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Harnessing Patients' Wishes to Drive Vascular Access Innovation

By Bridget M. Kuehn

Terry Litchfield, MPH, draws on five decades of experience when she argues for a more patient-centered approach to developing new vascular access options. Her experience stretches back to when her late husband Gerald started dialysis in 1968, and it continues in her current role as a consultant on patient-centered vascular access and as a Kidney Health Initiative (KHI) Patient and Family Partnership Council member.

"It was newsworthy in 1968 when someone started dialysis," Litchfield said. "I'm very pleased to say dialysis sustained his life for a long time. We lived overseas; have machine, will travel."

Now, she wants to make sure other patients have the opportunity to have full and fulfilling lives with the help of innovative vascular access options that meet their individual needs. Doing that, she notes, will require physicians and device makers to re-center their care processes around what's most important to patients. Litchfield spoke to *Kidney News* about how clinicians, researchers, regulators, and device developers are working to meet that demand. She also participated in the Novel Therapies for Vascular Access panel at Kidney Week 2018.

Priority disconnect

Too often, clinicians' and patients' vascular access priorities don't align. Litchfield noted, for example, that women have told her they are very concerned about body image and scarring on the arms. One woman confided to her that someone asked her if she was a cutter.

"What is really important to patients is often trivial to providers," Litchfield said.

The data backs her up. A recent survey of kidney patients and clinicians found that patients ranked catheter thrombosis, selection of vascular access type, clinician training in vascular access, and infections as their top priorities. Litchfield explained that patients want to avoid being hospitalized, they want a choice of access, and they want to know their clinician will do a good job. While providers agree about infection and access choice, they rank many patients' top priorities near the bottom of their lists.

"Providers want to preserve veins or keep existing accesses at all costs," she said. "I maintain vehemently quality of life trumps all."

Prabir Roy-Chaudhury, MD, PhD, chief of the division of nephrology at the University of Arizona, also emphasized the disconnect, citing data that patients rate the ability to travel, dialysis-free time, and not being washed out as higher than death, while physicians put things like death and drops in blood pressure high on the list despite their low ranking

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Breath Gas, or "Exhalome," Analysis of Volatile Organic Compounds Could Help Gauge AKI Severity

Dozens of volatile organic compounds (VOCs) are found at elevated concentrations in expired gas from critically ill patients with acute kidney injury (AKI), reports a study in *Critical Care Medicine*.

The study included 20 mechanically ventilated patients with AKI, along with a control group of critically ill patients without AKI. The mechanically ventilated patients also had indications for dialysis.

Intensities of VOCs in breath samples were measured using multicapillary column ion-mobility spectrometry. Each patient's "exhalome" was evaluated from 30 minutes before they started continuous venovenous hemodialysis through 7 hours after the start of dialysis.

The researchers hypothesized that AKI would be associated with a characteristic alteration of the VOC pattern, and that the changes would be reversed during hemodialysis.

Their analysis included 719 samples of expired air. Of the 60 signals they observed, 44 compounds were identified. During hemodialysis, 34 signals decreased while 26 signals were unchanged. Among the VOCs that decreased with dialysis were cyclohexanol, 3-hydroxy-

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Inside

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USMP/MG120/18-0006a(1) 1/19

Breath Gas

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2-butanone, 3-methylbutanal, and dimer of isoprene.

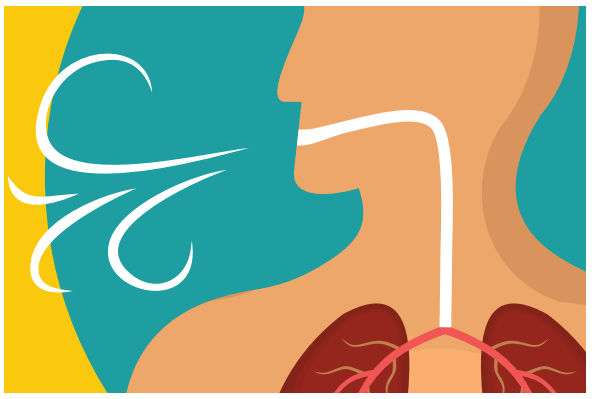
The hemodialysis-associated decreases in VOC signals included 30 of the 45 signals that were increased in the AKI group.

Many critically ill patients develop AKI requiring dialysis. Breath gas analysis might help to meet the need for real-time bedside assessment of kidney function in this group of patients, the authors of the study noted.

The study documents higher exhaled concentrations of 45 different VOCs that were greater in critically ill patients with AKI than in those with normal kidney function and finds that most of these VOCs decrease during continuous dialysis.

"Exhalome analysis may help to quantify the severity of acute kidney injury and to gauge the efficacy of dialysis," the authors said.

Hüppe T, et al. Volatile organic compounds in patients with acute kidney injury and changes during dialysis. *Crit Care Med* 2019; 47:239–246.



Vascular Access Innovation

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on patients' lists.

To help resolve this disconnect, Litchfield recommended that clinicians and device developers involve patients and patient organizations in the earliest stages of developing new vascular access options and keep them looped in throughout the process. This will help them make sure they build in patient priorities like fewer surgeries and interventions, smaller needles, hassle-free access, preserved body image, and a better quality of life.

"They want a better quality of life through less impact," Litchfield said.

Patients should be involved in study design to ensure that the questions being asked are relevant to them, she said. Patients who choose to participate should have clear and easy-to-understand consent forms, their transportation and other participation needs should be considered, and when the study is done they should be looped back in on the results.

Roy-Chaudhury agreed with the importance of engaging patients throughout the development process. He called it a "bedside to bench to bedside" approach, and said it is key to breaking the cycle of "a lack of innovation in vascular access that results in poor quality and outcomes at a very high cost burden."

Collaborative solutions

Collaborative efforts are currently underway to accelerate the development of new, more patient-centered vascular access options and to optimize the safety of existing options.

"The challenges of getting an innovative access device to the market are considerable," said Robert Lee, MD, medical officer in the US Food and Drug Administration's (FDA) Vascular Surgery Devices Branch.

But a March 2018 publication from the Kidney Health Initiative's (KHI) vascular access work group may help streamline the process by suggesting standardized endpoints for vascular access studies that have been shaped by input from the FDA, patients, device makers, and nephrologists.

"The standardized definition of clinical trial endpoints proposed by the work group are a positive step toward harmonizing outcomes in vascular access reporting," Lee said.

He noted that the FDA has begun using real-world data to evaluate new vascular access options by creating registries to track patient outcomes after a device becomes available. The agency has already used this approach in the evaluation of two vascular access devices, Lee said.

"This has shifted some of the balance of evidence collection to post-market clinical data that would have been tough to gather in a traditional clinical trial setting," he said.

The FDA is also increasingly partnering with patients, Lee said, noting the agency's patient advisory committee and partnership with ASN in KHI. The agency looks to patient preferences to guide its regulatory decisions. Lee explained that patients may be willing to accept a higher level of risk associated with new devices if they place a very high value on the potential benefits of the device.

"Patient preference information may be particularly useful in evaluating a device when patient decisions are preference-sensitive," he said, for example, in situations where multiple comparable options are available or when patients' views about the benefits or acceptable risks associated with a device vary.

The US Centers for Disease Control and Prevention (CDC) and ASN have also undertaken an effort to reduce infections by ensuring that more clinicians follow their evidence-based guidelines for vascular access care. Alan Kliger, MD, clinical professor of medicine at Yale University, noted that infections claim the lives of 8000 to 10,000 patients on dialysis each year, accounting for 10% of dialysis-related deaths.

"Central venous catheters are a major source of this morbidity and mortality, caused by infection," Kliger noted. Yet, many clinicians aren't using proven techniques to prevent them. Nephrologists Transforming Dialysis Safety (NTDS), a collaboration between ASN and the CDC, includes a vascular access working group. NTDS plans to release an interactive curriculum for clinicians in 2019, and is also working with the CDC to develop new procedures to identify bloodstream infections and recommendations for drawing blood cultures.

Kliger acknowledged that sharing best practices isn't enough. In busy dialysis units, standard procedures may be bypassed in a crunch, he noted. So, the CDC has provided funding for NTDS to hire human factors engineers to evaluate vascular access procedures at six dialysis facilities and suggest ways of re-engineering the process to be safer.

"Significant progress can be made," Kliger said. "But we need to provide that platform for collaborations where patients come together, caregivers come together, policymakers come together, [and] industries come together in order to find the right solutions for the future."

Innovative access

Both Roy-Chaudhury and Litchfield are optimistic about emerging vascular access options. Litchfield noted that the FDA approved two devices to create percutaneous arteriovenous fistulas in 2018. Roy-Chaudhury explained the devices use magnets and radio frequency electrodes to create a connection between artery and vein without the need for surgery. He noted he has worked with companies developing the devices.

"No surgical scar or tissue trauma at the creation of the fistula site," he said. "No operating room hassles."

Both noted there are other promising devices in the pipeline. Ultimately, Roy-Chaudhury said, having a large menu of options that can be matched to patients' needs and desires will be essential.

"We need to individualize [patients'] vascular access care by pairing specific novel patient-centered therapies with specific clinical and biological phenotypes in order to get the best results for individual patients," he said.

