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Kidney News

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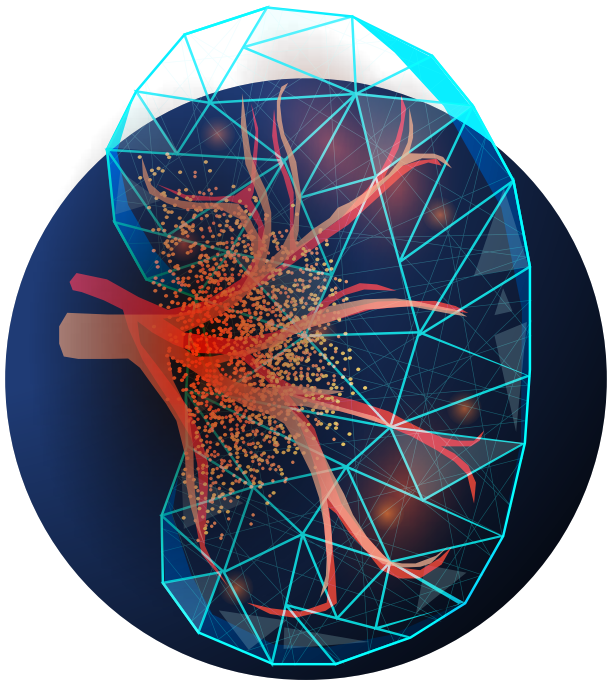
New Cell Atlas Identifies Genetic Signature for Fibrosis

By Bridget M. Kuehn



Rapidly evolving technology and a growing body of multiomic data on individual kidney cells are yielding new insights into a fundamental aspect of kidney diseases: fibrosis.

Fibrosis is a shared characteristic of kidney diseases regardless of the cause. Clinicians use a pathological analysis of fibrosis in biopsy tissue from a patient's kidneys to assess disease progression, but its predictions have limitations. Nephrologists and patients have long wished for better tools for predicting kidney disease progression. Now, a study published in *Nature Genetics*, detailing the findings of the latest single-cell multiomic kidney atlas, provides new insights on fibrosis that may improve clinicians' ability to predict a prognosis or to suggest potential targets for antifibrotic therapies (1).

"We truly feel that we could revolutionize diagnostics and prognostics for kidney disease development using spatial transcriptomics and AI [artificial intelligence] [of such large datasets]," said the study's senior author, Katalin Susztak, MD, PhD, a professor at the University of Pennsylvania. Susztak co-leads the Penn-CHOP Kidney Innovation Center, a research collaboration between the University of Pennsylvania and the Children's Hospital of Philadelphia focused on early detection, prevention, and treatment of kidney diseases and their complications across the lifespan (2).

Comprehensive kidney atlas

Since then, they have shifted their focus to developing a comprehensive, single-cell human kidney atlas, leveraging a rapidly evolving toolset and a growing body of single-cell multiomic data generated by laboratories across the country.

"The ability to interrogate human tissue helps find things that we think are probably most clinically important and potentially actionable," said the *Nature Genetics*' study (1) co-lead author, Jonathan Levinsohn, MD, PhD, a pediatric nephrology fellow in the Division of Nephrology at the Children's Hospital of Philadelphia. He explained that mouse models do not fully recapitulate human disease. He also noted that having "unbiased" comprehensive data may lead to new insights into kidney diseases that might be missed by individual researchers asking more narrow research questions.

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Awake Kidney Transplants Enhance Recovery, May Increase Access to Transplantation

By Karen Blum

It was a standard open kidney transplant operation, with a twist: Surgeons at Northwestern Medicine in Chicago on May 24th transplanted a live donor kidney into 28-year-old patient John Nicholas. What was the difference? Nicholas was awake throughout the procedure.

In a setup similar to a cesarean delivery, Nicholas was given spinal rather than general anesthesia, and a drape blocked his view of the operating field. He chatted with the surgical team during the procedure, chose his favorite music to listen to (the rock band The Killers), and was able to view the donor kidney before it was implanted. Less than 24 hours later, he was discharged pain-free to his home, where he continues to recover well.

Nicholas, an engineer, was the perfect candidate for this trial, said his nephrologist Cybele Ghossein, MD. "He was young; thin; otherwise healthy; and willing, able, and interested in anything that moved medicine forward," said Ghossein, a professor of medicine at Northwestern University Feinberg School of Medicine who has cared for Nicholas for about 2½ years. Additionally, there was time to plan the procedure, as Nicholas was not yet on dialysis and had a living donor.

The transplant team had been thinking of ways to potentially improve the patient experience and decrease hospital length of stay, said Vinayak Rohan, MD, one of the

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Inside

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INDICATION

XPHOZAH (tenapanor) 30 mg BID is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

- Pediatric patients under 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

WARNINGS AND PRECAUTIONS

Diarrhea

Patients may experience severe diarrhea. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

MOST COMMON ADVERSE REACTIONS

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials.

Please see Brief Summary of full Prescribing Information on the following page.

Reference: XPHOZAH® (tenapanor) full Prescribing Information. Waltham, MA: Ardelyx, Inc.; 2023.

ardelyx®

XPHOZAH (tenapanor) tablets, for oral use
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

XPHOZAH is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

4 CONTRAINDICATIONS

XPHOZAH is contraindicated in patients under 6 years of age because of the risk of diarrhea and serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5)]*.

XPHOZAH is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea was the most common adverse reaction in XPHOZAH-treated patients with CKD on dialysis *[see Dosage and Administration (2) in the full Prescribing Information, Contraindications (4) and Adverse Reactions (6.1)]*. In clinical trials, diarrhea was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

6 ADVERSE REACTIONS

6.1 Clinical Trial 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 practice.

The safety data described below reflect data from 754 adults with CKD on dialysis taking XPHOZAH in clinical trials as monotherapy and in combination with phosphate binders. Among the 754 patients, 258 patients were exposed to tenapanor for at least 26 weeks and 75 were exposed to tenapanor for at least one year. *[see Clinical Studies (14) in the full Prescribing Information]*.

Most Common Adverse Reaction

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in the XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with XPHOZAH. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with XPHOZAH (30 mg twice daily for five days), the peak exposure (Cmax) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by 50 to 65% compared to when enalapril was administered alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. However, the decrease in enalaprilat's exposure with XPHOZAH may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Therefore, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis is not required when enalapril is coadministered with XPHOZAH.

7.2 Sodium Polystyrene Sulfonate

Separate administration XPHOZAH and sodium polystyrene sulfonate (SPS) by at least 3 hours. SPS binds to many commonly prescribed oral medicines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Therefore, maternal use is not expected to result in fetal exposure to the drug.

The available data on XPHOZAH exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.2 times the maximum recommended human dose and in rabbits at doses up to 15 times the maximum recommended human dose (based on body surface area) *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

The estimated background risk of major birth defects and miscarriage for women with CKD on dialysis with hyperphosphatemia is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.2 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 15 times the maximum recommended human dose, based on body surface area). In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 16.5 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XPHOZAH and any potential adverse effects on the breastfed infant from XPHOZAH or from the underlying maternal condition.

8.4 Pediatric Use

Risk Summary

XPHOZAH is contraindicated in patients less than 6 years of age. In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week old rats; approximate human age-equivalent of less than 2 years of age) and in older juvenile rats (approximate human age-equivalent of 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

The safety and effectiveness of XPHOZAH in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups.

In juvenile rats administered tenapanor at 0.03, 0.1, or 0.3 mg/kg/day on PND 5 through PND 61, treatment-related mortalities were observed at 0.3 mg/kg/day. Lower mean body weight gains were noted in the 0.3 mg/kg/day group males and females compared to the control group primarily during PND 12–24 but continuing sporadically during the remainder of the dosing period; corresponding lower mean food consumption was noted in this group during PND 21–33. As a result, mean body weights were up to 15.8% and 16.8% lower in males and females, respectively, compared to the control group; the greatest difference was on PND 24 for males and PND 21 for females. Mean body weight in the 0.3 mg/kg/day group males was only 3.9% lower than the control group on PND 61. There were no tenapanor-related effects on mean body weights, body weight gains, or food consumption in the 0.03 and 0.1 mg/kg/day group males and females. A dosage level of 0.1 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for juvenile toxicity of tenapanor *[see Contraindications (4), Warnings and Precautions (5.1)]*.

In a 21-day oral dose range finding study in older (weaned) juvenile rats administered tenapanor at 0.1, 1, or 5 mg/kg/day on PND 21 through PND 41 (approximate human age-equivalent of 2 to 12 years of age), treatment-related mortalities or moribundities were observed during the first two days of the study in the 1 mg/kg/day males and the 5 mg/kg/day males and females. Watery feces, decreased food consumption, and lower mean body weight were also observed in the 1 and 5 mg/kg/day groups.

In weaned juvenile rats administered tenapanor at 0.1, 0.3, and 0.7 (males) or 1 (females) mg/kg/day on PND 21 through PND 80, no mortalities were observed. Significant decreases in mean body weights were observed in the 0.3 and 0.7 mg/kg/day males throughout the dosing period (up to 20.3% lower than control) and in the 1 mg/kg/day females between PND 23 to 35 (up to 16.7% lower than control), with food consumption notably decreased on PND 21 to 29. There were also reductions in tibia length between PND 76 and 80 in the 0.3 and 0.7 mg/kg/day males, and between PND 36 and 64 in the 0.7 mg/kg/day males, which were not observed during the 14-day recovery period. The NOAEL was considered to be 0.1 mg/kg/day for juvenile toxicity of tenapanor.

8.5 Geriatric Use

Of 1010 adult patients with CKD on dialysis randomized and treated in two randomized, double-blind, placebo-controlled randomized withdrawal clinical trials for XPHOZAH (TEN-02-201 and TEN-02-301) as well as a third randomized, double-blind, placebo-controlled trial (TEN-02-202) for XPHOZAH in combination with phosphate binders, 282 (28%) were 65 years of age and older. Clinical studies of XPHOZAH did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently than younger patients.

10 OVERDOSAGE

No data are available regarding overdosage of XPHOZAH in patients. Based on nonclinical data, overdose of XPHOZAH may result in gastrointestinal adverse effects such as diarrhea, as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

Instruct patients to contact their healthcare provider if they experience severe diarrhea *[see Warnings and Precautions (5.1)]*.

- Instruct patients not to use stool softeners or laxatives with XPHOZAH.

Administration and Handling Instructions

Instruct Patients:

- To take XPHOZAH just prior to the first and last meals of the day *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- Patients should be counseled not to take XPHOZAH right before a hemodialysis session, and to take XPHOZAH right before the next meal, as some patients may experience diarrhea after taking XPHOZAH.
- If a dose is missed, take the dose just before the next meal. Do not take 2 doses at the same time *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- To keep XPHOZAH in a dry place. Protect from moisture. Keep in the original bottle. Do not remove desiccant from the bottle. Keep bottles tightly closed *[see How Supplied/Storage and Handling (16) in the full Prescribing Information]*.

