoid referring to 'albuminuria' or 'proteinuria' as 'decreased kidney function.' Albuminuria and proteinuria are markers of kidney damage, rather than measures of kidney function."

Organization names

As this internal debate continues, the "patient-facing" movement continued in July 2021, when the British Renal Society and the Renal Association completed a merger. The organizations agreed to drop the "renal" in favor of the name UK Kidney Association. The new name was "widely supported … as the preferred term for the UK professional organization representing all healthcare professionals involved in the care of patients with kidney disease," the association's presidents Sharlene Greenwood and Paul Cockwell said in a statement to *Kidney News*.

In contrast, in the United States, the National Renal Administrators Association recently kept the "renal" when it changed its name to the Renal Healthcare Association.

Organizations continually grapple with the language they use to present themselves to the world, and ASN is no exception, according to ASN's Ibrahim: "All three words—American, society, and nephrology—have generated discussions. Because ASN is an international organization, with members in more than 130 countries, we've considered changing American to something more global. Many people also associate a society with a club, and we're a much broader, dynamic organization than that. Finally, with the emphasis on kidney health, the term nephrology merits consideration. That's part of the reason why we branded in July 2019 the ASN Alliance for Kidney Health, which includes ASN, KidneyCure, Nephrologists Transforming Dialysis Safety, the Kidney Health Initiative, and KidneyX." ■

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Personalized Nephrology: Genomic Implementation Tools Help Nephrologists Deliver on the Promises of Precision Nephrology

By Jordan G. Nestor

Creating personalized care plans through genomic implementation

Chronic kidney disease and kidney failure affect over 20 million Americans and confer substantial morbidity and mortality. Recent studies show that genomic sequencing approaches, such as exome sequencing, can identify a specific monogenic disease in 10% to 35% of kidney disease patients (1–6). Hereditary nephropathies are genotypically and phenotypically heterogenous and are often difficult to diagnose because of overlapping, nonspecific features (e.g., elevated serum creatinine, proteinuria, etc.). The establishment of a molecular diagnosis can support personalized nephrology care by informing targeted workup, disease prognosis, choice of therapy, and/or family counseling. However, genomic sequencing technologies are still emerging diagnostic tools, and despite their increased use in medicine subspecialties like nephrology, many physicians may lack the requisite knowledge and experience to apply genomic findings into clinical practice. This can be exhibited particularly if one is called upon to interpret unsolicited genomic findings, such as when patients undergo sequencing through their participation in genomic research, expanded carrier screening as part of family planning, or direct-to-consumer testing to learn about their ancestry. Overall, nephrologists' lack of familiarity in utilizing genomic data poses a significant barrier to their participation in precision medicine efforts and to broader implementation of genomics in routine nephrology care. However, these barriers can be overcome with customized tools tailored to nephrologists' needs (Figure 1).

The workflow and technology imperatives

Although consensus guidelines are available for the evaluation and/or management of some hereditary nephropathies (e.g., autosomal dominant polycystic kidney disease, Alport syndrome, etc.), these resources may be difficult to access in real time and at the point of care. Furthermore, they often require nephrologists to already suspect a hereditary etiology for an individual's kidney disease. Thus, there is great need for technologic solutions that support nephrologists' use of genomic data at the point of care, despite their level of expertise in clinical genomics. However, the development of novel, nephrology-tailored tools that clinicians will want to use, such as interactive electronic health record (EHR)-integrated, genome-informed clinical decision support tools, requires further study into the informational and workflow support needs of the intended user (7, 8). Insights into nephrologists' unmet needs will inform the design of tools that are versatile enough to be used across diverse practice settings, address specific knowledge gaps, and potentially increase users' willingness to deliver more personalized nephrology care. Development of these novel aids relies on nephrologists' participation in genomic implementation and bioinformatics research. For example, Columbia University needs US nephrologists, particularly those who practice outside of large academic institutions, to share their user experiences with existing decision aids and technology-based tools and to help us pilot preliminary decision support tools intended for the EHR. Technologic tools tailored to address nephrologists' needs will allow us to provide more personalized care, work toward improving long-term outcomes in our patients, and deliver on the promises of precision nephrology. ■