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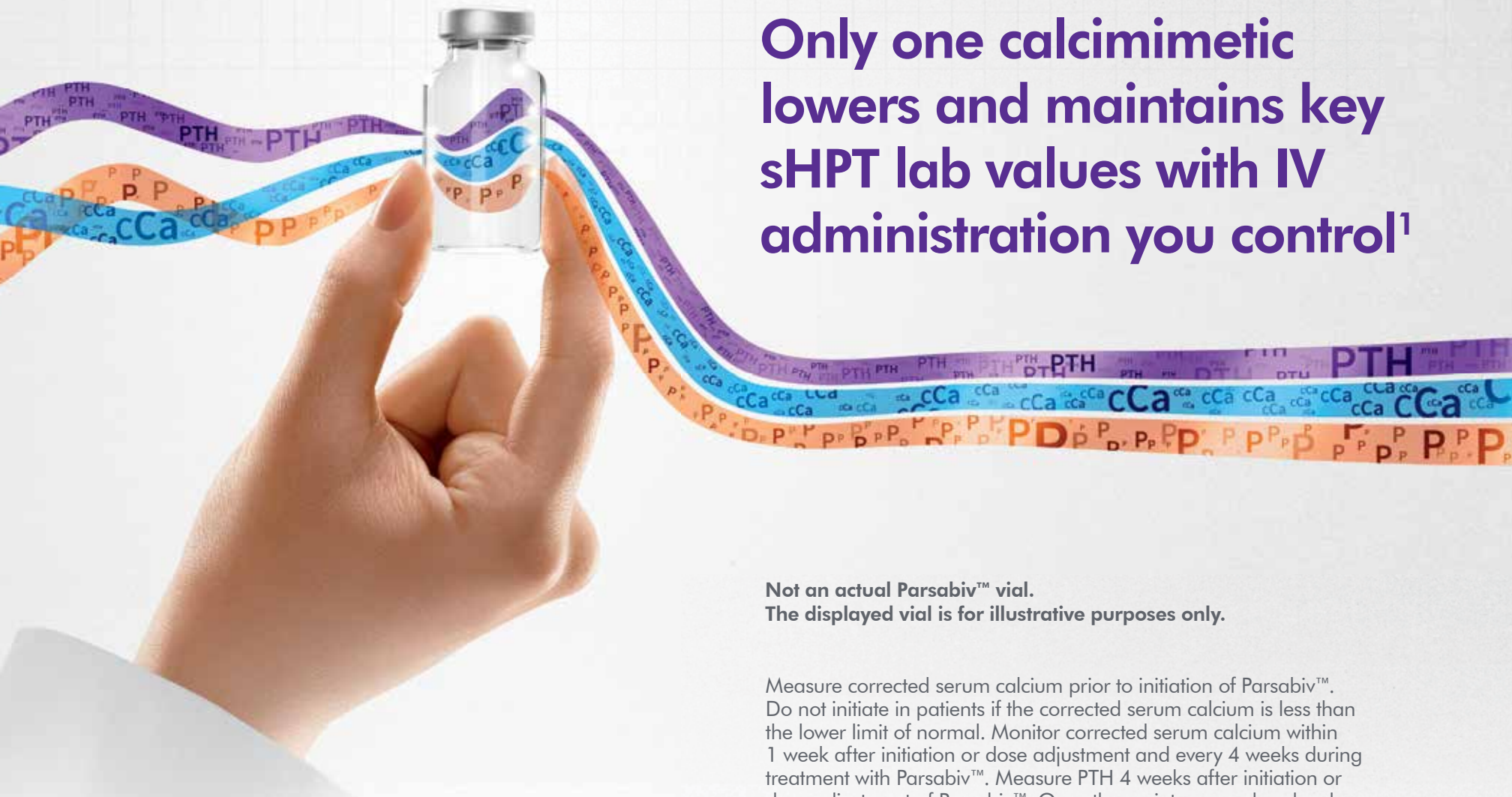

Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

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

Indication

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

Limitations of Use:

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

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

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

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

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

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

QT Interval Prolongation and Ventricular Arrhythmia

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

Seizures

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

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

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

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

Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

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

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

Adynamic Bone

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

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

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

Description of Selected Adverse Reactions

Hypocalcemia

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

Hypophosphatemia

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

QTc Interval Prolongation Secondary to Hypocalcemia

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

Hypersensitivity

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

Immunogenicity

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

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

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Data

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

Pediatric Use

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

Geriatric Use

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

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

OVERDOSAGE

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

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Technology Roadmap Outlines Future Research Approaches

Many areas of medicine have seen great leaps in innovative therapies in recent years, but treatment for kidney disease has scarcely changed since the introduction of dialysis some 60 years ago.

ASN's Kidney Health Initiative responded to this perceived lag by pushing toward a new treatment paradigm in its "Technology Roadmap for Innovative Approaches to Renal Replacement Therapy."

"This roadmap identifies challenges and opportunities and encourages diversity of thought and attraction of expertise from various scientific and engineering communities," according to Joseph V. Bonventre, MD, PhD, of Brigham and Women's Hospital and Harvard Medical School in Boston. Bonventre led a multidisciplinary team that included healthcare clinicians and researchers, patients, industry partners, product developers, payers, and federal agencies during a two-year development process. The roadmap was introduced at ASN Kidney Week 2018.

The roadmap tries to break down the tasks that could lead to this paradigm shift in a way that "will help to bring innovators from various fields into the kidney space with new ideas, out-of-the-box approaches, and substantive financial resources from corporate, philanthropic, and venture capital communities," Bonventre said.

Potential prize applicants to the Kidney Innovation Accelerator, KidneyX, a public-private partnership between the ASN and the US Department of Health and Human Services, are urged to read the roadmap as they consider their projects.

Multiple solution pathways

Because it can't be known which approaches or research areas will bear the most fruit, the roadmap calls for exploring "multiple solution pathways" to "allow technologies and advances to be developed in parallel, rather than sequentially, offering greater opportunities to move toward more effective RRT and improved patient quality of life."

Within these "multiple solution pathways," the roadmap tries to progressively break down tasks into discrete pieces that researchers can independently take on and that might attract people from other fields—while trying to simultaneously move toward both short-term improvements to patient experience and longer-term innovations. It categorizes four "solution approaches"—enhanced dialysis, portable/wearable technologies, implantable/biohybrid technologies, and a regenerated kidney—and specifies goals for each approach. For example, the goals for the implantable/biohybrid approach are to:

- Develop products that closely mimic normal physiology,
- Develop suitable organs for transplantation (e.g., xenotransplantation, chimeras), and
- Develop a bioengineered kidney.

The roadmap then becomes even more specific with a section that provides the "design requirements for ensured success" for the "function/components" of RRT access, blood filtration, electrolyte hemostasis, fluid regulation, toxin removal/secretion, and filtrate transport and drainage.

For each of these components, the roadmap provides specifications for "minimum technical design requirements." For example, under blood filtration, it specifies the ability to generate a filtrate of at least 40 liters per day. (See Table 1 for more examples.)

Enabling change

The next section of the report, titled "Enabling change through focused research and design," identifies ever-more-specific nuggets of information that can be put together independently to advance toward the overall goals.

"We dive very deep in our detail," said Prabir Roy-Chaudhury, MD, PhD, of the University of Arizona and the Southern Arizona VA Healthcare System in Tucson and another member of the roadmap task force. "For all of the different domains that we call system enablers, there are questions to address, such as: how do you develop the right vascular access, how do you get the right biomaterials, how do you develop the right sorts of cells that may need to go onto these devices, how do you miniaturize things, how do you monitor things, and how do you quality control things." The activities are also assigned a timeframe—near-term to long-term—for achieving them (Table 1).

"[These kinds of tasks] could be tackled by individuals who may not know anything about the kidney" but have applicable expertise, Bonventre said. "We are hoping to draw people into the field to work on these programs."

"My dream would be that there is a little company out there that has perfected a way of filtering seawater, and if we get word out to them of this opportunity, that small company with a great idea could come into the filtration business, not for seawater, but could develop better filters for blood," Roy-Chaudhury said. "We don't know the direction that new technology that we want to get developed will go."

Cancer treatment is being transformed by immunotherapy's approach of unmasking cancer's ability to hide from the immune system. It's an emerging paradigm shift from chemotherapy's approach of attacking the body's fastest growing cells to switching on the body's own immune system—could nephrology find a similar shift to a completely different approach?

"We have tried to be quite agnostic in defining the way the solution should look. We focused on design criteria and incorporated some ideas about directions, but we really didn't want to be prescriptive because we don't want to hold back any kind of innovation. For example, the replacement product doesn't have to look anything like a kidney," Bonventre said.

Directions of future research

In choosing the direction of their endeavors, researchers could benefit from examining the roadmap because it will likely be used in choosing which projects will receive grants and funding.

The roadmap notes: "One key near-term funding opportunity is the newly established Kidney Innovation Accelerator (KidneyX). . . .The research priorities in this roadmap offer a strategic development and implementation pathway to support KidneyX's emphasis on expediting the development of innovative new therapies across the spectrum of kidney care."

Applications for the first step in this funding, the KidneyX: Redesign Dialysis prize challenge, closed February 28, 2019. The $2.6 million prize competition sought "proposals for solutions or components of solutions that offer patients significant alternatives to dialysis as it is generally practiced today," according to the prize announcement. KidneyX: Redesign Dialysis Phase 1 awardees will be announced by April 30, 2019.

KidneyX Phase 2 will begin April 15, 2019.

"We want to get this roadmap out into schools of engineering and medicine. We want to publish information in different types of journals—nephrology, medicine, engineering—and use social media extensively," Roy-Chaudhury concludes. "We hope that the presence of a roadmap will bring in funding and investment from different sources, both public and private."