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New Cell Atlas Identifies Genetic Signature for Fibrosis

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In the study, the team used 81 human biopsy samples from 58 study participants without health problems or with hypertension or diabetes. Then, they used single-cell RNA sequencing of more than 300,000 kidney cells to map them in the kidney. They ultimately identified 44 types of kidney cells and 114 subtypes.

The researchers combined their data with data from the Kidney Precision Medicine Project (KPMP) to validate and improve the accuracy of their single-cell analysis. The KPMP published its kidney cell atlas last year (5, 6). That atlas resulted from a collaboration between KPMP and the Human BioMolecular Atlas Program. The KPMP atlas aims to help track the transition from healthy cells to kidney disease and transform kidney disease care. With hopes of spurring research by other groups and accelerating progress, the KPMP has made its data publicly available for other researchers to use.

"We were very happy that [Susztak] was able to use all 300,000 cells from the dataset to power some of her work to get more detailed cell types," said Sanjay Jain, MD, PhD, professor of medicine, pathology, and pediatrics and director of the Kidney Translational Research Center at Washington University School of Medicine in St. Louis, MO, and one of the KPMP study's (6) principal investigators. "She also used spatial transcriptomics, as we did in our atlas, focusing on some microenvironments in pathological areas," he continued.

Tapping that resource allowed Susztak and her colleagues to double the size of their dataset to include single-cell multiomic data on more than 600,000 kidney cells. Susztak explained that combining the data from multiple laboratories is essential to guard against potential biases in data generated by just one laboratory. It also helps increase confidence in their discoveries when multiple laboratories' work reinforces another. Jain agreed that having multiple laboratories working with and generating atlas data increases confidence in the results. "Collaboration is better than competition," Susztak added.

The website created to host the data from Susztak's team will provide a launch pad for inquiries by other kidney disease researchers. She explained that researchers can use the interactive tools that she and her colleagues developed to search the atlas by cell type and compare what happens in healthy kidneys or kidneys affected by hypertension or diabetes. They can also search for genes that they may be studying to evaluate where they are being expressed and how they change in disease conditions. The data are also available for download. Susztak suggested that the atlas may also be a valuable tool for clinicians in training to learn more about kidney function.

"Our paper provides a very comprehensive single-cell reference atlas for healthy kidneys and for kidneys in disease states [like hypertension and diabetes]," Susztak said. "Researchers can use this atlas like a GPS [Global Positioning System] map [of the kidney]."

Fibrosis fingerprints

Susztak and her colleagues used AI technology to identify four distinct cellular microenvironments or neighborhoods—glomerular, immune, tubule, and fibrotic. Their atlas provides new information on the behavior and interactions of cells in these neighborhoods. "Spatial technologies can give us greater insight and perhaps help us understand not just associations [among different cells] but maybe get some insight into the mechanism of why those things go together," she said.

Susztak was particularly interested in the fibrotic niche. Her laboratory focuses on studying the effects of hypertension and diabetes, which together cause approximately 75% of kidney diseases in the United States. Some kidney diseases like immunoglobulin A nephropathy (an autoimmune condition) or focal segmental glomerulosclerosis (which causes scar tissue on the glomeruli) have specific cellular, genetic, or molecular signatures. But kidney diseases caused by hypertension or diabetes have few hallmarks besides fibrosis, she explained.

The team's AI analyses revealed a distinct gene signature in fibrotic cells associated with kidney disease progression. The results are particularly impressive because the AI algorithm did not have prior knowledge of genes linked to fibrosis, making its findings completely independent of previous research. "It told us about new genes, pathways, and interactions in the fibrotic niche," Susztak said. "We created an unbiased [genetic] signature profile that can predict patient prognosis in datasets [in which] this information is not available and then predicted patients' outcomes better than the pathologist was able to," she said.

Jain said that it is challenging for clinicians to predict which patients will develop kidney diseases. The KPMP identified signatures of kidney decline in the proximal tubule and some stromal areas that were associated with kidney function decline, which may also have some value in helping predict progression. "We are excited to see a lot of output from the community to solve this issue of categorizing patients together early on and determining whether someone will recover or progress," he said.

Larger datasets, more insight

Susztak wants to expand the datasets for kidney mapping by spatially mapping cells from as many patients' kidney biopsies as possible and is seeking funding to achieve this goal. "We want diverse samples so the computer can learn to identify different patterns and pick out rare diseases," she said.

Growing the datasets may help AI tools pick up patient-level differences in kidney diseases, helping scientists better understand the mechanisms of different types of kidney diseases and potentially suggest new treatment targets. Identifying patient-level differences in kidney diseases may help clinicians better match existing therapies to patients' needs. For example, Levinsohn noted that physicians may be able to use the information to select an antihypertensive treatment based on what is happening in the patient's cells.

Susztak and her colleagues are currently building algorithms to help clinicians analyze patients' single-cell multiomic data and compare those data with reference samples. She explained that each patient's kidney disease is unique and that understanding patient-level differences may help clinicians to personalize care. "We are working on tools that will make [single-cell multiomic kidney data] applicable for individual clinicians," she said.

Levinsohn noted that developing and refining ways to analyze these massive datasets and extract the most important information will be another important goal for researchers in this area over the next several years. But he is hopeful that the work will help reveal the complex interactions that lead to kidney diseases and how they differ from patient to patient. "It is going to take a while and probably a few more technology improvements and data analysis improvements before we can take a look at the snapshots [provided by single-cell analysis] and tell the story in full of what it means to individuals," he said.

> **"We created an unbiased [genetic] signature profile that can predict patient prognosis in datasets [in which] this information is not available and then predicted patients' outcomes better than the pathologist was able to."**

Jain and his colleagues are similarly focused on building methods to analyze these growing datasets and tease out clinically important insights from the potential noise in them. The goal, he said, is to advance precision medicine for kidney diseases. "We need more datasets and knowledge base, but these [two kidney atlases] are a good initial start," he said.

Although direct clinical applications remain on the horizon, Susztak and her colleagues believe that they may be able to use this type of precision diagnostic tool to help design clinical trials or to repurpose existing drugs. "We want more and better treatments for patients with kidney diseases," she said. ■

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Correction

The article "Paraquat Poisoning 101 for the Nephrologist" by Nikhil Saxena and Divya Bajpai published in the August 2024 issue of *Kidney News* contained an incorrect statement. The original article stated, "It has also been hypothesized that paraquat acts as a noncompetitive inhibitor of paraquat uptake at the level of the renal tubule."

The sentence should read:

"It has also been hypothesized that paraquat acts as a noncompetitive inhibitor of creatinine uptake at the level of the renal tubule."

Awake Kidney Transplants Enhance Recovery, May Increase Access to Transplantation

Continued from cover

surgeons who performed the procedure. Kidney transplant operations have become so standardized that surgeons can perform them in under 2 hours, he said, coupled with efforts regarding pain management to minimize the use of opioids and enhanced recovery after surgery protocols that focus on optimal fluid intake and movement before and after operations. "Kidney transplantation is really a transformation process for somebody who is undergoing dialysis," Rohan said. "We are excited every time we see a kidney looking good and making urine. If [a patient] can be part of it, that would be amazing. These are the kind[s] of things which made us say, 'Hey, can we do this?'"

Because Nicholas had been interested in clinical trials, the transplant team reached out to him to assess his commitment. He talked through the option with Ghossein as well before moving forward. "This is a wonderful new option," Ghossein said, noting that it could be useful in situations in which general anesthesia is too risky for a patient or in which a patient might previously have had a bad reaction. "General anesthesia carries a risk. We don't think of it that way because we do it all the time…you're put on a ventilator, the grogginess after, the recovery for weeks. In someone who doesn't necessarily need it, why complicate a transplant with this added issue?"

When patients with chronic kidney disease first meet with a nephrologist, the thought of transplant can be overwhelming, and the patient is often fearful and anxious, Ghossein said. "Thankfully, we sometimes have the benefit of time to build a relationship with the patient and get them to the point where they are not as fearful of going through the transplant. Once you get them to that point, the idea of maybe you can do it without general anesthesia doesn't feel as big of a barrier."

Although spinal anesthesia had been used decades earlier during transplant operations in India and the Republic of Turkey, Rohan noted, the transplant made news headlines nationwide. "We were pleasantly surprised by the amount of media attention we got," he said. "We thought it was a very interesting concept, but I think media loved it because it was not just about the technique; it was the patient experience."

The team has since performed two similar procedures, he said. The second surgery involved a 74-year-old man who was at first fearful but encouraged by his daughter, his kidney donor. Just 1 day after the operation, the man had a pain score of 2 out of 10 and was eating and drinking normally, Rohan shared: "He said, 'This is the best experience I've ever had.'" That patient was discharged in 36 hours.

The success of these procedures and enhanced recovery time presents a promising opportunity in the transplantation field, opening possibilities for patients in the United States. Since the procedure on Nicholas, the surgical team has received emails from multiple patients around the country potentially interested in the procedure because of tracheal issues or glottic stenosis from a previous surgery. Older patients also may be good candidates, as they can become disoriented from general anesthesia, Rohan explained.

"Transplantation is a serious thing," Rohan added. "But making it more humanized and making people think it is not all that bad, I think, will encourage a lot of people to [undergo a transplant] who are maybe sitting on the fence." ■

Top: Nicholas in the operating room seeing the donor kidney.
Bottom: Nicholas and the transplant team at the end of surgery.
Credit: Northwestern Medicine.

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ASN President's Update

Winning With Kidney Diseases Depends on How You Feel

By Deidra C. Crews

As the summer season draws to an end for many of us, I am sure that you, like me, were captivated by the Summer Olympic and Paralympic Games in Paris, France. Whether rooting for our compatriots to make it onto the medal stand or binge-watching events we never knew were included in the Olympics—in my case, that was skateboarding—Paris 2024 was a great source of inspiration and wonder for us all.

I was particularly inspired by the story of Sunisa "Suni" Lee, a gymnast on Team U.S.A. Known for high-flying, dazzling performances, Lee earned two bronze medals in individual events (uneven bars and the all-around competition) and a gold medal in the team finals. But perhaps her greatest recent victory was one much more familiar to those of us in the kidney community. Before this summer's competition, Lee shared that early in 2023, as a college sophomore, she woke up one day to find that "nearly her entire body was swollen" (1). She was subsequently diagnosed with two forms of kidney diseases said to be "rare" and "incurable" (1, 2). Following treatment, Lee's recovery has been remarkable, as we were able to glean from her outstanding performance at the Olympics. And she is not the only athlete known to have faced kidney diseases either prior, during, or after their professional or Olympic careers (Table).

When I hear of extraordinary things that athletes and other people with kidney diseases do and their stories of overcoming setbacks due to their conditions, I often try to imagine what it took for them to *feel* well enough to accomplish amazing things. How did they overcome the common symptoms, such as insomnia, fatigue, cramping, and anxiety, that many people living with kidney diseases experience (3, 4)? What can be done to support others who also want to feel well enough to "win" with kidney diseases?