Jordan G. Nestor, MD, specializes in precision medicine and the diagnosis and management of hereditary nephropathies. She is an Assistant Professor of Medicine and a Junior Investigator in the Division of Nephrology at Columbia University, New York, NY. Under the mentorship of Ali G. Gharavi, MD, and Chunhua Weng, PhD, her research focuses on facilitating broader genomic implementation in nephrology through the development of novel bioinformatic solutions. For questions or to share your interest in participating in genomic implementation initiatives at Columbia University, please email her at jgn2108@cumc.columbia.edu.

The author reports no conflicts of interest.

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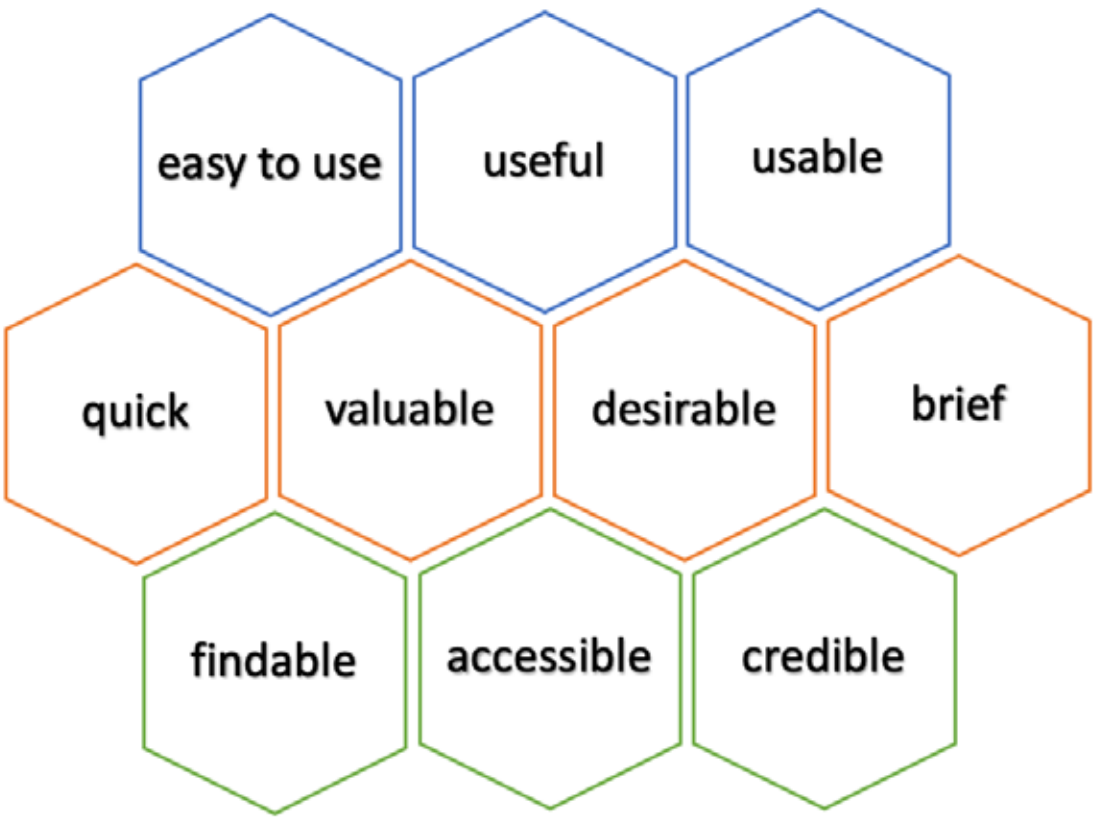
Figure 1. User experience: needs and values



Understanding the intended users' needs and values is essential for the development of EHR-integrated decision support tools that effectively enhance clinicians' use of genomic data.

Figure adapted with permission from Peter Morville (2004).

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