Table 1. Examples of requirements and activities from Technology Roadmap

Section on Design Requirements for Ensured Success
Minimum Technical Design Requirements for Blood Filtration
Non-fouling and able to maintain continuous performance (duration defined by product and clinical context)
Generates a filtrate of at least 40 L/day (~30 mL/min for 24-hour therapy)
Size selective, with no loss of essential blood proteins (e.g., albumin)
Component materials and design must be biocompatible and hemocompatible
Section on "Enabling Change Through Focused Research and Design: Kidney Function"
Blood filtration activities
Near-term (2019–2022):
Develop a size-selective blood filter capable of 40 L/day filtrate with minimal or no use of anticoagulants or anti-clotting agents
Mid-term (2023–2025):
Develop a size-selective, non-clotting blood filter (connected to circulation with or without pump) that is capable of 40 L/day filtrate and will freely pass electrolytes and non-protein-bound toxins
Long-term (2026+):
Demonstrate a size-selective, non-clotting filter capable of 40 L/day filtrate with 12–24 months of continuous performance
Section on "Enabling Change Through Focused Research and Design: System Enablers"
Biomaterials Development
Near-term (2019–2022):
Develop a scaffold or membrane device capable of allowing oxygenation and nutrient access for transporting epithelial cells and demonstrate activity ex vivo
Mid-term (2023–2025):
Develop and demonstrate structural support/scaffold that maintains desired function in vivo
Biological and Immunological Modulation
Near-term (2019–2022):
Genetically engineer animal to inactivate viral and pathogenic organisms for xenotransplantation
Mid-term (2023–2025):
Generate suitable transgenic donor animals for xenotransplantation
Long-term (2026+):
Demonstrate long-term graft survival in nephrectomized animals

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FRESENIUS MEDICAL CARE
RENAL TECHNOLOGIES

Kidney News is pleased to present this edition's special section on precision medicine. The ability to derive diagnosis and care, specific to the individual patient and the exact timing and nature of their disease process, is anticipated to result in a huge leap forward in the efficacy and safety of treatment. A *PubMed* search revealed more than 50,000 articles about this topic, including more than 1600 articles when restricted to "kidney," and the rate of new articles is rapidly climbing. It thus seemed appropriate to review this approach with our audience. The first 4 articles were kindly curated and organized by our Europe editor, Professor Gert Mayer, and review new technology and approaches for the utilization of precision medicine in common kidney disease scenarios. The final 2 articles were kindly provided by the authors to round out this month's section and make it more comprehensive, focusing on the efforts of the Kidney Precision Medicine project. We hope you find them of interest.

Richard Lafayette, MD, Editor-in-Chief, Kidney News

PRECISION MEDICINE in Diabetic Kidney Disease

By Paul Perco and Hiddo J. L. Heerspink

Approximately 415 million adults worldwide had diabetes mellitus (DM) in 2015, and even though over 650 billion USD were allocated for treatment, about 5 million individuals died. The impact of DM will continue to grow because the prevalence is expected to increase by more than 50% within the next 30 years (1). The rise in prevalence of diabetes will be accompanied by a significant rise in DM-associated complications such as diabetic kidney disease (DKD) (2).

Two aspects of glomerular function, urinary albumin excretion and estimated GFR (eGFR), are used in clinical practice for defining stages of DKD (microalbuminuria, progressing to macroalbuminuria, followed by a loss of eGFR). This system is, however, sufficient only as long as the pathophysiology of the disease is simple, can be captured by easily accessible specific parameters, and most of all is similar in (at least most) patients. However, the concept of DKD being a "simple and uniform" disease has been challenged for a long time. On the basis of clinical observations, we have to conclude that contrary to our current uniform phenotypical categorization of patients with DKD using eGFR and urinary albumin excretion, the pathophysiology is multifactorial in nature.

Optimal glycemic control and renin-angiotensin-aldosterone system intervention is the cornerstone of treatment for slowing the progression of kidney function decline in patients with type 2 DM. Even though these strategies have contributed to a reduction in the risk for the development of ESRD, a substantial number of patients still continue to progress to ESRD. This can be explained in part by a large interindividual variation in treatment response. This induces uncertainty in optimal treatment selection and interferes with the development of novel drugs.

Identifying specific molecular processes associated with a specific phenotype of DKD and biomarkers associated with these processes based on molecular models of DKD can be used to characterize the progression of patients based on individual pathophysiology and may help to tailor treatment. A better understanding of deregulated DKD mechanisms in disease development and progression is therefore crucial, and the combination of molecular, clinical, and histologic data to decipher DKD pathophysiology and to unravel a drug's mechanism of action at the molecular level might be the way forward to improve DKD therapy (3).

The large fraction of clinical trials in DKD still follow the classical one-size-fits-all approach with assigning a large

Continued on page 12 >

Precision Medicine

Continued from page 11

(heterogeneous) population to either a treatment or a placebo arm. The use of biomarkers to enhance clinical trial design by either enriching the population for high-risk patients or patients who are more likely to respond to the drug under investigation is now quite common in oncology, but only a few trials are available in the field of nephrology. Two example trials in the context of DKD are the PRIORITY (Proteomic prediction and renin angiotensin aldosterone system inhibition prevention of early diabetic nephropathy in type 2 diabetic patients with normoalbuminuria) study and the SONAR (Study of Diabetic Nephropathy with Atrasentan) using biomarkers to enrich for high-risk patients and to identify treatment responders, respectively. The question, however, remains: what to do with patients not responding to the new drug in an enrichment trial?

The way forward might be to investigate multiple therapies in so-called platform trials (Figure 1). A platform trial signifies an experimental platform in which the effects of multiple interventions on one or more conditions can be tested, using modern adaptive designs and statistical approaches, including Bayesian analyses. The advantages of platform trials are 1) the availability of multiple compounds, thereby the ability to successively test patients until they show a biomarker response to a treatment, at which point they would be randomized to that treatment or to placebo plus standard of care; 2) the availability of a common master protocol to streamline clinical trial conduct; and 3) the possibility of optimization of treatment to improve efficacy and lower adverse events based on predictive and monitoring biomarkers (4, 5). Predictive biomarkers for the different treatment options for DKD patients are therefore key elements in the setup of platform trials (6).

The BEAt-DKD project, which receives funding from the European Union within the Innovative Medicines Initiative framework, involves 31 partners from 11 countries. The major aim of this public–private partnership is to improve the prevention and management of DKD by molecular profiling and patient stratification of DKD patients. The first major project results include the validation of prognostic protein DKD biomarkers in the early stages of the disease and the identification of five major subgroups of diabetes that are associated with disease outcome (7, 8). One work package is specifically dedicated to the optimization of clinical trial design in DKD, with BEAt-DKD members actively engaging with representatives of the regulatory agencies in Europe and the United States regarding this issue. Future plans also foresee joining forces with other consortia such as another EU-funded research project entitled Rhapsody (https://imi-rhapsody.eu/) or the Kidney Precision Medicine Project (KPMP) (https://kpmp.org/) in the United States to further increase the chances of success in enhancing the treatment options for DKD patients.

The identification of predictive and monitoring biomarkers for the DKD treatment regimens listed in Table 1 is one of the major research areas of the BEAt-DKD (Biomarker Enterprise to Attack Diabetic Kidney Disease) (https://www.beat-dkd.eu/) project.

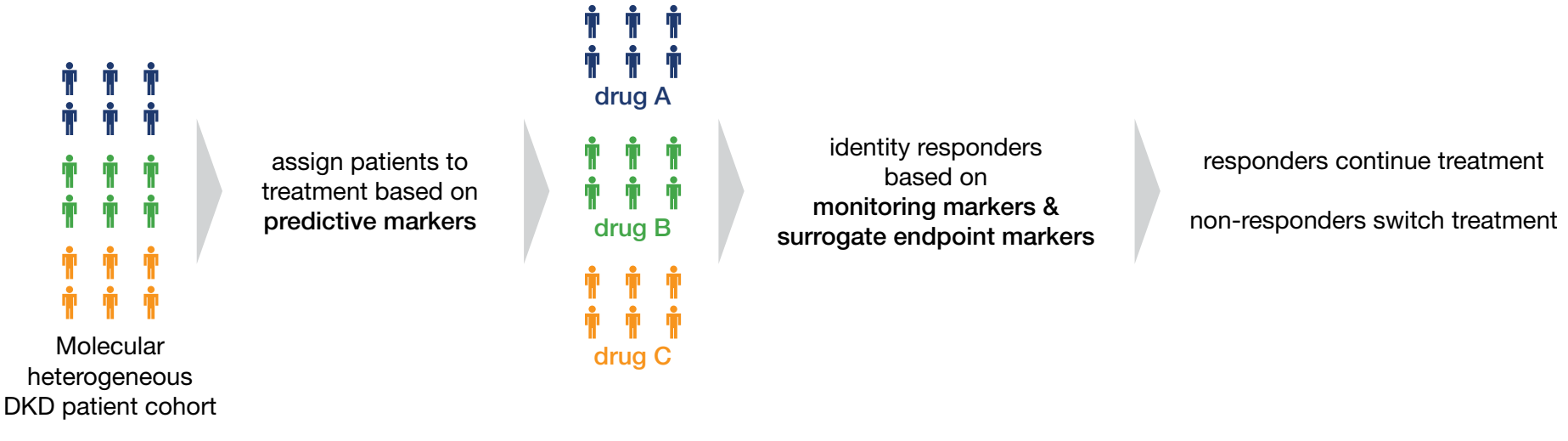
Paul Perco, PhD, is associated with the Medical University, Innsbruck, Austria. Hiddo J. L. Heerspink, PhD, is associated with the University Medical Center, Groningen, Austria.

Table 1. Drug classes and compounds investigated within the BEAt-DKD project

Drug class	Compound
Angiotensin converting enzyme inhibitors	Lisinopril
Angiotensin II receptor blockers	Losartan
Dipeptidyl peptidase-4 inhibitors	Linagliptin
Endothelin receptor antagonists	Atrasentan
SGLT2 inhibitors	Canagliflozin, dapagliflozin
Statins	Atorvastatin, rosuvastatin

Abbreviation: DKD, diabetic kidney disease. BEAt-DKD, Biomarker Enterprise to Attack Diabetic Kidney Disease; SGLT2, sodium/glucose cotransporter 2.

Figure 1. Simplified design of a platform trial. One of the possibilities of a platform is to use biomarkers to stratify a large heterogeneous cohort of DKD patients to the most promising treatment options



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Identifying Patients at High Risk for Short-Term Chronic Kidney Disease Progression: Still a Challenge?

By Danilo Fliser

The number of patients with chronic kidney disease (CKD) increases steadily. However, the individual course of kidney disease may be variable, and accurate identification of patients who will definitely experience progression is challenging (1).