Patient-reported outcome measures are validated questionnaires that have been developed for patients to report directly how they are feeling and how well they are functioning in their daily lives. Such measures focus on their health conditions and the associated treatments, bypassing interpretation of their responses by clinicians or other members of the health care teams (5). When first developed, patient-reported outcomes were primarily used in research studies. However, over the past quarter-century, with the advent of more widespread use of electronic health records and digital health technologies, patient-reported outcomes are now being incorporated into patient self-management and clinical care delivery.

The use of patient-reported outcomes has led to some favorable traditional (or "hard") clinical endpoints. In a randomized clinical trial in oncology, for example, the addition of electronic patient-reported symptom monitoring into the routine care of patients with metastatic cancer resulted in better survival as compared with usual care (6). The investigators noted that one potential driver of the survival benefit of participants in the symptom-monitoring arm of this trial was that they were more likely to receive early responses from health professionals to their symptoms that could have prevented downstream adverse events.

Apart from annual assessments such as the Kidney Disease Quality of Life 36 (KDQOL-36), which is mandated by the Centers for Medicare & Medicaid Services as a condition of coverage for dialysis facilities under the Medicare program (7), patient-reported outcomes are not routinely measured in US kidney care. And they are especially underutilized for people with kidney diseases not requiring dialysis. Although valid and reliable measures exist for adult and pediatric patients with kidney diseases (8–10), patient-reported outcome measures would need to be incorporated into care workflows to fully reap the potential benefits of their routine assessment, while also both addressing barriers to their completion by people living with kidney diseases and barriers to reviewing and acting on symptom burden by nephrologists and other clinicians (11, 12).

We could expect that people with higher literacy, greater comfort in navigating electronic patient portals, and those who are more at ease with other platforms would be more likely to complete patient-reported outcome measures. As such, it would be imperative to ensure that their application does not worsen disparities regarding who receives high-quality kidney care. I could imagine, and I actively hope though, that by standardizing these sorts of measures and providing assistance in completing them where needed (e.g., over the telephone or while in the clinic waiting room), patient populations who are historically marginalized might derive significant benefits. For example, symptom assessment via patient-reported outcome measures might allow for more timely identification of people approaching a need for initiation of kidney replacement therapy, which could have implications for mitigating disparities in referral for vascular access surgery and referral for transplantation, among other care processes.

A looming question, however, is if we were to routinely assess patient-reported outcomes in kidney care, as some experts have endorsed, do we have the ability to alleviate the symptoms that patients would report? Can we actually help people to *feel* better? I am encouraged by clinical trials demonstrating the effectiveness of both some nonpharmacologic (e.g., acupuncture for uremic pruritus [13]) and pharmacologic (e.g., melatonin for sleep disturbances [14]) therapies in the treatment of some common symptoms experienced by people with kidney diseases, yet significant evidence gaps remain (15). These gaps can and should be addressed by greater investment in clinical trials including patient-reported outcomes as endpoints.

It is equally important to recognize those like Lee who use their platforms to raise awareness about kidney diseases. ASN awards the President's Medal to individuals who have helped advance the society's mission to create a world without kidney diseases by educating and informing, driving breakthroughs and innovation, and advocating for policies that create transformative changes in kidney medicine throughout the world. Recent recipients of the ASN President's Medal include photojournalist Ed Kashi; actor and comedian George Lopez; former member of Congress Jim McDermott, MD; and Griffin P. Rodgers, MD, who directs the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

On Thursday, October 24, 2024, I will recognize Alonzo Mourning with the ASN President's Medal. ASN's members, leadership, staff, and I sincerely appreciate how Mourning has leveraged his platform as a world-famous athlete and

Table. Examples of athletes who have lived with kidney diseases

Athlete	Sport/event	Kidney disease history
Sean Elliott	Basketball	FSGS, transplant recipient
Ed Hearn	Baseball	FSGS, three-time transplant recipient
Paul Hutchins	Football	FSGS, double kidney transplant recipient
Chris Kemoeatu	Football	Hereditary kidney disease, kidney transplant recipient from his brother, also a football player
Sunisa "Suni" Lee	Gymnastics	Rare kidney diseases
Aries Merritt	Hurdles	Rare congenital kidney disease, transplant recipient
Alonzo Mourning	Basketball	FSGS, transplant recipient
Jeremy Newberry	Football	Kidney disease caused by painkillers
Pelé	Soccer	Kidney removed, underwent surgery for kidney stones
Amy Purdy	Para-snowboarding	Kidney failure following hospitalization for septic shock, transplant recipient from her father
Jon Rankin	Track and field	FSGS
Clyde Simms	Soccer	FSGS, transplant recipient

FSGS, focal segmental glomerulosclerosis.
Sources: University Kidney Research Organization (16) and Goff (17).

applied his lived experience to raise awareness about kidney diseases. I am particularly inspired by the impact of his efforts on communities disproportionately affected by kidney diseases, including Black Americans. Through remarkable advocacy on behalf of people living with kidney diseases, he has contributed meaningfully to the kidney community and helped advance ASN's mission.

Not every person with kidney diseases will win Olympic medals like Suni Lee or become a member of the Naismith Memorial Basketball Hall of Fame like Alonzo Mourning. The same can be said of us mere mortals who are neither Olympians nor professional athletes, despite not living with kidney diseases. What is important is that we help everyone *feel* like winners, and that starts with understanding the day-to-day experiences of people living with kidney diseases and helping them alleviate the symptoms that concern them most. ■

Deidra C. Crews, MD, ScM, FASN, is professor of medicine at Johns Hopkins University School of Medicine, deputy director of the Johns Hopkins Center for Health Equity, and ASN president.

To comment on Dr. Crews' editorial, please contact email@asn-online.org.

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Kidney News' Newest Editorial Fellows Share Their Views on Improving Nephrology Training

In July, three nephrology fellows were selected to join the ASN *Kidney News* Editorial Fellows Program for 2-year terms: Timothy M. Chow, MD, Johns Hopkins School of Medicine, Baltimore, MD; Annie Liu, DO, MS, MPH, Massachusetts General Hospital and Brigham and Women's Hospital, Boston, MA; and Jordy Salcedo-Giraldo, MD, Children's National Hospital, Washington, DC.

As part of the application process, they were asked to write a short editorial on the topic, Training in Nephrology 2024: What Can Be Changed? We welcome Drs. Chow, Liu, and Salcedo-Giraldo to the *Kidney News* editorial team and invite you to read their visionary editorials.

Training in Nephrology 2024: What Can Be Changed?

Timothy M. Chow

Nephrology today benefits from an unprecedented wealth of research efforts and findings that have given nephrologists more resources and tools in their mission to care for patients with kidney diseases. With this volume have come findings that may contradict previous ones, treatments that require complex statistical analyses, and a heterogeneity of quality of evidence. Each of these emphasizes a growing and significant need to be able to critically analyze and safely implement the literature to patient care. This need represents an area of improvement for current nephrology training.

Journal clubs, first started by Sir William Osler, MDCM, as a way to discuss and share costs of literature, have evolved to now also be a component of curriculum to teach critical analysis (1, 2). However, in addition to being inconsistent in implementation, reviews have found that this addition does not improve critical appraisal skills in trainees (3).

Further, while both internal medicine and nephrology trainees are assessed on "evidence-based and informed practice" as part of ACGME's [Accreditation Council for Graduate Medical Education's] milestones, the criteria for meeting this competency are not well described and are evaluated locally by the program (4, 5). Current ABIM [American Board of Internal Medicine] initial certification blueprints for internal medicine and nephrology allocate less than 2% of questions to "primarily epidemiology" and do not mention methods or statistical analyses (6, 7). This highlights that there are limited evaluation and structured standards for critical analysis and implementation.

Special attention must be made on critical analysis and implementation of the literature, as trainees will be responsible for evaluating literature on their own in practice. By empowering current educators, engaging national organizations, and collaborating with journals, the nephrology community can ensure trainee success and take the lead in medicine in creating formal teaching standards and evaluation of these essential skills. ■

Timothy M. Chow, MD, is a third-year clinical and research fellow in the Division of Nephrology at Johns Hopkins School of Medicine in Baltimore, MD, where he is also completing his master's degree in clinical epidemiology at the Bloomberg School of Public Health. He is interested in renal and cardiovascular outcomes as well as the care of patients with rare diseases.

The author reports no conflicts of interest.

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Annie Liu

As someone who once dabbled in becoming a philosophy major, it seems only fitting to borrow a quote from Socrates to describe the shifts occurring in modern medical practices: "The secret of change is to focus all your energy not on fighting the old, but on building the new." Gone are the days when physicians solely dictated care; they now become part of the decision-making process and make recommendations alongside patients, their families, and professionals across various disciplines. With this shift comes heightened responsibilities for physicians, necessitating broad discussions to ensure informed decisions, despite varying levels of medical literacy.

It comes as no surprise that patients expect similar coordination and care delivery within nephrology. However, there exists a gap in how trainees navigate complex conversations and deliver patient-centered care aligned with individual goals. For instance, the intricacies involved in discussing and setting expectations for different dialysis modalities: in-center versus home hemodialysis versus peritoneal dialysis—or not pursuing dialysis altogether and opting for conservative kidney management—require careful consideration and communication. There is also an opportunity for improvement in the integration of artificial intelligence into nephrology training to enhance patient access and promote health equity. The recent 2023 Match cycle illustrated a looming concern: a decrease in trained nephrologists in a shrinking pool despite the growing number of individuals with kidney diseases in the United States. It emphasizes the urgency to incorporate artificial intelligence in training to expand patient access, improve care delivery, and hopefully mitigate physician burnout.

In this era, I feel hopeful about the future of nephrology due to the technologies that are constantly being developed, the cultural shift toward supporting care teams, and the recognition of the imperative need to embrace change and "build the new." ■

Annie Liu, DO, MS, MPH, is a third-year clinical and research fellow in the Nephrology Division at Massachusetts General Hospital and Brigham and Women's Hospital, Boston, MA. With an interest in palliative care, her research aims to address challenges in communication about serious illness for patients experiencing kidney failure, particularly in improving prognostication and prognostic awareness among patients and their caregivers.

The author reports no conflicts of interest.

Jordy Salcedo-Giraldo

Nephrology is often perceived as a complex and intimidating field, deterring many aspiring medical professionals from considering it as a possible career option. As we look toward nephrology training in 2024 and beyond, we must address these misconceptions and cultivate interest in the field of nephrology starting at earlier stages of medical education. By introducing students to nephrology concepts and career opportunities at earlier stages of training, such as during medical school or even in undergraduate studies, we can dispel myths and showcase the rewarding aspects of our specialty.

To bring this vision to life, organizations like ASN can play a pivotal role. ASN could actively engage with medical students at conferences, offering educational lectures and workshops on unique topics such as dialysis and kidney biopsies that trainees may not have the opportunity to experience otherwise. By participating in conferences hosted by organizations such as The Latino Medical Student Association and the Student National Medical Association, ASN can broaden its outreach efforts and enhance diversity within the field.

Moreover, targeting undergraduate students through specialized programs could further stimulate interest in nephrology. A summer initiative in which undergraduate students collaborate on research projects with their local hospitals or institutions' nephrology departments would not only provide valuable research experience for the students but also expose students to the excitement and impact of nephrology research.

By embracing early education and outreach initiatives, we have the potential to transform the landscape of nephrology training. We can empower the next generation of nephrologists by making our field more accessible, inclusive, and inspiring from the start of their medical journeys.

Jordy Salcedo-Giraldo, MD, is a second-year pediatric nephrology fellow at Children's National Hospital, Washington, DC. His research focuses on nephrogenetics to improve understanding and care for pediatric patients and those with autosomal-dominant polycystic kidney disease. Dr. Salcedo-Giraldo is a strong advocate for improving care in populations that are underserved, specifically Hispanic, Latino, and Spanish-origin communities.

The author reports no conflicts of interest.

The Dog's Name Is Important: Experience in Clinic With an AI-Powered Scribe

By Katherine Kwon

Several artificial intelligence (AI) applications promise to reduce the work associated with charting patient encounters. I had the opportunity to test-drive one AI-powered medical scribe for my outpatient clinic.

Prewriting went much faster with the scribe program. I did not need to organize the information that I came across during my chart review. I could speak the details of a hospital stay, notable medication needs, or changes in lab data, and the AI scribe would summarize these and place them in the proper sections. I was able to cut my prewriting time down from 90 minutes for a full day of clinic to 20 minutes.

During the patient visit, I found it liberating to not have to type while listening. I was more conscientious of carefully outlining my reasoning to assist the tool in accuracy, and the patients noticed and appreciated the extra effort as well. The scribe took about 40 seconds to generate a note from the encounter, which I could transfer into the electronic medical record (EMR) and edit as needed. The overall visit length did not change, but I was able to spend much more time in direct conversation with my patients and less time in tedious documentation.

Regarding accuracy, I was impressed with the tool's ability to capture and organize tangents and additional pieces of information. If patients mentioned a past problem with a medication or an element of their medical history, it was reliably documented. However, I found that the application struggled with cause and effect. An event such as a medication change based on a side effect was often incorrectly summarized. I tried to counteract this by restating the information back to the patient, but this did not improve the tool's accuracy. Medication reconciliation was also a challenge; I found myself deleting a lot of the verbiage that the scribe placed in the medication section of the note, simply because it was redundant and looked messy in paragraph form.

Another area needing improvement was the capture of the small human details that go to the heart of the doctor-patient relationship. One patient shared at length how their recent bereavement had affected their motivation to care for themselves. Another talked about the joy he had from his new puppy. All of these stories, which I tend to capture in a few phrases in my written notes, were left off completely by the AI scribe. I include these details and refer back to them to develop rapport with my patients. The dog's name is important!

If I am being frank, the AI scribe is a terrible writer. It uses the passive voice all of the time, relies on jargon words like "utilize" far too much, and creates a note that is very boring to read. When I reviewed these notes weeks later, they did not help jog my memory of the patient's personality and the nature of our interactions. As someone who likes to write and appreciates good writing, I really disliked the scribe's style. My notes are one of the primary ways that I interact with colleagues; my writing serves as my professional voice. I would place significant value on an AI program that could write the way I do.

Finally, so much of the cognitive work that takes place in the EMR happens outside of the written note itself, and the tool offered no shortcuts. Medications, history elements, and diagnosis codes must all be placed in their own discrete data fields. It would be a significant leap forward to discuss the diagnosis during the visit and have the scribe code the encounter correctly or to order the labs and medications we discuss. So far, this capability is not offered.

AI scribes offer a great deal of promise to reduce the burdens of charting, although significant improvements are still needed (Table). Practicing physicians should seek to give their input along the entire pathway of AI development. The EMR was not really designed with us in mind. Let's not make the same mistake with the next generation of technology.

Katherine Kwon, MD, FASN, is a regional medical director for Panoramic Health, a value-based care company, as well as a private practice nephrologist at Lake Michigan Nephrology, St. Joseph, MI.

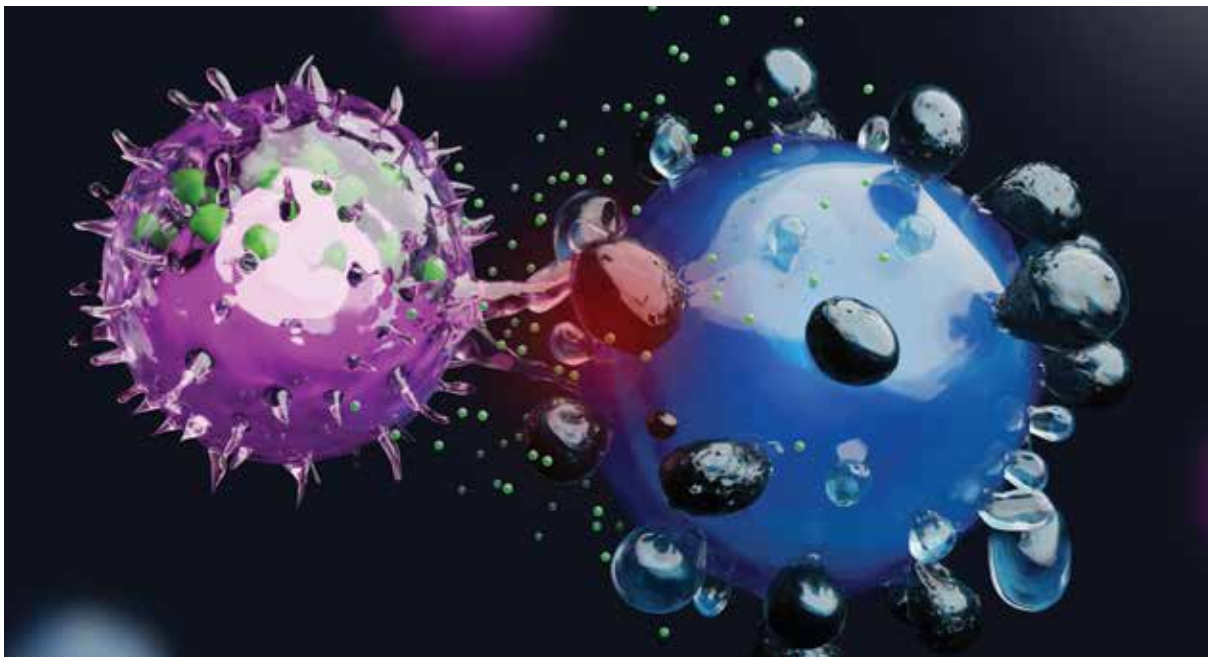
The author reports no conflicts of interest.

Table. Advantages and disadvantages of using the AI scribe

Pros	Cons
Faster precharting and reliably organized collected information	Incorrect statements that need to be recognized and corrected
Less typing, more eye contact during the patient encounter	Personal writing style replaced by stilted, formulaic prose
Good capture of disjointed history elements	Inconsistent capture of information deemed not relevant by the AI tool
Patient understanding enhanced by clear repetition of the plan	No assistance with coding, orders, or other discrete data entry

Transcriptomic Immune Signatures in Chronic Active Antibody-Mediated Rejection: NK Cells and More

By Kieran Manion and Ana Konvalinka



As the primary cause of long-term allograft loss, chronic active antibody-mediated rejection (CA-ABMR) is a critical focal point of kidney transplant research. Recent studies have increasingly focused on molecular mechanisms and cell types that may distinguish CA-ABMR from other forms of rejection as a means of identifying potential therapeutic targets or predictive biomarkers; however, the factors underlying the development of CA-ABMR remain up for debate.

In their recent article, Transcriptomic Signatures of Chronic Active Antibody-Mediated Rejection Deciphered by RNA Sequencing of Human Kidney Allografts, Shah and colleagues performed bulk RNA sequencing of kidney allograft biopsies to provide a comprehensive look at transcriptomic differences among CA-ABMR, active ABMR, and T cell-mediated rejection (TCMR) compared with stable allografts (1). They identified a cytolytic gene signature that is increased in CA-ABMR compared with both no rejection and active ABMR but shared with TCMR, and the authors mapped this signature to natural killer (NK) cells using a gene set enrichment analysis and deconvolution analysis. As confirmation of this NK cell signature, they were able to find the same enhanced gene expression in several publicly available datasets and identified increased proportions of NK cells in biopsies from CA-ABMR and TCMR kidney allograft recipients, compared with active ABMR, through direct immunohistochemistry.

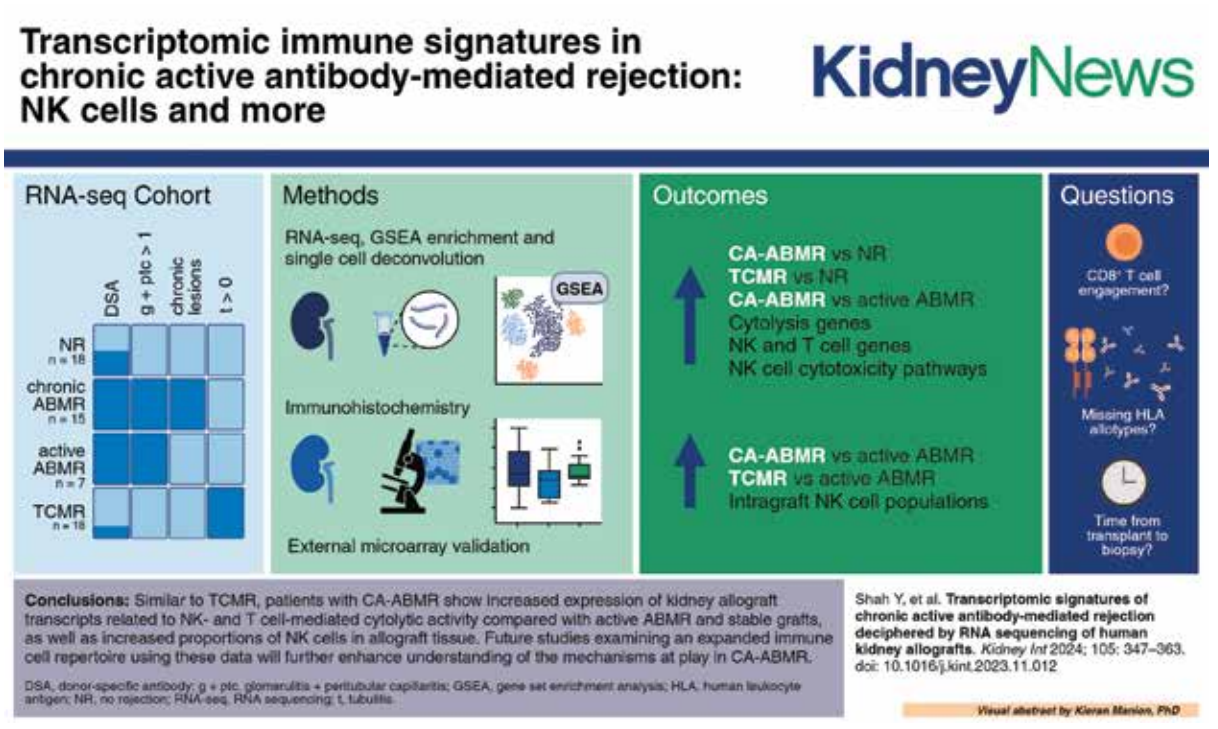
While this study effectively pairs high throughput analysis with external validation to address an important aspect of kidney transplant rejection, it has several notable limitations. The focus on NK cells at the expense of other immune populations represents a missed opportunity given the breadth of the dataset. Indeed, the authors identify significant shifts in a variety of immune cell subsets between both active ABMR/CA-ABMR and TCMR/CA-ABMR. Given that the authors were able to image NK cells directly in allograft biopsies, along with some discrepancy between the immune cell proportions determined through deconvolution versus by immunohistochemistry, there is also a question of whether this type of high throughput analysis is required or suitable for cell identification. Similarly, it is curious that the authors did not address the possibility of $CD8^+$ T cells as the source of the increased cytolytic signature in CA-ABMR, particularly given the extensive evidence showing that these cells are significantly increased in CA-ABMR and are linked to the likelihood of allograft failure (2–4).