Established biomarkers for prediction of CKD progression are estimated GFR (eGFR) and albuminuria. In the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, patients with CKD of different causes are categorized as having a low, moderate, high, or very high risk for kidney disease progression, according to their (baseline) eGFR and albuminuria (2). Nevertheless, in 1.7 million participants from 35 cohorts with 12,344 ESRD events, CKD progression was highly variable even in patients within the same KDIGO risk category (3). Therefore, the use of kidney failure risk equations for prediction of eGFR loss during long-term follow-up was recently proposed, because these equations include additional clinical and biochemical variables besides eGFR and albuminuria (4). Whereas refining these equations with the inclusion of even more putative progression factors can improve their accuracy, the individual CKD course is variable and difficult to predict by general equations, particularly under disease-modifying interventions. In addition, recent studies revealed that (e.g., in many patients with diabetes) advanced CKD (i.e., eGFR <60 mL/min per 1.73 m^2) may be present even in the absence of higher-grade albuminuria (5). Therefore, biomarkers that indicate (short-term) eGFR loss are desirable.

Recently, Dickkopf-3 (DKK3) has been identified as a stress-induced, renal tubular epithelia-derived, secreted glycoprotein that induces tubulointerstitial fibrosis in experimental animals through its action on the canonical Wnt/β-catenin signaling pathway (6). Genetic and antibody-mediated abrogation of DKK3 led to significantly decreased interstitial matrix accumulation, reduced tubular atrophy, and hence preserved kidney function in various mouse models of CKD. Notably, the profibrotic effects of DKK3 in the kidney were independent of the cause of initial damage. Mechanistically, DKK3 deficiency caused diminished canonical Wnt/β-catenin signaling in tubular epithelial cells, which was accompanied by an antifibrogenic inflammatory response within the injured kidney, highlighting the crucial role of the Wnt/β-catenin pathway in renal tubulointerstitial injury.

Importantly, DKK3 is embryonically expressed and is detectable in urine after birth only under tubular stress conditions. It may then serve as a noninvasive diagnostic tool for ongoing kidney injury and (short-term) eGFR loss. This was tested by Zewinger et al. (7) in 575 patients with CKD of various causes from the CARE FOR HOMe study, in which eGFR and urinary DKK3 levels were assessed in one-year blocks at regular follow-up visits (in total, 2035 patient years were available for analysis).

After complete adjustment for all potential progression confounders such as age, gender, blood pressure, smoking, diabetes, eGFR, and albuminuria, urinary DKK3 remained a significant and independent indicator of eGFR decline within the following 12-month period. Moreover, urinary DKK3 significantly improved prediction of kidney function loss in comparison with eGFR or albuminuria alone—a finding that underlines the independent role of urinary DKK3 as a significant marker for CKD progression. In this respect, urinary DKK3/creatinine above 4000 pg/mg was independently associated with a mean annual decline in eGFR of 7.6% (95% confidence interval −10.9 to −4.2%; p <0.001).

The results of the CARE FOR HOMe study were further validated in patients with IgA nephropathy (IgAN) from the randomized STOP-IgAN trial (8). In this multicenter randomized controlled trial, patients with active biopsy-proven IgAN entered a 6-month run-in phase, in which supportive care therapy (e.g., strict blood pressure control including blockade of the renin-angiotensin system) was optimized.

Patients who had persistent proteinuria of at least 0.75 g per day were randomly assigned to receive either supportive care alone or supportive care plus immunosuppressive therapy. Urinary DKK3 was measured in all available urine samples from participants in the 6-month run-in phase and the 6-month early randomized treatment phase (7). During the run-in phase, urinary DKK3 above median was associated with a mean eGFR decline of 19.1% (95% confidence interval −24.2 to −14.0%; p <0.001 vs. reference) after adjustment for all potential confounders.

Also, in participants of the STOP-IgAN trial, the addition of DKK3 to a model comprising eGFR and albuminuria significantly increased its predictive power for short-term eGFR loss (7). During the early treatment phase, a rise in urinary DKK3/creatinine concentrations was associated with a significant decline of eGFR, whereas stable or decreasing urinary DKK3/creatinine levels indicated a more favorable course of kidney function (Figure 1). Changes in urinary DKK3 were independently associated with changes in eGFR even after adjustment for albuminuria or randomization to the treatment arms. The former finding is of particular interest, inasmuch as the development of albuminuria—a putative indicator of glomerular damage—and increased tubular secretion of DKK3 in the urine may not be related to the same pathophysiologic mechanism. This is corroborated by the CARE FOR HOMe study results, in which increased urinary DKK3 indicated significant loss of kidney function even in the absence of albuminuria. Therefore, it might be inferred that persistently elevated urinary DKK3 levels indicate ongoing tubular "stress" and lead to progressive tubulointerstitial fibrosis independent of eGFR and albuminuria and of the type of kidney disease.

As discussed above, the high individual variability of CKD progression could be well observed in the early treatment phase of the STOP-IgAN trial. Here, a carefully selected cohort of patients with active disease experienced an unpredictable course of kidney function within 6 months. Nevertheless, changes in urinary DKK3/creatinine concentrations helped to identify those patients with fast eGFR decline during this period.

Based on these observations, urinary DKK3 not only may represent a biomarker for short-term eGFR loss but may be involved in its pathogenesis, as indicated by experimental studies. Measurement of DKK3 in urine therefore represents a novel tool for the identification of patients at high risk for short-term eGFR loss, regardless of the cause of kidney injury and beyond currently established biomarkers. In this respect, monitoring of DKK3 excretion in the urine may improve the treatment of patients with CKD as a personalized medicine approach, because urinary DKK3/creatinine levels could be used as a tool to supervise and, if necessary, also intensify therapeutic intervention to halt CKD progression.

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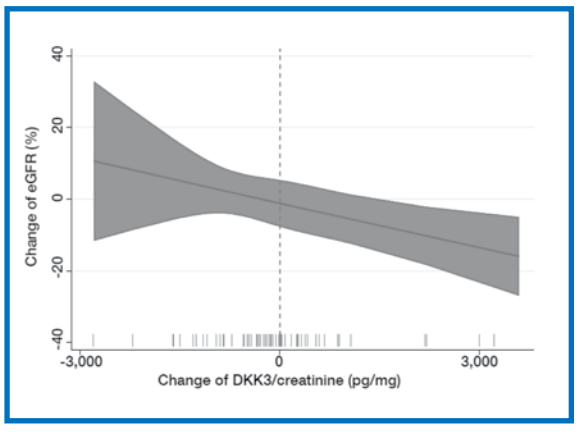
Figure 1. Restricted cubic spline plot of the association between change in eGFR and urinary concentrations of Dickkopf-3 (DKK) and creatinine during the early treatment phase in participants of the STOP-IgAN trial



Adjustments were made for age, gender, body mass index, systolic blood pressure, smoking status, eGFR, and log albuminuria. Blue spikes indicate individual changes of urinary DKK/creatinine concentrations. Note that rising urinary DKK/creatinine concentrations (values >0) are associated with loss of kidney function, whereas declining urinary DKK/creatinine concentrations (values <0) are associated with stable or even improving kidney function within the 6-month early treatment period.

IgA Nephropathy

By Jürgen Floege

IgA nephropathy (IgAN) is a disease with a highly diverse course, and, as such, by definition has always required a personalized or stratified approach (call it "precision" if you like the term).

At one end of the extreme are patients with isolated hematuria, little to no proteinuria, and normal GFR and blood pressure, who have been considered to have "benign IgAN" in the past. Here, recent Swedish data with 20 to 25 years of follow-up show that about a third of these patients will experience spontaneous remission, another third to one-half have persistent urinary abnormalities but preserved GFR, and a quarter will experience chronic kidney disease (CKD) with 5% in CKD stages 4 to 5 (1). The bad news is that these 5% cannot be identified prospectively; thus, prolonged follow-up of such early IgAN patients is necessary.

At the other end of the extreme are the very rare patients with a vasculitic course of IgAN, who have a dismal renal prognosis with and without immunosuppression (2). These patients should not be confused with the IgAN patient with few crescents in the biopsy specimen but a stable GFR. Although large recent studies identify crescents as an adverse prognostic sign (3), it is important to realize that crescents can also occur in the "benign IgAN" group described above (4). Thus, crescents do not equal rapidly progressive glomerulonephritis in IgAN, they do not necessarily require immunosuppression, and many individuals will likely resolve with adequate supportive therapy, in particular, blood pressure reduction. In such patients, the clinical course rather than the biopsy should be the main criterion in designing rational therapeutic approaches.

The typical IgAN patient coming to the attention of a nephrologist is in the middle of the above extremes, i.e., has some proteinuria (usually non-nephrotic), microhematuria, and hypertension, and often has already lost a significant amount of GFR. In these patients, a comprehensive supportive approach—not just "give an ACE inhibitor"—can markedly slow down progression of the disease, and such patients derive no added benefit from immunosuppressive therapy but rather just experience more adverse events (5).

In Asian patients with a high average proteinuria (2.4 g/day) and a baseline GFR around 60 mL/min/1.73 m^2, systemic high-dose corticosteroid therapy slowed down progressive GFR loss, but that recent trial had to be terminated early because of an excess of adverse, sometimes lethal, events (6). A follow-up study (TESTING 2) with a lower corticosteroid dose has started. An emerging alternative option is intestinal steroid therapy using enteric-coated budesonide (7). The rationale of this therapy is based on some evidence for a disturbed intestinal mucosal barrier in IgAN. A phase III trial with that compound has recently started. Other immunosuppressive agents, including rituximab, mycophenolate mofetil, azathioprine, cyclophosphamide, and some newer agents so far have not yielded consistent therapeutic benefit. Whether ethnicity should affect the choice of immunosuppression is not known.