From a methodologic standpoint, the significantly longer time between transplant and indication biopsy for CA-ABMR cases versus comparator groups represents an important confounder that could limit the generalizability of the results, particularly given the cross-sectional nature of the study. Additionally, the decision to define donor-specific antibodies' positivity on the basis of mean fluorescent intensity, as well as incomplete donor human leukocyte antigen allele genotyping, leaves room for possible cases of mixed rejection within the TCMR group, which could explain some of the observed similarity between CA-ABMR and TCMR in this study.

Despite these considerations, the NK cell signature identified in CA-ABMR is robust and adds another layer to the existing literature in support of NK cell importance in ABMR at the transcriptional level. Overall, this research represents an important contribution to the timely question of what distinguishes CA-ABMR from its other manifestations and provides a transcriptomic dataset that could be mined in future studies. ■

Kieran Manion, PhD, and Ana Konvalinka, MD, PhD, FRCPC, are with the Toronto General Hospital Research Institute and Ajmera Transplant Centre, University Health Network, Toronto, Ontario, Canada. Dr. Konvalinka is also with the University of Toronto, Ontario, Canada.

Dr. Manion reports no conflicts of interest. Dr. Konvalinka has an academic early access program agreement with Promega.



Visual abstract created with BioRender.com.

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Can Financial Incentives Effectively Promote Home Dialysis in the United States?

By Eugene Lin

The United States is in year 4 of a policy experiment aimed at determining whether large payment incentives can effectively promote more home dialysis use. The Centers for Medicare & Medicaid Services' (CMS') End-Stage Renal Disease (ESRD) Treatment Choices (ETC) Model randomized 30% of dialysis facilities and nephrologists in the United States to a mandatory payment model that holds care teams financially accountable for enrolling more patients into home dialysis (1). (To a lesser extent, ETC also holds care teams accountable for successfully waitlisting patients for transplant.) The payment incentives are large, ranging from +8% and −10% (−9% for nephrologists) of all Part B dialysis payments. One of ETC's selling points is its randomized nature, which makes it one of the true policy experiments implemented by CMS.

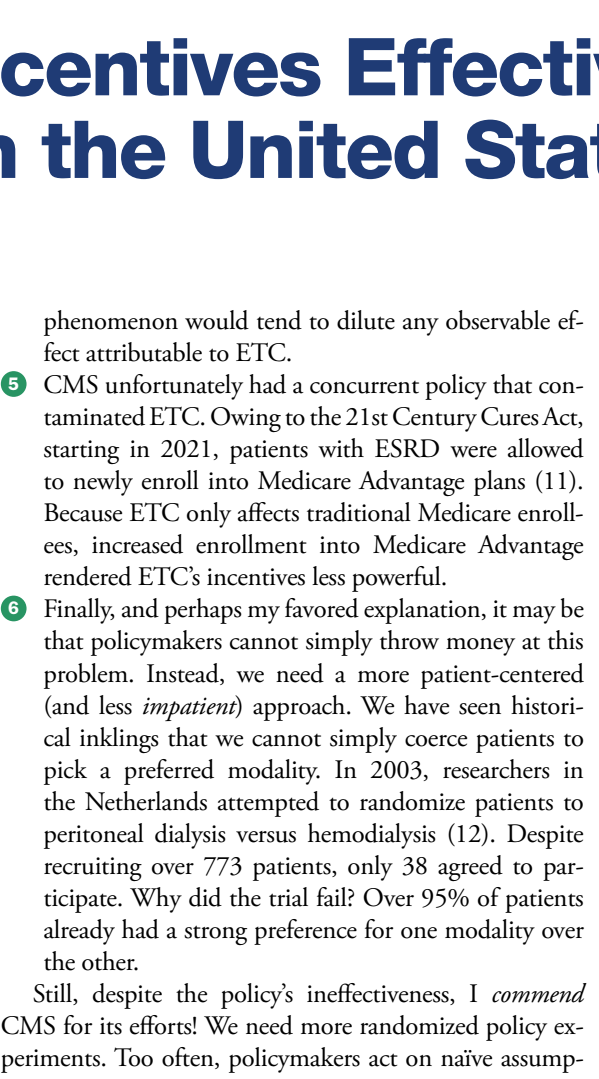
Unfortunately, ETC has been an unequivocal failure. CMS' own evaluation of the first 2 years demonstrated an increase in home dialysis use of 3.1 percentage points in participating regions and 3.2 percentage points in control regions (a nonsignificant difference) (2, 3). Similarly, an early peer-reviewed study showed similar findings in year 1 (4), and in June, Koukounas et al. corroborated these results for years 1 and 2 (5).

Although there are many structural hurdles to home dialysis use (e.g., lack of education and home dialysis infrastructure), policymakers and researchers understandably assumed that financial considerations were important. Indeed, the Government Accountability Office has shown that profit margins are highest for in-center hemodialysis, largely because recruiting patients to already existing in-center shifts allows facilities to inexpensively share fixed costs and labor costs (6). Financial bonuses should have changed relative profit margins in favor of home dialysis, at least for some patients. Additionally, because two dialysis chains own 75% of the market and have facilities in both participating and nonparticipating regions, it would have been straightforward to preferentially focus their attention on participating facilities.

My best guess, ex ante, is that these large payment incentives would have moved the needle at least an iota. So, why did the policy fail? I can think of at least six reasons.

1. Dialysis facilities may not be the right level of intervention. Home dialysis often requires a robust educational effort, often months before initiating dialysis (7). But, ETC also mandated participation by nephrologists, and one would think entrepreneurial nephrologists would have acted accordingly.
2. It can take years to launch a successful home dialysis program, from developing infrastructure to recruiting and training staff. CMS only gave care teams 4 months of notice between the time of randomization and implementation. However, we should have expected movement in the latter years of the model if this were the only explanation.
3. COVID-19 likely derailed any efforts made by facilities to develop home dialysis programs. The pandemic was catastrophic for patients receiving dialysis (8). Understandably, facilities pivoted away from new ventures and toward ensuring the safety of their patients (9).
4. Especially early in the pandemic, we witnessed increased mortality among populations receiving in-center hemodialysis relative to populations undergoing home dialysis (10). A side-effect is that the *number of patients* on home dialysis remained unchanged, but *the proportion* on home dialysis increased. This numerical phenomenon would tend to dilute any observable effect attributable to ETC.
5. CMS unfortunately had a concurrent policy that contaminated ETC. Owing to the 21st Century Cures Act, starting in 2021, patients with ESRD were allowed to newly enroll into Medicare Advantage plans (11). Because ETC only affects traditional Medicare enrollees, increased enrollment into Medicare Advantage rendered ETC's incentives less powerful.
6. Finally, and perhaps my favored explanation, it may be that policymakers cannot simply throw money at this problem. Instead, we need a more patient-centered (and less *impatient*) approach. We have seen historical inklings that we cannot simply coerce patients to pick a preferred modality. In 2003, researchers in the Netherlands attempted to randomize patients to peritoneal dialysis versus hemodialysis (12). Despite recruiting over 773 patients, only 38 agreed to participate. Why did the trial fail? Over 95% of patients already had a strong preference for one modality over the other.

Still, despite the policy's ineffectiveness, I *commend* CMS for its efforts! We need more randomized policy experiments. Too often, policymakers act on naïve assumptions without testing them. It was reasonable to assume that financial considerations were sufficient to move the needle on home dialysis. But now that we know otherwise, we should have some humility in admitting that increasing home dialysis use is difficult. My hope is that CMS (and care teams, academics, and researchers) goes back to the drawing board and designs new policy experiments that may push us to a more patient-centered approach to home dialysis. ■



Visual Graphic by Jia H. Ng, MD, MSCE

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The author reports no conflicts of interest.

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FILSPARI®
(sparsentan) tablets 200 mg/400 mg

For adults with primary IgA nephropathy at risk of rapid progression*

TURN DOWN PROTEINURIA

FILSPARI® is the **first and only** single molecule, endothelin-1 and angiotensin II receptor antagonist, binding to the endothelin type A (ET_A) receptor and angiotensin II type 1 (AT_1) receptor.[1]

Proven to provide **superior reduction in proteinuria** vs irbesartan at 36 weeks in a head-to-head study.[1†]

*Generally defined as UPCR of ≥1.5 g/g.

†Results based on an interim analysis from the PROTECT Study, an ongoing, randomized, double-blind, head-to-head, multicenter, global study in 281 patients with biopsy-proven IgA nephropathy. Patients who received FILSPARI (n=141) had an adjusted GM of UPCR of 1.2 g/g at baseline vs 1.2 g/g for patients who received irbesartan (n=140). The adjusted GM of UPCR at Week 36 was 0.7 g/g for FILSPARI-treated patients (n=135) vs 1.0 g/g for irbesartan-treated patients (n=128). The adjusted GMPC from baseline in UPCR at Week 36 was -45% (-51%, -38%) for the FILSPARI group vs -15% (-24%, -4%) for the irbesartan group (*P*<0.0001; ratio of adjusted GM relative to baseline [95% CI]: 0.65 [0.55, 0.77]).[1,2]

CI=confidence interval; GM=geometric mean; GMPC=geometric mean percent change; IgA=immunoglobulin A; UPCR=urine protein-to-creatinine ratio.

Learn more at FILSPARIhcp.com

INDICATIONS & USAGE

FILSPARI® (sparsentan) is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: HEPATOTOXICITY AND EMBRYO-FETAL TOXICITY

Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients and pharmacies must enroll in the program.

Hepatotoxicity

Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.

Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN.

FILSPARI should generally be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

FILSPARI can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment and one month after discontinuation of treatment with FILSPARI. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

Contraindications

Use of FILSPARI is contraindicated in patients who are pregnant. Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

Please see additional Important Safety Information on adjacent page.

Warnings and Precautions

- **Hepatotoxicity:** Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge. While no concurrent elevations in bilirubin >2-times ULN or cases of liver failure were observed in FILSPARI-treated patients, some ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and monthly for the first 12 months, then every 3 months during treatment.

  Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended.

  Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity. Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity.
- **Embryo-Fetal Toxicity:** FILSPARI can cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with FILSPARI, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.
- **FILSPARI REMS:** For all patients, FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity. Important requirements of the FILSPARI REMS program include the following:
  - Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
  - All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
  - Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

  Further information is available at www.filsparirems.com or 1-833-513-1325.
- **Hypotension:** Hypotension has been observed in patients treated with ARBs and ERAs. There was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan. In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status. If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of FILSPARI. A transient hypotensive response is not a contraindication to further dosing of FILSPARI, which can be given once blood pressure has stabilized.
- **Acute Kidney Injury:** Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause kidney injury. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.
- **Hyperkalemia:** Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease, taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.
- **Fluid Retention:** Fluid retention may occur with ERAs, and has been observed in clinical studies with FILSPARI. FILSPARI has not been evaluated in patients with heart failure. If clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or modify the dose of diuretic treatment then consider modifying the dose of FILSPARI.

Most common adverse reactions

The most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia.

Drug interactions

- **Renin-Angiotensin System (RAS) Inhibitors and ERAs:** Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren. Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).
- **Strong and Moderate CYP3A Inhibitors:** Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration. Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC which may increase the risk of FILSPARI adverse reactions.
- **Strong CYP3A Inducers:** Avoid concomitant use with a strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan C_{max} and AUC, which may reduce FILSPARI efficacy.
- **Antacids and Acid Reducing Agents:** Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI. Sparsentan exhibits pH-dependent solubility. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy.
- **Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors:** Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure.
- **CYP2B6, 2C9, and 2C19 Substrates:** Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information. Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates, which may reduce efficacy related to these substrates.
- **P-gp and BCRP Substrates:** Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI. Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates, which may increase the risk of adverse reactions related to these substrates.
- **Agents Increasing Serum Potassium:** Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

Use in specific populations

- **Pregnancy / Females and Males of Reproductive Potential:** FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy. Advise pregnant patients of the potential risk to the fetus.
  - **Pregnancy Testing:** Verify that patients who can become pregnant are not pregnant prior to initiating FILSPARI, monthly during treatment, and one month after discontinuation of treatment. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to their pregnancy and the fetus.
  - **Contraception:** Patients who can become pregnant who are using FILSPARI must use an effective method of contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI to prevent pregnancy.
- **Lactation:** Advise patients not to breastfeed during treatment with FILSPARI.
- **Hepatic Impairment:** Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C) because of the potential risk of serious liver injury.

For additional Important Safety Information, please see Brief Summary of the full Prescribing Information on the following pages, and the full Prescribing Information, including BOXED WARNING.

References: 1. FILSPARI Prescribing Information. San Diego, CA: Travere Therapeutics, Inc. **2.** Data on file; Travere Therapeutics, Inc.

TRAVERE® THERAPEUTICS

Brief Summary of full Prescribing Information for FILSPARI™ (sparsentan) tablets, for oral use

Initial U.S. Approval: 2023

INDICATIONS AND USAGE

FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on a reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

WARNING: HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients, and pharmacies must enroll in the program.

Hepatotoxicity

Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.

Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN.

FILSPARI should generally be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

FILSPARI can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment, and one month after discontinuation of treatment with FILSPARI. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

CONTRAINDICATIONS

Use of FILSPARI is contraindicated in patients who are pregnant.

Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge. While no concurrent elevations in bilirubin >2-times ULN or cases of liver failure were observed in FILSPARI-treated patients in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and monthly for the first 12 months, then every 3 months during treatment.

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended.

Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity.

Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

Based on data from animal reproduction studies, FILSPARI can cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with FILSPARI, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

FILSPARI REMS

For all patients, FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity.

Important requirements of the FILSPARI REMS include the following:

- Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
- All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
- Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

Further information is available at www.filsparirems.com or 1-833-513-1325.

Hypotension

Hypotension has been observed in patients treated with ARBs and endothelin receptor antagonists (ERAs) and was observed in clinical studies with FILSPARI. In the PROTECT trial, there was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan.

In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status.

If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of FILSPARI. A transient hypotensive response is not a contraindication to further dosing of FILSPARI, which can be given once blood pressure has stabilized.

Acute Kidney Injury

Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause acute kidney injury. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.

Hyperkalemia

Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease or taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.

Fluid Retention

Fluid retention may occur with endothelin receptor antagonists and has been observed in clinical studies with FILSPARI. FILSPARI has not been evaluated in patients with heart failure.

If clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or modify the dose of diuretic treatment then consider modifying the dose of FILSPARI.

Clinical Trials Experience

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

The safety of FILSPARI was evaluated in PROTECT (NCT03762850), a randomized, double-blind, active-controlled clinical study in adults with IgAN.

The data below reflect FILSPARI exposure in 202 patients with a median duration of 73 weeks (up to 110 weeks).

The most common adverse reactions are presented in the table below.

Adverse Reactions[1] Reported in ≥2% in Subjects Treated with FILSPARI

	FILSPARI (N = 202) n (%)	Irbesartan (N = 202) n (%)
Peripheral edema	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalemia	27 (13)	21 (10)
Anemia	10 (5)	5 (2)
Acute kidney injury	9 (4)	2 (1)
Transaminase elevations[2]	5 (2.5)	4 (2)

[1] Data presented include all Treatment-Emergent Adverse Events reported

[2] Elevations in ALT or AST >3-fold ULN reported as Adverse Events of Interest

Laboratory Tests

Initiation of FILSPARI may cause an initial small decrease in estimated glomerular filtration rate (eGFR) that occurs within the first 4 weeks of starting therapy and then stabilizes.

The incidence of a hemoglobin decrease >2 g/dL compared to baseline and below the lower limit of normal was greater for the FILSPARI arm (11%) compared to the irbesartan arm (5%). This decrease is thought to be in part due to hemodilution. There were no treatment discontinuations due to anemia or hemoglobin decrease in the PROTECT study.

DRUG INTERACTIONS

Renin-Angiotensin System (RAS) Inhibitors and ERAs

Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren.

Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).

Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration.

Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors. No FILSPARI dose adjustment is needed.

Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC, which may increase the risk of FILSPARI adverse reactions.

Strong CYP3A Inducers

Avoid concomitant use with a strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan C_{max} and AUC, which may reduce FILSPARI efficacy.

Antacids and Acid Reducing Agents

Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI. Sparsentan exhibits pH-dependent solubility. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors

Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure. These effects are usually reversible.

CYP2B6, 2C9, and 2C19 Substrates

Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information. Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates, which may reduce efficacy related to these substrates.

P-gp and BCRP Substrates

Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI. Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates, which may increase the risk of adverse reactions related to these substrates.

Agents Increasing Serum Potassium

Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy. Available data from reports of pregnancy in clinical trials with FILSPARI are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of sparsentan to pregnant rats throughout organogenesis at 10-times the maximum recommended human dose (MRHD) in mg/day caused teratogenic effects in rats, including craniofacial malformations, skeletal abnormalities, increased embryo-fetal lethality, and reduced fetal weights. Advise pregnant patients of the potential risk to the fetus.

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

Lactation

Risk Summary

There are no data on the presence of sparsentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for adverse reactions, such as hypotension in breastfed infants, advise patients not to breastfeed during treatment with FILSPARI.

Females and Males of Reproductive Potential

Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy.

Pregnancy Testing

Verify that patients who can become pregnant are not pregnant prior to initiating FILSPARI, monthly during treatment, and one month after discontinuation of treatment. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to their pregnancy and the fetus.

Contraception

Patients who can become pregnant who are using FILSPARI must use an effective method of contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI to prevent pregnancy.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in the PROTECT study of FILSPARI, 15 (7.4%) were 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C) because of the potential risk of serious liver injury.

OVERDOSAGE

There is no experience with overdose with FILSPARI. Sparsentan has been given in doses up to 1600 mg/day in healthy volunteers, or up to 400 mg/day in patients. Overdose of FILSPARI may result in decreased blood pressure. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because sparsentan is highly protein-bound.

PATIENT COUNSELING INFORMATION

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

Restricted access

Advise the patient that FILSPARI is only available through a restricted access program called the FILSPARI REMS.

As a component of the FILSPARI REMS, prescribers must review the contents of the FILSPARI Medication Guide with the patient before initiating FILSPARI.

Instruct patients that the risks associated with FILSPARI include:

Hepatotoxicity

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop taking FILSPARI and seek medical attention.

Embryo-Fetal Toxicity

Educate and counsel patients who can become pregnant about the need to use reliable methods of contraception prior to treatment with FILSPARI, during treatment and for one month after treatment discontinuation. Patients who can become pregnant must have pregnancy tests prior to treatment with FILSPARI, monthly during treatment, and one month after treatment discontinuation.

Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel patients who can become pregnant on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise patients to contact their gynecologist or healthcare provider if they want to change the form of birth control which is used to ensure that another acceptable form of birth control is selected.

Advise the patient that FILSPARI is available only from certified pharmacies that are enrolled in the FILSPARI REMS.

Patients must sign the FILSPARI REMS Patient Enrollment Form to confirm that they understand the risks of FILSPARI.

Lactation

Advise patients not to breastfeed during treatment with FILSPARI.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medications, over-the-counter drugs, vitamins/supplements, herbal products, and grapefruit.

Other Risks Associated with FILSPARI

Inform patients of other risks associated with FILSPARI, including:

- Hypotension: Advise patients to remain hydrated.
- Hyperkalemia: Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting their healthcare provider.

This information is not comprehensive. Visit FILSPARI.com or call 1-877-659-5518 to obtain the full Prescribing Information.

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TRAVERE™ THERAPEUTICS

ASN Offers Suggestions to Strengthen Proposed Kidney Transplant Model

By Rachel Nell Meyer

What would change for Americans awaiting a kidney transplant if transplant programs stood to gain—or lose—significantly more revenue based on much they increased transplant rates, if patients were informed of donor kidneys offered to them and declined on their behalf, or if the federal government graded transplant success over the long term instead of 90-day or 1-year outcomes metrics?

These are a few of the bold questions that the Center for Medicare and Medicaid Innovation (CMMI) aims to ask, test, and answer over the course of a proposed 6-year mandatory payment model for adult kidney transplant programs. CMMI—which over the last decade and under three sequential presidential administrations has increasingly aimed to improve care for people with kidney failure, particularly to incentivize greater access to transplantation—released the Increasing Organ Transplant Access (IOTA) model for public comment in May 2024 (Figure 1). ASN has long advocated for a kidney transplant-focused model at CMMI, and the hallmarks of IOTA reflect many of the key components that ASN has called for in its advocacy efforts (Figure 2).