Our stratified approach to the therapy of IgAN is shown in Figure 1. Currently, the 2012 KDIGO guidelines on the treatment of glomerular disease are being updated; publication can be expected in mid-2019.

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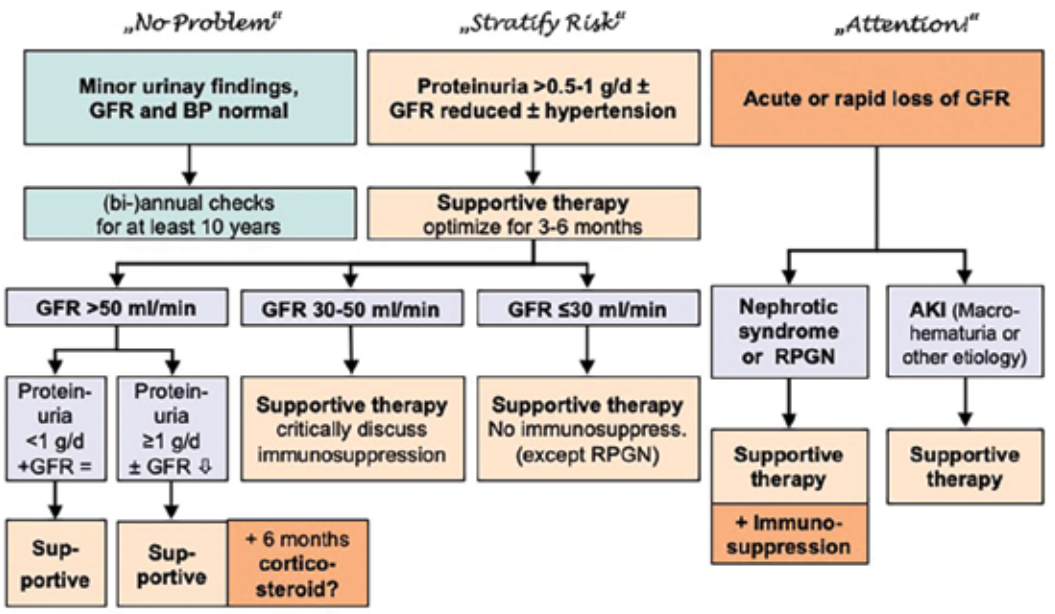
Figure 1. Synopsis of suggested therapeutic approaches to patients with IgAN depending on clinical setting



Modified with permission from Floege and Eitner (8).

PERSONALIZED RENAL TRANSPLANTATION: A View from the EU 28+ Countries

By Roman Reindl-Schwaighofer, Andreas Heinzel, and Rainer Oberbauer

Kidney transplantation is the prototypical example of the routine practice of personalized/individualized therapy. To optimize individual outcomes, donors and recipients are matched on the basis of their HLA genotypes, and histocompatibility is further tested in vitro. The mandatory medical immunosuppression therapy is adjusted based on the results of these tests and the clinical course.

Because full HLA matching occurs only in homozygous twins, and recognizable antigens differ between HLA type mismatches, in silico tools for epitope matching such as the PIRCHE score or the HLAMatchmaker may facilitate a refined risk stratification of the alloresponse (1).

In addition, optimal HLA matching is rarely achieved because other important factors need to be considered in allocation algorithms. For example, in deceased donor transplantation, most patients die with a functioning graft; therefore, some countries such as the United States and Australia have changed their allocation procedures to match the donor organ quality with the expected recipient survival to avoid futility.

Because individual prediction of posttransplantation survival is imprecise, a different allocation strategy exists in most European transplant networks. Of note, several different transplant networks with different allocation algorithms exist in the Europe 28+ region, and the rate of live donor transplantation ranges from more than 90% (Turkey, Iceland) to less than 10% (Croatia, Italy). Therefore, no general comparison is possible. For example, in Eurotransplant, covering eight countries, regular allocation following special programs assigns each single HLA class I (A, B) and class II (DR) match equal "bonus points" equivalent to 2 years of active waitlisting.

A solution to optimize HLA matching also in live donor transplantation would be to include not only HLA or AB0 incompatible pairs into an organ exchange network but also poorly matched younger potential live donor recipients with a likely need for a retransplant after some years.

Since the emergence of a calcineurin inhibitor (CNI)-based immunosuppressive triple regimen as the standard, and owing to disappointing results from interventional studies on humoral alloimmunity, new individualized approaches are needed to further improve outcomes.

New approaches and outlook

Evidence is emerging that non-HLA alloimmunity also plays an important role in long-term graft attrition, and this may explain some of the chronic humoral alloimmune processes in the absence of anti-HLA donor-specific antibodies.

Opelz et al. (2) found in their analysis of over 3000 HLA identical sibling transplants a graded risk of graft loss depending on the degree of overall sensitization against a test panel of healthy volunteers (of note, HLA–DP mismatch was not determined in that study). In addition, it is clinically well known that in patients with Alport syndrome, anticollagen antibodies may develop after transplantation, and few of these patients experience premature graft loss.

Besides the known genetic variability of individuals by roughly 10 million single nucleotide polymorphisms, MacArthur et al. (3) were among the first to show that each individual human has roughly 10 to 20 full loss-of-function mutations. Together with differences of nonsynonymous single nucleotide polymorphisms in the genome, these may contribute to indirect allorecognition (Figure 1).

These examples support the hypothesis that non-HLA alloimmunity has a clinical consequence. The iGeneTrain consortium (4) seeks to elucidate some of these enigmas, and recently Reindl-Schwaighofer et al. (5) showed that in fact non-HLA incompatibilities on a genomewide level contribute to graft loss. This association was observed to be independent of HLA matching and other known risk factors for graft loss. Given the many genomewide individual donor-to-recipient mismatches, it is likely that matching will not be an option, at least in the setting of deceased donor transplantation. Live donors, however, may be included into a paired exchange program if stratification based on genotyping yields many incompatibilities with the recipient and thus a higher risk of graft loss. Certainly, these results and strategies need to be validated and potentially implemented by others.

Another fascinating approach to track the alloimmune response individually became available with the new sequencing technologies. Next-generation sequencing of the highly diverse T cell receptor repertoire allows for tracking of individual alloreactive T cells. Recently an analysis on that topic was published by DeWolf et al. (6). If one may speculate further, it may potentially be possible to determine the epitope's amino acid by the T cell receptor genetic sequence, as has been shown by Dash et al. (7) and Reindl-Schwaighofer et al. (8) in a selected group of infections.

These great areas of scientific progress may allow the transplantation physician in the future to individualize immunosuppressive therapy, not only through level monitoring but also according to sequentially measured alloresponse readouts.

Thus, research into HLA alloimmunity has led to great clinical progress and the development of solid-phase technologies that are now standard in all transplantation centers. Maybe we need to redo this research, also taking non-HLA effects into account. It is exciting to have technologies available that allow further improvement of kidney transplantation research and also ultimately provide better and individual treatment for our patients.

Roman Reindl-Schwaighofer, Andreas Heinzel, and Rainer Oberbauer are associated with the Medical University of Vienna, Austria.

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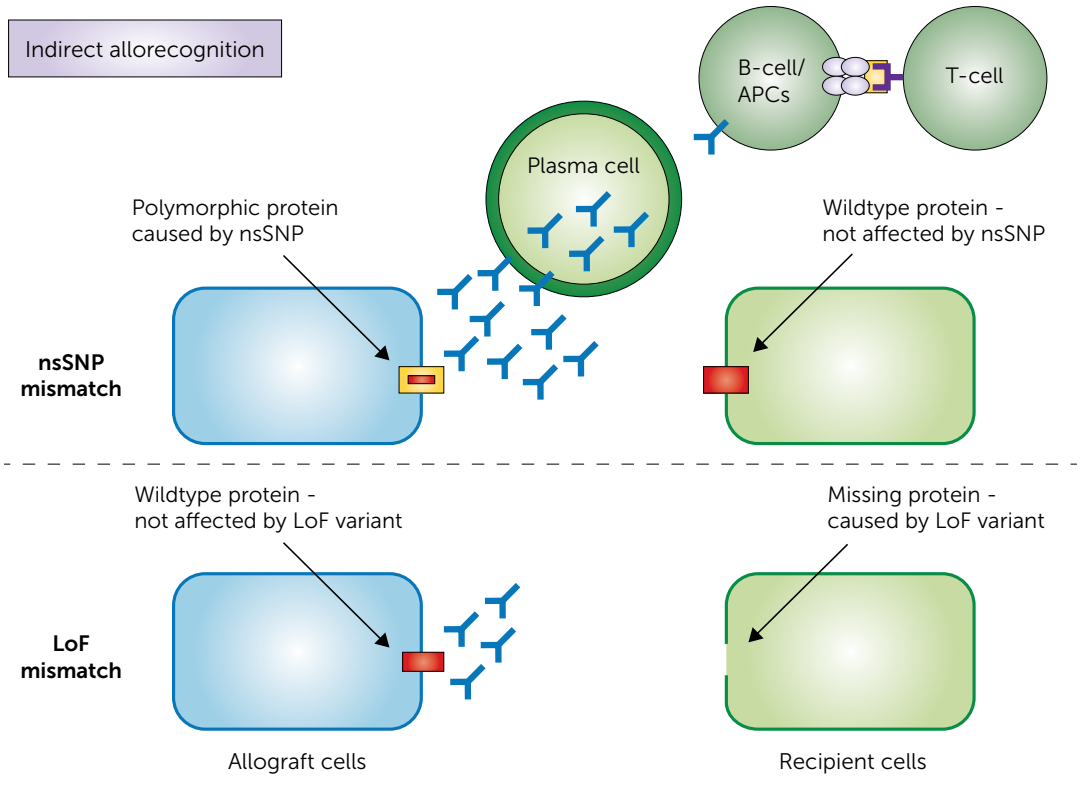
Figure 1. Concept of indirect allorecognition of polymorphic proteins (nonsynonymous SNPs, upper panel) and "loss of function" (homozygous knockout) variant mismatches (lower panel) between donors and recipients



SNP = single nucleotide polymorphism; LoF = loss of function. Reprinted with permission from Reindl-Schwaighofer R, et al. (9).

Kidney Precision Medicine Project: **Hope for the Future**

By Jonathan Himmelfarb

Jonathan Himmelfarb

The Kidney Precision Medicine Project (KPMP) is a transformative initiative funded by the National Institute of Diabetes and Digestive and Kidney Diseases. It is designed to tackle the major public health burdens resulting from acute kidney injury (AKI) and chronic kidney disease (CKD). The rationale for KPMP is straightforward: Despite the significant impact of AKI and CKD on patient outcomes, no proven safe and effective therapies exist for AKI, and only a few are available for CKD.

The landscape of treatment for these kidney disease syndromes has not changed substantially in many years, and we have a poor understanding of AKI and CKD heterogeneity between individuals. Thus, at present we are not close to the precision medicine goal of finding the right treatment at the right time for the right patient with CKD and AKI.

The KPMP is focused on finding new ways to treat AKI and CKD by safely and ethically obtaining and evaluating human kidney biopsy specimens from individuals who volunteer to participate. The kidney tissue will be analyzed in multiple ways, including intensive cutting-edge molecular analysis and the innovative use of digital histopathologic analysis coupled with machine-learning tools. This kidney tissue will be used to create a human kidney tissue atlas in health and disease as a publicly available resource for patients, caregivers, and researchers.

The KPMP focuses on people who have very common types of kidney disease for which we don't really know the best treatment. With this focus, we can have the most impact in improving the outcomes for people everywhere living with kidney diseases. If we are successful, the KPMP will allow the entire kidney community to discover critical cells, pathways, and targets for novel therapies and to eventually devise individualized treatments based on these new insights. This is the essence of what kidney precision medicine is all about: bringing the right treatments at the right dose at the right time to the right patient with kidney disease.

There are several unique and exciting components to KPMP. One of the most important aspects of this project is that we've put patients at the forefront of our study. Patients are involved in all aspects of the study as equitable partners in KPMP. For example, our Community Engagement Committee is primarily made up of kidney disease patients who have helped develop our approach to informed consent and have provided multiple recommendations during protocol development. In addition to broad patient involvement, KPMP has a large and diverse group of stakeholders, each dedicated to the long-term success of the project. Also, KPMP is committed to fostering the development of junior investigator careers, including providing funding and travel awards for early-career investigators to attend our face-to-face meetings. We hope that KPMP contributes to fostering the next generation by strengthening the pipeline of researchers, clinicians, and educators.

On a personal level, it is both humbling and inspiring to be able to serve as part of the leadership for this historic project. For my entire professional life, I've taken care of patients with varying stages and types of kidney disease and have wished for more and better treatment options. I am hopeful that at the end of the day, this project will help us fully understand our patients' medical conditions in ways that we often do not understand now, and completely change the way we care for our patients for the better.

Jonathan Himmelfarb, MD, is professor of medicine at the University of Washington, director of the Kidney Research Institute, and co-director of the Center for Dialysis Innovation. He is co-principal investigator for the Central Hub of the Kidney Precision Medicine Project.

Perspectives from a Junior Investigator in the Kidney Precision Medicine Project

By Laura H. Mariani

Laura H. Mariani

"The future belongs to those who believe in the beauty of their dreams."

— Eleanor Roosevelt

Working with the Kidney Precision Medicine Project (KPMP) consortium as a junior investigator is a tremendous opportunity for me, with tangible training experiences and many more intangible moments for professional growth and creativity.

Certainly, the tangible training experiences are exceptional, and the KPMP consortium has not only allowed, but encouraged, contributions from junior investigators, allowing us to learn best by doing. In particular, each research team from a recruitment site interpreted the request for application independently and proposed an approach relevant to their own institutions to recruit patients with either chronic kidney disease or acute kidney injury for a kidney biopsy to be used for research. But as the recruitment sites were assembled and became a single KPMP research team, the protocols were harmonized and transformed to a shared approach, accommodating differences in institutions and patient populations along with the needs of the tissue interrogation sites.

I learned the true value of multidisciplinary perspectives to accomplish this task and other tasks of a large consortium. The products are made infinitely better by the inclusion of perspectives from patients, clinicians, study coordinators, clinician and basic scientists, programmers, biostatisticians, ethicists, and, perhaps most important, project managers to keep everyone on task.

And then, to be able to participate in translating a protocol into the nuts-and-bolts tools necessary to launch a multisite study is the sort of invaluable training experience provided to KPMP junior investigators. There is no better way to really understand a study than to help write the manual of procedures, draft questions on case report forms, sit with a programmer building

the data collection system, or train a study coordinator. This process of iterative improvement, listening to unique perspectives, and creativity to address barriers and compromise applies to scientific tasks well beyond protocol development to study execution, data generation, interpretation, and communication.

These tangible training experiences occur simultaneously with the intangible experiences. Principally, the consortium expands the pool of mentors and collaborators just by the number and diversity of the KPMP scientific team.

KPMP supports a travel award program for trainees and junior faculty to attend the in-person investigators' meetings and bring their work to a poster session. As junior investigators, we often work on projects in very small groups at our home institutions. To be able to discuss not only individual projects but also ideas, hypotheses, data sources, and approaches with investigators beyond our home institutions is instrumental in expanding our scientific training and resources. This exchange happens at the poster sessions and also in the main meeting and during working group calls in between. To listen to scientists with different approaches and training share data and ideas, but also, and perhaps more valuably, critiques, limitations, and suggested alternatives truly broadens my tools and scientific knowledge. Not unlike pursuing clinical training in more than one institution wherein you learn that there are multiple ways to practice high-quality clinical medicine, KPMP fosters a community of mentors and trainees who teach one another the value and limitations of a much-expanded number of approaches.

The fundamental overarching benefit of being a junior investigator in KPMP is the pursuit of a beautiful dream: to leverage the explosion of high-dimensional data generation, tissue image analysis, machine learning, and bioinformatics analyses to answer fundamental questions about some of the most common kidney conditions: diabetic and hypertensive CKD and AKI. Not only do we describe these conditions and their presentations but we build a resource based on human tissue, which can be used by the entire nephrology community to transform our clinical practice and allow us to answer the most basic questions asked by our patients: 1) What disease do I have? 2) What will happen to me? And 3) What can you do about it?

The KPMP embraces this goal by committing to truly open science by building the kidney tissue atlas, which will make the data, so generously provided by participants, readily available and accessible to researchers outside of KPMP and also to patients and clinicians to tackle these fundamental questions.

When I read the personal statements of nephrology fellowship applicants, I am reminded of the enthusiasm that nephrology can inspire as applicants describe their satisfaction in grasping renal physiology, the devastation at watching kidney failure in their patients, and their awe of the importance of the healthy kidney to other organ systems. KPMP captures that enthusiasm by bringing together investigators who want to tackle big questions by working collaboratively and openly. That enthusiasm is infectious.

It is easy to believe in the big dream that the conversations I have with my patients now will be vastly different in the future as we discuss the best medication, out of many choices, to protect their kidneys from injury, speed recovery, and prevent progression to kidney failure. ■

Laura H. Mariani, MD, is an assistant professor of medicine at the University of Michigan, Ann Arbor, Michigan.

Policy Update

Trend of Falling Applications Resulting in Decrease of KUH Funding Must Be Reversed

By Ryan Murray

After a sustained effort in support of National Institutes of Health (NIH) funding by the American Society of Nephrology (ASN) and the broader kidney community, Congress passed a $2 billion funding increase for NIH for fiscal year (FY) 2019. Additionally, the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) received a 5% increase that was widely celebrated by the kidney community.

Unfortunately, the gains seen by NIH and NIDDK have not translated into funding for the Division of Kidney, Urologic, & Hematologic Diseases (KUH), which saw a 2% decrease in total funding. NIDDK is a payline-driven funding program that "follows the science," meaning that Divisions that receive more applications receive more funding and are, therefore, able to provide more awards. So, while NIDDK has continued to see its budget increase due to congressional appropriations, the allocations to KUH have lagged when compared to other NIDDK Divisions.

A central portion of the NIDDK portfolio are R01s, which contributed to 93% of the NIDDK increase in total awarded dollars from 2017 to 2018. Despite its significance to the overall NIDDK portfolio, KUH has seen a slow erosion of its R01s over the years and experienced an 8.7% decrease in R01 applications from 2018 to 2019. More troubling is that this trend will continue to grow unless there is a significant increase of early stage investigators (ESI) applying for funding; however, KUH saw ESI applications fall a staggering 27% in only one year—2018 to 2019.

Compounding the problem is the fact that the kidney community is losing the battle on two fronts. Not only are the total number of KUH applications stagnant compared to the rest of NIDDK, but the applications are historically awarded less funding. The average total cost of NIDDK competing R01 awards in 2018 was $484,019, while the average in KUH was $461,000. ASN leadership strongly encourages every investigator applying for funding to explicitly ask for what their study needs and to justify those numbers.

"Kidney patients are desperately waiting in our dialysis clinics, hospitals, and offices for new therapies. It is solely up to us now, as a community, to generate hope that reaches from patients and their families to potential future nephrologists by prioritizing existing and emerging programs that bolster cutting-edge investigative activities and attract the best minds to the nephrology specialty. ASN has initiated several programs with this goal in mind and will continue to identify new opportunities with the goal of stemming this tide," Crystal A. Gadegbeku, MD, FASN, ASN Policy and Advocacy Committee Chair, said in a recent statement.