For example, the model is largely focused on maximizing access to transplantation and ensuring that access is more equitable—ASN's maxim for transplant policy advocacy. As proposed, the model encourages transplant programs to help patients overcome root-cause socioeconomic-related barriers to transplantation and offers greater reimbursement to programs that transplant those with limited financial resources. It also emphasizes transparency for patients—a tenet of ASN advocacy—such as requiring programs to make their waitlist-acceptance criteria public and informing patients on a retrospective basis about kidneys that were declined on their behalf but successfully transplanted into other patients. The latter consideration is a phenomenon that happens more frequently than many realize. According to a previous study, candidates who died while awaiting a transplant received a median of 16 offers that were declined for them but may have ultimately been transplanted into another candidate (1). CMMI also proposed greater focus on long-term graft survival, a long-time ASN recommendation that the society encouraged CMMI to bolster even further, and increasing organ-offer acceptance rates.

Although fully supporting IOTA's aims, the society offered extensive suggestions for strengthening IOTA, with the goals of ensuring kidney transplant programs' ability to succeed in the model and enabling the model to achieve increased access to transplantation for all patients. Members of the ASN Quality Committee and the ASN Transplant Workgroup participated in an intense multiweek analysis of the proposed IOTA model to inform the society's input to CMMI. Chief among ASN's recommendations were:

1. **Set performance targets at realistically attainable thresholds for IOTA participants.** It is well documented that fewer patients receive kidney transplants than needed and that too many viable kidneys go unused, so IOTA's focus on increasing transplant rates is welcome. However, CMMI is well known for establishing "stretch" goals for its model participants. Because ASN's analysis revealed that the transplant growth rates that CMMI proposed were functionally impossible to achieve, the society developed an alternative approach to incentivizing transplant rate growth that strikes a balance between ambitiousness and attainability for kidney transplant programs. ASN also recommended that CMMI set different expectations for growth based on kidney transplant program volume.

2. **Show me the money!** Success in IOTA will require greater resources dedicated to kidney transplant programs and meaningful changes in program operation—changes unlikely to be spurred by the modest per-transplant upside ($8000) and downside ($2000) incentives that CMMI proposed. ASN recommended that CMMI increase the scale of the incentives to ensure that the model is sufficiently powered to attract attention and investment in kidney transplant programs, which will be crucial to enable achievement of IOTA's goals. Specifically, ASN recommended a $15,125 upside risk maximum and a $3750 downside risk maximum.

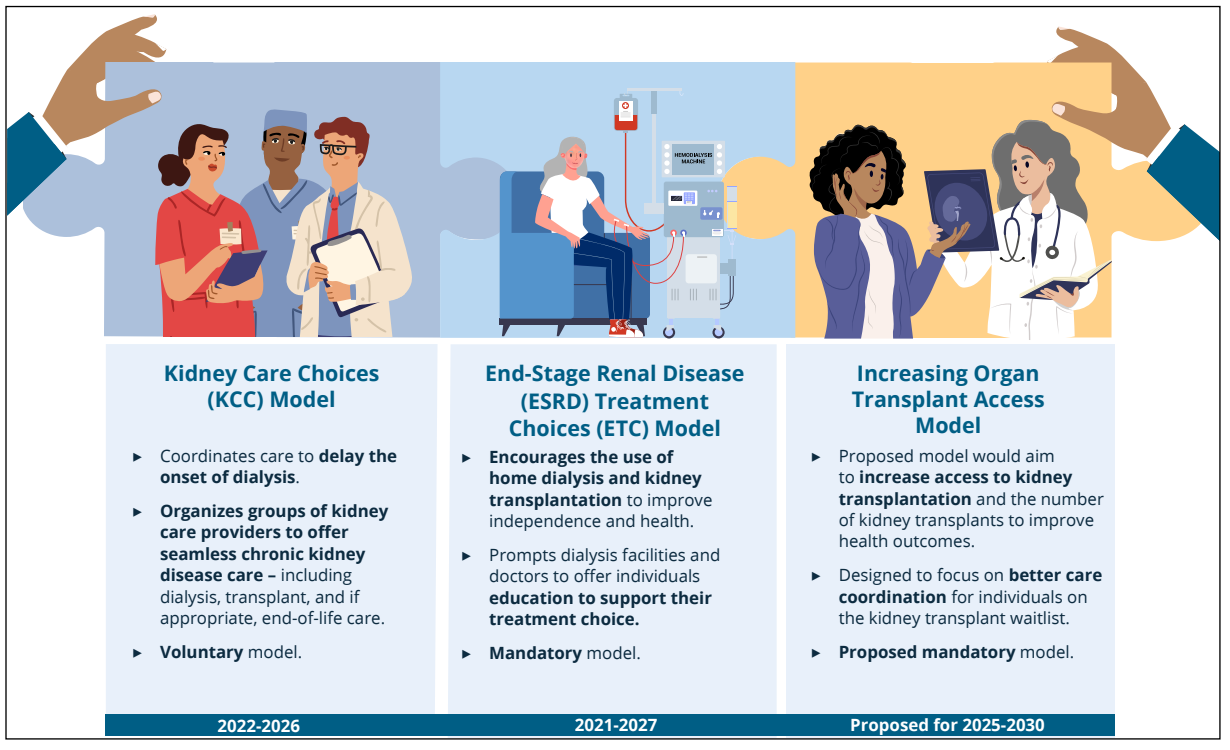
3. **Finalize health-equity boosters.** ASN strongly supported CMMI's proposal to encourage greater focus on equity in access to kidney transplantation by applying a 1.2× multiplier that boosts IOTA participants' performance scores when they successfully transplant patients who are socioeconomically limited. Building on this concept, ASN also recommended that CMMI consider additional performance score multipliers to encourage IOTA participants to make gains on other key goals related to promoting equity and avoiding organ discards:
   a) Apply the same 1.2× multiplier for patients who are socioeconomically limited to long-term outcomes as CMMI proposed applying for those patients' initial transplant.
   b) Add a multiplier to encourage appropriate use of "hard-to-place" kidneys, which are likely to accrue more cold ischemia time and experience delayed graft function regardless of organ quality.
   c) Add a multiplier to encourage more pre-emptive transplantation, which constitutes fewer than 3% of all transplants despite being optimal from clinical and cost-savings' perspectives relative to maintenance dialysis.

4. **Increase focus on long-term outcomes.** ASN and CMMI share the goals of both increasing access to kidney transplantation and improving long-term outcomes. To balance the appropriate increased emphasis proposed in IOTA on transplanting kidneys or including patients who may not be transplanted under current regulatory dynamics, as well as appropriately encouraging increased emphasis on successful long-term outcomes, ASN recommended that CMMI:
   a) Place greater weight on long-term outcomes (via a composite graft survival-rate metric over 6 years) than originally proposed.
   b) Integrate risk adjustment for at least a few variables.
   c) As noted above, apply the same 1.2× multiplier for patients who are socioeconomically limited to long-term outcomes as CMMI proposed applying for those patients' initial transplant.

5. **Fund efforts to support patients**. CMMI proposed a bevy of innovative waivers allowing IOTA to help more patients receive and keep a kidney transplant healthy in ways that the current rules do not permit, including providing in-home care, cost offsets for immunosuppressive drugs, and transportation. ASN strongly supports these concepts, which could help many patients overcome barriers to transplantation, but urged the Centers for Medicare & Medicaid Services to identify a source of funding to support IOTA participants in conducting these efforts.

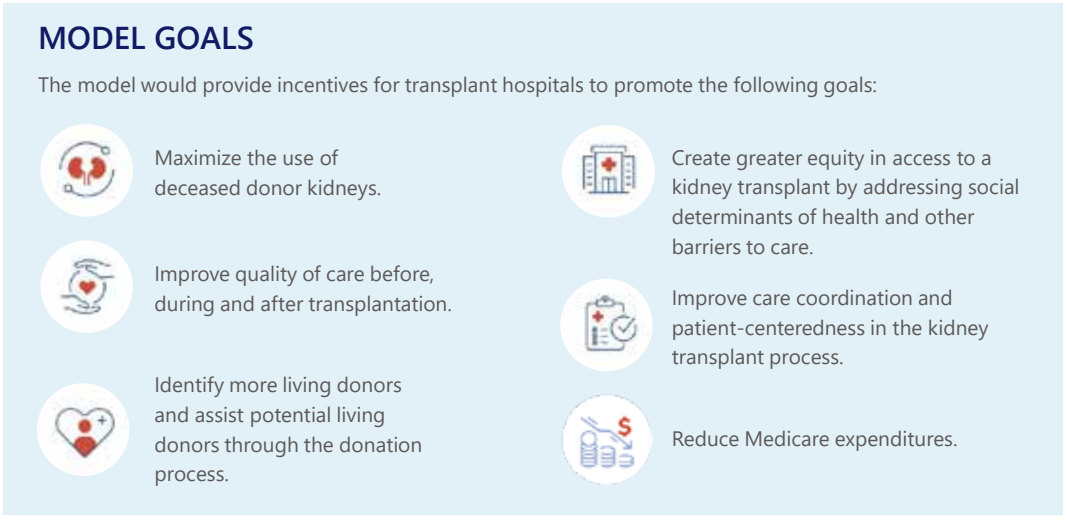
6. **Clarify covered costs.** ASN asked CMMI to affirm that pretransplant costs incurred by IOTA participants under the model, such as additional resources needed to maintain an active waitlist and providing additional support for patients to complete their evaluation, which are currently covered through the Organ Acquisition Cost Center, would also be covered under the Organ Acquisition Cost Center. This affirmation would clarify that IOTA participants have a pathway to cover many of the additional

Figure 1. The Center for Medicare and Medicaid Innovation's ongoing and proposed kidney care models



Source: Centers for Medicare & Medicaid Services. https://www.cms.gov/files/document/chronic-kidney-disease-comparison-infographic.pdf

Figure 2. The Center for Medicare and Medicaid Innovation's IOTA model goals



Source: Centers for Medicare & Medicaid Services. https://www.cms.gov/files/document/iota-model-fs.pdf

costs they incur themselves in its efforts to increase equitable access to kidney transplantation and transplant rates.

7 **Check the savings' math.** Despite the promise of IOTA to catalyze major patient-centered changes in kidney transplantation, CMMI estimated a modest additional 2625 transplants over the course of the 6-year model and less than $70 million in total savings. ASN's analysis suggests that the growth in both kidney transplants and savings to the Medicare program could be significantly greater, and the society urged CMMI to revisit the overall savings' assumptions and calculations for the model.

ASN also supported CMMI's proposal that nephrologists, nephrology practices, and dialysis facilities could elect to participate as formal IOTA "collaborators." Particularly for nephrologists, nephrology practices, and dialysis facilities participating in ongoing CMMI kidney care models, such as the Comprehensive Kidney Care Contracting pathway in the Kidney Care Choices voluntary model and End-Stage Renal Disease Treatment Choices mandatory model, collaboration with IOTA participants could align favorably to facilitate patient access to kidney transplantation in new ways.