ASN has launched several initiatives to foster interest in careers in nephrology and research and to advance the careers of those who have already entered the nephrology workforce including:

- **Kidney STARS** (Students and Residents) provides complementary membership to the society, $1000 in travel support, and complementary registration to attend the ASN Annual Meeting at Kidney Week, in Washington, DC, and tailored events and networking opportunities onsite.
- **Kidney TREKS (Tutored Research and Education for Kidney Scholars)** seeks to accomplish the same goal through a weeklong research course retreat and long-term mentorship program.
- **KidneyX**, a new public-private partnership between ASN and the U.S. Department of Health and Human Services (HHS), aims to accelerate breakthroughs to promising new technologies for people with kidney diseases and tangentially spur interest in nephrology by positioning it as an exciting and growing field.
- **ASN Foundation for Kidney Research Career Development Grants Program** provides funding for young faculty to foster evolution to an independent research career and a successful application for a National Institutes of Health (NIH) full R01 grant or equivalent. By the end of the grant period, a recipient will have an independent research career and be competitive for federal and nonfederal funding.

Similarly, NIDDK has several programs geared toward fostering the next generation of kidney investigators with the goal of ensuring they become an independent researcher:

- **NIH Summer Internship Program in Biomedical Research (SIP)** provides a developmental training experience to promising high school, undergraduate, and graduate students who have expressed a strong interest in or are studying disciplines related to biomedical sciences.
- **Postbaccalaureate Intramural Research Training** program provides recent college graduates who are planning to apply to graduate or professional school an opportunity to spend one or two years performing full-time research at the NIH.
- **Undergraduate Scholarship Program** offers competitive scholarships to students from disadvantaged backgrounds who are committed to careers in biomedical, behavioral, and social science health-related research. The program offers paid research training at the NIH during the summer and paid employment and training at the NIH after graduation.
- **Predoctoral to Postdoctoral Fellow Transition Award** seeks to recruit exceptional graduate students who are recognized by their institutions for their high potential and to incentivize them to pursue a Kidney, Urologic or Hematologic postdoctoral position.

ASN encourages its members to share both its and NIDDK's unique opportunities with potential researchers who are interested and eligible. The society will continue to advocate for increases to the NIH and NIDDK budgets. By being united and fighting this battle on multiple fronts, we can make certain that any budget increase NIDDK receives from congressional appropriations is reflected in a proportional increase to KUH. ASN will keep readers apprised of future developments. ■

Findings

High-Dose Iron Lowers Mortality in Dialysis Patients

Proactive, high-dose intravenous iron reduces mortality and major cardiovascular events in hemodialysis patients, reports a randomized trial in *The New England Journal of Medicine*.

The Proactive IV Iron Therapy in Dialysis Patients (PIVOTAL) trial included 2141 adults undergoing maintenance hemodialysis and receiving an erythropoiesis-stimulating agent (ESA) at 50 UK sites. One group was assigned to a proactive high-dose iron strategy: iron sucrose 400 mg IV administered monthly, unless ferritin concentration was greater than 700 µg/L or transferrin saturation was 40% or higher. The other group received a low-dose reactive iron strategy: IV iron sucrose in doses of 0 to 400 mg monthly, triggered by ferritin concentration less than 200 µg/L or transferrin saturation less than 20%.

The main outcome of interest was a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed as time to first event. The same outcomes were evaluated as recurrent events. Secondary outcomes included death, infections, and ESA dose.

At a median 2.1 years' follow-up, median monthly iron dose was 264 mg with the proactive high-dose IV iron strategy compared to 145 mg with the reactive low-dose strategy. Median monthly ESA doses were 29,757 versus 38,805 IU, respectively, for a difference of -7539 IU.

A primary endpoint event occurred in 29.3% of patients in the high-dose group versus 32.3% in the low-dose group, with statistically significant hazard ratios for both noninferiority and superiority. The high-dose strategy was also superior on a composite secondary endpoint of fatal or nonfatal myocardial infarction: hazard ratio 0.69. There were 429 recurrent events in the high-dose group versus 507 in the low-dose group: rate ratio 0.77. Infection and hospitalization rates were similar between groups.

Intravenous iron is a standard part of care for maintenance hemodialysis patients. Large doses of iron are increasingly used to lower required doses of ESAs. With a lack of comparative studies, the use of high-dose iron varies widely.

In the PIVOTAL trial, a proactive, high-dose IV iron strategy is superior to a reactive, low-dose strategy. The high-dose strategy reduces the risk of death or major adverse cardiovascular events, as well as ESA dose. The results reflect a correction since the findings were presented at ASN Kidney Week 2018, with improvement in outcomes related to adjudicated myocardial infarction, nonfatal stroke, or hospitalization for heart failure [Macdougall IC, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019; 380:447–458].

Obesity-Related Factors Affect RCC Risk

Obesity and related health risks, including diastolic blood pressure and fasting insulin level, are confirmed as risk factors for renal cell carcinoma (RCC), according to a study in the open-access journal *PLoS Medicine*.

Using a Mendelian randomization framework, the researchers analyzed gene variants associated with 13 obesity-related factors, identified from large-scale genome-wide association studies. The variants were used as proxies for measures of obesity, blood pressure, lipids, type 2 diabetes, insulin, and glucose. These factors were analyzed for association with the development of RCC in 10,784 cases and 20,406 controls. For each risk factor, odds ratios (ORs) for a 1-standard deviation increase in RCC risk were calculated.

Three measures of obesity were associated with RCC risk: body mass index, OR 1.56; waist-to-hip ratio, OR 1.63; and body fat percentage, OR 1.66. Significant associations were also found for diastolic blood pressure, OR 1.28, and fasting insulin, OR 1.82. Risk of RCC was unrelated to systolic blood pressure, lipid levels, overall type 2

diabetes, or fasting glucose. There was a "nominal" positive association for variants related to insulin resistance, rather than beta-cell dysfunction.

Observational studies have identified obesity-related factors associated with increased risk of RCC. However, these studies can't show which obesity-related risks are directly related to the risk of developing RCC.

The Mendelian randomization study provides "robust and confirmatory evidence" that obesity is a risk factor for RCC. Diastolic (but not systolic) blood pressure and fasting insulin are also associated with RCC risk. The researchers conclude: "This study provided some novel insights into the pathways involved in mediating the risk increase in RCC that is caused by obesity, most notably through insulin and DBP, but further research is needed to fully elucidate the important relationship between obesity and RCC" [Johansson M, et al. The influence of obesity-related factors in the etiology of renal cell carcinoma—A mendelian randomization study. *PLoS Med* 16: e1002724. https://doi.org/10.1371/journal.pmed.1002724].

Nearly Half of Americans Affected by CVD

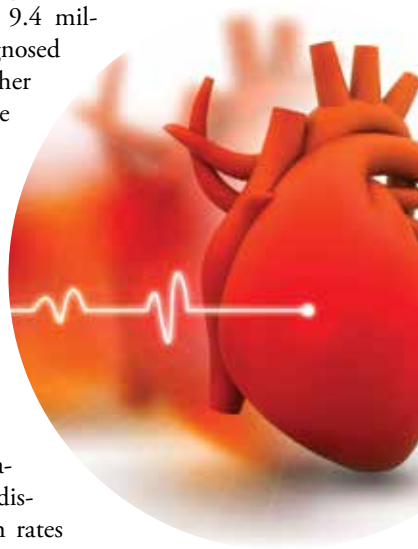
Forty-eight percent of US adults have some type of cardiovascular disease (CVD), according to the American Heart Association's 2019 Statistical Update, published in *Circulation*.

Incorporating data from a wide range of sources, the annual report provides a comprehensive overview of the impact of heart disease, stroke, and cardiovascular risk factors, nationally and globally. Based on NHANES data from 2013 to 2016, the US prevalence of CVD in US adults—including coronary heart disease, heart failure, stroke, and hypertension—is estimated at 48.0% overall, with 121.5 million Americans affected in 2016.

The 48% figure represents an increase over past years, mainly reflecting a change in the American Heart Association/American College of Cardiology definition of hypertension: 130/80 mm Hg, compared to the previous definition of 140/90 mm Hg. Excluding hypertension, the estimated prevalence of CVD is 9.0%.

The data also show an increase in US CVD deaths: from 836,546 in 2015 to 840,678 in 2016. The rise in CVD mortality comes after decades of steady declines, which continue to be reflected in the worldwide figures: from 17.9 million in 2015 to 17.6 million in 2016. There are encouraging trends in some key CVD risk factors, especially decreases in smoking and physical inactivity.

Based on NHANES 2013–2016 data, 26 million adults have diagnosed diabetes mellitus, while 9.4 million have undiagnosed diabetes and another 91.8 million have prediabetes. United States Renal Data System data suggest that 14.8% of adults have chronic kidney disease, rising to 32.6% for those aged 60 years or older. The report notes that patients with kidney disease have very high rates of comorbid CVD, including nearly two-thirds (65.8%) in patients aged 66 or older. Both all-cause and CVD mortality increase steadily with declining kidney function and rising albumin-to-creatinine ratio.



The full report includes a wealth of data on the rates and impact of CVD, with an expanded focus on the global burden of CVD. The Annual Statistical Report is an important part of understanding the "challenges and opportunities" for reducing the burden of heart disease and stroke, according to an online commentary by Mariell Jessup, MD, Chief Science and Medical Officer, American Heart Association.

The data "hold us accountable and help us chart our progress and determine if and how we need to adjust our efforts," Jessup writes. "By quantifying the impact of our collective work, we learn how to better invest our resources as we pursue longer, healthier lives for all" [Benjamin EJ, et al., on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation* 2019;139:e1–e473].

PATIENT-REPORTED **OUTCOMES**

Patient-reported outcomes (PROs), or measures elicited directly from patients, can provide insights into patients' well-being that cannot be captured by laboratory values. PROs, which can include measures of physical symptoms, emotional health, and treatment preferences, have been shown to enhance shared decision-making between physicians and patients, enhance workflow efficiency when used regularly, and allow for more nuanced predictions of disease trajectory (1–3). The US Food and Drug Administration and the Standard Protocol Items: Recommendations for Interventional Trials PRO extension have each emphasized the need to include PROs as clinical trial endpoints, and kidney patients have prioritized that PROs be included in their overall treatment plans (4–6). As a result, PROs have continued to gain attention and interest in the nephrology community.

In this piece, Devika Nair, MD, a postdoctoral clinical research fellow in nephrology at Vanderbilt University, whose own research interests involve PROs, interviews Debbie Gibson, MD, professor of medicine in pediatric nephrology, and Noelle Carlozzi, PhD, associate professor of medicine in physical medicine and rehabilitation, both at the University of Michigan's Institute for Healthcare Policy and Innovation. She also interviews Derek Forfang, a kidney transplant patient and passionate patient advocate, who is a member of the National Kidney Foundation's Kidney Advocacy Committee, Public Policy Committee, and a member of the Kidney Patient Advisory Council.

Drs. Gibson and Carlozzi discuss the limitations in and opportunities for incorporating PROs into clinical care and research, and Mr. Forfang provides his perspective as a patient and research partner.

DN = Devika Nair; DG = Debbie Gibson;
NC = Noelle Carlozzi; DK = Derek Forfang

DN: What are some limitations of current PROs and challenges to incorporating them into care?

DG and NC: Several of the PROs we are currently using are relatively new, and as such we are still collecting data about their clinical utility (both strengths and weaknesses). These data are integral to using PROs effectively in a clinical setting. PROs also need to be used in conjunction with other reports to provide a full clinical picture. For example, the intersection between patient report, clinician report, and biomarker data is, in and of itself, a very important piece of information. The congruence and discrepancies can provide a rich clinical picture and present new challenges. Ultimately, PROs give patients a voice to highlight the different aspects of care that are important to them.

DG: Relatively few disease-specific PROs have been developed for individual kidney diseases. The use of generic PROs may be reasonable but they will benefit from a dedicated effort to ensure that concepts important to patients are included in the PRO and that the response range is appropriate for these patients.

DN: What are some ways PROs can be better incorporated? What can healthcare professionals do with the information obtained from PROs?

NC: Ideally, PROs could be incorporated into a patient visit, and things could be flagged that the clinician might want to address in the clinic visit, either because it indicates that something has changed for the patient or because there is an elevation that might suggest a clinically significant problem. In this manner, appropriate referrals might be made. Information from PROs may also raise patient-specific concerns that might otherwise not be addressed during a clinical care visit.

DG: In practice today, many health systems are collecting PROs. Some use the electronic health system to gather the responses and plot longitudinal results to facilitate the use of PROs in the clinical setting. PROs are being collected in dialysis facilities as well. This information can be incorporated into the routine clinical data review to inform patient interactions and management decisions. Currently, many practices and health systems do not have a comprehensive approach to PRO assessment and tracking. Although progress is being made, we encourage healthcare professionals to take the time to review the results and include this review in patient interactions.

DN: What are some future areas that researchers and clinicians need to focus on with regard to PROs? What about the need to move beyond health-related quality of life?

NC: Health-related quality of life (HRQOL) is the impact of a disease on an individual's physical, mental, and social health and well-being. Several different symptoms are commonly included under this umbrella. There are certainly aspects of HRQOL that we don't currently capture (meaning that measures are not currently available to assess all of the different factors that relate to HRQOL). In particular, although we have several measures that are generic (meaning they can be used to assess symptoms and problems across multiple health conditions), we frequently lack disease-specific measures—or measures that capture the different aspects of a disease that are more unique. In many ways, there is still a lot of work to be done in terms of HRQOL and capturing the concerns that are most relevant to our patients.

DG: We have many opportunities. Consider the need to generate evidence to support intervention(s) for specific PRO findings, generate evidence to facilitate interpretation of the PRO results as absolute values or change in scores from one assessment to the next, generate PROs fit for adults and children, and generate observer-reported outcomes (ObsROs) for parents or family members to report on signs of disease when the patient is unable to do so. This is an area rich in opportunities, and I believe our healthcare delivery will benefit greatly as this area of assessment matures.

DN: Can you tell me a little bit about your role as a patient advocate?

DF: As an ESRD patient who has dealt with diabetes for almost my entire life, my focus is on chronic disease and its impact on my patient population. Having a leadership role in the patient community, I feel my role is to help other patients understand that PRO measurements can affect our care. The Centers for Medicare & Medicaid Services (CMS) Quality Incentive Program and Dialysis Facility Compare programs are two good examples of opportunities for this.

DN: What do you think are some challenges that patients and members of their care team face when responding to PROs?

DF: Transparency is key to having patients better align their goals with their care team. I believe most patients don't understand measures or even know they exist; I know I didn't. I thought measures were something the clinic had to worry about, and I thought they had nothing to do with me individually. Having a basic understanding of the difference between clinical measures and a PRO is also important.

DN: In your opinion, what are some future areas for focus in the development of additional PROs?

DF: I'm thinking about the six areas defined by the Meaningful Measures Initiative. One area that

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FOR YOUR CKD PATIENTS

When you see risk factors of confirmed hyperkalemia...[1]

Indication and Usage

VELTASSA is indicated for the treatment of hyperkalemia.

Limitation of Use: VELTASSA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

ACE=angiotensin-converting enzyme; CKD=chronic kidney disease.

PATIENT PORTRAYAL

Consider once-daily, sodium-free VELTASSA

IMPORTANT INFORMATION

Contraindications: VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components.

Worsening of Gastrointestinal Motility: Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in clinical studies.

Hypomagnesemia: VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels.

Adverse Reactions: The most common adverse reactions (incidence ≥2%) are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence. Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA and included edema of the lips.

Please see Brief Summary of Prescribing Information on following page.

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Patient-Reported Outcomes

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stands out is the goal to "Strengthen Person and Family Engagement as Partners in [Their] Care." This measure is broken down to three areas. The first involves care being personalized and aligned with patient goals. Last year I participated in a CMS Technical Expert Panel on PROs. Two topics prioritized by patients and providers involved patients' life goals and the need for patients to feel safe in their dialysis facilities. Understanding what is important to patients and creating an individual care plan around their culture, goals, and values can help better activate patients in their own care. If a patient desires to travel, work, see friends more often, or transition to a more palliative approach, each of these should be a topic of discussion when a care plan is developed.

A second area involves a patient's experience and his or her functional outcomes. We already have some PROs that measure this, such as the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH-CAHPS) Survey and the Kidney Disease Quality of Life (KDQOL) instrument, but certain things still aren't captured. I think the ICH-CAHPS could be improved, both by making the survey questions more specific, adding questions around fear or perception of retaliation, and by including patients in the debriefing of the results when facilities receive their scores. The KDQOL instrument doesn't take into account how patients adapt to their changing functional status. I took the survey recently and scored fairly low because I've been in a wheelchair for the past 2 years, but I feel that the quality of my life is very good. I travel, socialize, have interests and hobbies, and the work I do volunteering is extremely rewarding. So, although the wheelchair has been limiting in some ways, I still continue to achieve and do the things that are important in my life. PROs should create a dialogue between the patient and the care team, both to improve quality of care and to improve outcomes that are important to patients.

The third area involves ensuring that end-of-life care is delivered according to a patient's preferences.

DN: What do you wish clinicians and healthcare providers knew about PROs?

DF: I know PROs can be burdensome, but if the right questions are asked and the answers allow for meaningful feedback to patients and providers, they are worth the time. If I were a clinician I would want to know my patients' culture, goals, and values, because this could reduce nonadherence, improve shared decision-making, and so on. I would also want my patients to understand my goals for them as a clinician. We need to better align our goals, and PROs are a new way to measure success, but more importantly, they open communication. We as patients can help our clinics achieve success if we are welcome to speak up and get involved. We want to partner with you.

DN: Thanks to everyone for your valuable insights into this important issue.

Suggested Reading

1. Patient-reported outcomes. The National Quality Forum. July 17, 2018. https://www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx.
2. Hughes TM, et al. Association of shared decision-making on patient-reported health outcomes and healthcare utilization. *Am J Surg* 2018; 216:7–12.
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4. United States Food and Drug Administration. Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims. *Federal Register* 2009; 74:65132–65133.
5. Calvert M, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO extension. *JAMA* 2018; 319:483–494.
6. Urquhard-Secord R, et al. Patient and caregiver priorities for outcomes in hemodialysis: An international nominal group technique study. *Am J Kidney Dis* 2016; 68:444–454.

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Winning the ASN Policy Races for 2018

1. **Enacted law for telehealth reimbursement**
   Allowed you to be reimbursed for seeing home dialysis patients via telehealth starting January 2019

2. **Opposed proposals to devalue cognitive care reimbursement**
   Fought to protect you from Medicare proposal to drastically lower E&M payments

3. **Increased funding for kidney research**
   Grew your pool of research funding, securing a $3B increase for the NIH, with a substantial increase for NIDDK

4. **Launched KidneyX to foster innovation**
   Partnered with the federal government to accelerate the development of new kidney therapies to improve the lives of your patients through a series of prize competitions

5. **Protected your latitude to prescribe home dialysis**
   Fought ill-informed Medicare contractors' Local Coverage Decision proposals limiting access to home dialysis

6. **Improved veterans' access to transplantation**
   Secured passage of law veterans and their living organ donors to receive transplant services at closer-to-home transplant centers

7. **Advanced protections for living organ donors**
   Secured Congressional report language clarifying that living donors should qualify for Family Medical Leave Act protections

8. **Created new tools to improve patient empowerment**
   Partnered with the Department of Veterans Affairs Center for Innovation to develop a new mobile app to empower your patients by tracking nutrition, fitness and medication information

9. **United Kidney Community on Capitol Hill**
   Brought together ~20 patient and health professional organizations for fourth annual Kidney Community Advocacy Day to advocate for you and your patients

10. **Informed you of ASN's advocacy on your behalf**
    Launched the monthly Policy and Advocacy Insider email newsletter to keep you abreast of what ASN is doing for you and how you can get involved

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