Related, one of the most significant challenges to accomplishing ASN's and CMMI's shared goal of maximizing patient access to kidney transplantation is the shortage of transplant nephrologists and other transplant professionals—a shortage that, ironically, will worsen as the shared goal of increasing transplant rates is attained. In many areas, post-transplant care and the model's success will be dependent on IOTA participants engaging general nephrologists as key IOTA collaborators. ASN offered several recommendations to bolster general nephrology participation in transplant care for CMMI's consideration:

- Create, within IOTA, a Monthly Capitated Payment for post-transplant care. With a secure, regular revenue stream for post-transplant care, as there is in dialysis care, community nephrologists may engage more readily in the care of these patients.
- Establish a relative value unit adjustment for the care of transplant patients in the model regardless of the nephrologist type (e.g., transplant or general nephrologist).
- Increase resources for IOTA participants to support more robust, longer-term post-transplant care coordination with general nephrology partners for patients who are referred back to the transplant center.

CMMI will likely release a final rule regarding IOTA and responding to ASN and other commentators' input in late fall or early winter. If finalized, the model could take effect as early as January 2025, although ASN and many other commentators recommended a later start date to give IOTA participants and their hospitals and health systems ample time to tee themselves up for success. In the meantime, ASN will continue to advocate across the Department of Health and Human Services and on Capitol Hill in support of increased patient access to transplantation, advances in equity in kidney transplant, and greater transparency for patients across the kidney transplant journey. ■

Rachel Nell Meyer is the strategic policy advisor to the executive vice president at ASN.

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Patient-Centered Innovation Needed in Transplant

By Bridget M. Kuehn

Katie Hallum, 22, was just 18 years old when she was diagnosed with immunoglobulin A nephropathy. One and a half years later, she crashed into kidney failure and underwent dialysis. However, with a kidney transplant from a stranger who Hallum met on TikTok roughly 1 year ago, she got a new lease on life. She recently graduated from The University of Oklahoma and became a full-time Indigenous Affairs reporter for the National Public Radio Member Station KOSU in central Oklahoma.

"I was going to get up here and tell you how 'cushy' my life has been [since the transplant]," Hallum said during the June Kidney Innovation Conference in Washington, DC. "But then I thought, no, I'll tell you the true story."

Like many transplant recipients who participated in the conference, which was sponsored by the Kidney Health Initiative, the Kidney Innovation Accelerator (KidneyX), and KidneyCure, Hallum highlighted some of the ways that having a transplant has improved her life. But she and other speakers also drew attention to ongoing challenges and the need for patient-centered innovation to help patients navigate the emotional, clinical, and other challenges of living with a transplant.

"My hope is that, starting with the conversations we are having today, we can build on the hopes and dreams of Katie and thousands like her, not only in the United States but elsewhere in the world," said Ogo Egbuna, MD, MSc, FASN, a transplant nephrologist working at Vertex Pharmaceuticals and a member of the Kidney Health Initiative's Board of Directors. Egbuna moderated a session at the conference focusing on kidney transplant innovation.

"The fight's not over"

Hallum remembers following a strict routine while she was on dialysis, but since her transplant, she has been surprised to find herself suddenly being disorganized, showing up late, or procrastinating. When she spoke with her nephrologist about it, he suggested that perhaps she was now able to act like a 22 year old. Hallum said that she was put off by the suggestion. But a post-transplant comment from a former boyfriend, who knew her when she underwent dialysis, helped her realize the emotional toll her condition had taken on her.

"He said, 'Your words have meaning now,'" she shared. "He said [that] when we dated, 'You would tell me things like you feel happy and are grateful to be alive, that nothing ever gets you down. I could see that you only *thought* you believed those things, but now you mean them.'"

After the conversation, Hallum cried for the first time post-transplant. "I was like, 'I don't know who I am anymore, but I know who I am going to be,'" she said, citing her recent graduation, new job, and law school application.

Yet, despite the benefits of her transplant, she noted the ongoing demands of her care. Instead of frequent dialysis adjustments, she now faces frequent magnetic resonance imaging procedures when something is wrong, computed tomography scans for headaches, bone density tests, and cancer screenings. "The fight's not over," she said. "I've switched from seeing a dialysis doctor to seeing a transplant nephrologist. I have always hoped that there would be one day [when] I don't have to worry about getting some weird cancer from my immunosuppressive, and I don't have to worry about my immunoglobulin A nephropathy coming back, which you all know will eventually happen."

Hallum shared that she is tired of worrying about protein numbers or that getting sick will harm her kidneys. She is also exasperated by medication alarms. Hallum, who enjoys figure skating, has also had to worry about falls because some of her medications have precipitated osteoporosis. "I'm glad I'm young because I hope that one day, there's some sort of innovation in the transplant field that makes sure my words [about how I am doing] forever hold meaning," she reflected.

Medication misadventures

Hallum is certainly not alone in her frustration. Anne Rohall-Andrade, JD, a health care attorney and disability advocate, donated one of her kidneys to her then-13-year-old daughter. Her daughter, now age 18, had developed kidney disease, cerebral palsy, and a seizure disorder as a result of an extremely premature birth at 24 weeks gestation due to twin-to-twin transfusion syndrome, a condition in which one twin is deprived of fluids due to a problem with the placenta.

"My daughter is in that place where she's transitioning from being a little kid to going off to college," Rohall-Andrade said. "Many of you who are caregivers or parents probably understand that is a tough transition for any kid, but especially a kid with chronic illness."

Rohall-Andrade called for medication innovations. She noted that her daughter's tacrolimus (Prograf) and mycophenolate are her "frenemies" and require strict adherence to schedules. Whereas birth control or diabetes medications can be administered through a patch or other devices, Rohall-Andrade said that her daughter wonders why post-transplant regimens cannot be delivered similarly.

At the time of her presentation, Rohall-Andrade's daughter was in an intensive care unit but had urged her not to cancel her talk. Her daughter had been rushed to an emergency department during an episode of low blood pressure caused by a medication titration problem. The ordeal turned into days in an intensive care unit undergoing tests for sepsis, despite Rohall-Andrade sharing her concerns that her daughter's two blood pressure medications coupled with a 10-pound weight loss might be the root of the problem.

"Doctors need to listen to parents and patients," she said. She argued that there also needs to be better coordination between emergency departments and transplant nephrologists and their interoperability with electronic health records. Rohall-Andrade

noted that her daughter was admitted to the emergency department in the nearest hospital, which did not have access to her electronic health records. Rohall-Andrade had to call her daughter's pediatric nephrology transplant team and urge the hospital's nephrologists treating her daughter to talk with the team to get up to speed on her care.

Hallum would also like more tolerable drug regimens with fewer side effects. Hallum explained that she was being treated with the lowest possible dose of Prograf. Her body still reacts poorly, and she has variable blood levels of the drug. She would also like to stop taking mycophenolic acid (Myfortic), which has contributed to difficulties with keeping food down and low body weight—she was just 83 pounds when she left the hospital post-transplant. She said that her doctors have tried to manage her side effects with very low doses, switching to other medications, or adding new ones. "I wish that instead of throwing more pills at the side effects caused by these immunosuppressants, we could kind of get to the bottom of why they cause side effects," Hallum said.

Living donor support

As a living donor herself, Rohall-Andrade remarked that living donors need better, clearer information. She noted that most donors hear about better outcomes for recipients from living donors as well as potential standard surgical risks, like bleeding or anesthesia problems. However, donors receive little information about their long-term prognosis.

Most living donors are very healthy because of the screening involved, and most do well, she said. However, Rohall-Andrade noted few studies of long-term health for living donors. An informal survey that she conducted of 75 living donors in two online support groups found that many living donors get mixed messages about their need for long-term follow-up care. Half of the respondents reported that the transplant team told them that seeing a primary care physician and undergoing laboratory tests (blood, urine, and other fluids) was good enough for their follow-up care. The other half said that the team advised them to see a nephrologist. Many respondents also reported a lack of information on their long-term health. "I'm in many, many support groups for living donors, and I hear the same concerns and questions from these donors post-donation," Rohall-Andrade said.

Many living donors, especially those who are altruistic, reported being ostracized by their families, who do not understand why they would take the risk of being a donor. Survey respondents also reported impacts on their mental health. Some reported a temporary sense of loss after the donation. They may be upset if their recipient does not take care of the allograft. For example, Rohall-Andrade described donors who have been devastated when their recipient developed an alcohol addiction or was not being compliant with their medications. "There is incredible grief when a donor, particularly [a donor who is altruistic], finds out that the kidney recipient isn't taking care of their body," she said.

Although only five of the surveyed donors said that they regretted the decision, respondents noted financial hardships caused by the need to take time off of work, a temporary loss of the ability to care for children or aged parents, and the need for loved ones to take time off of work to care for the donor. "There are a lot of challenges that need to be addressed," Rohall-Andrade said. She noted that it can be particularly challenging when a parent of the pediatric transplant recipient is the donor and the child's primary caregiver, as she is.

"We've allowed ourselves as clinicians and surgeons to accept what we have. We as a transplant [community] have accepted that level, and we lost sight of 5- and 10-year outcomes."

Roslyn Mannon, MD, FASN, chair of ASN's Policy and Advocacy Committee and a professor in the Division of Nephrology at the University of Nebraska, cited two pieces of legislation making their way through the US Congress that may help address some financial challenges for donors. One is the Living Donor Protection Act (1), which would prevent health, life, and disability insurance discrimination against donors and specifies that they are eligible for job-protected medical leave. The other is the Honor Our Living Donors Act (2, 3), which would expand the number of donors who qualify for wage, travel, or caregiver reimbursement. "We are so close, and I'm so appreciative of all the representatives who have helped move this forward," Mannon said.

Stalled clinical innovation

Egbuna noted huge strides in understanding the immune response to transplant and advances in the development of small molecules, diagnostics, and biologics, yet these have not yet translated into improved allograft recipient survival. Mannon blamed complacency in the field, which has reached close to 100% graft and patient survival in the short term. "We've allowed ourselves as clinicians and surgeons to accept what we have," she said. "We as a transplant [community] have accepted that level, and we lost sight of 5- and 10-year outcomes."

As a result, the field has stuck with the trio of corticosteroids, antimetabolite immunosuppressants, and calcineurin inhibitors that helped dramatically improve outcomes. However, this triad comes with significant "baggage" for recipients, such as neurologic problems, gastrointestinal disruption, and long-term toxicity, Mannon said.

She noted a shortage in clinical trials of new biologics or other drugs for transplant recipients and highlighted financial and other disincentives to such research for drug companies. She suggested that the lack of new US Food and Drug Administration (FDA)-approved surrogate endpoints, patient-centered outcome targets for transplant trials, and low uptake of some newer transplant drugs are contributors. "It's really ourselves, the industry, and the FDA. We're all kind of complicit in how we got here," Mannon said.

Mannon noted that there are currently unmet needs among transplant recipients for antivirals to treat the BK virus and for therapies to treat antibody-mediated organ rejection. She also stated that among transplant patients who die, many have functioning allografts but have other conditions like diabetes or cardiovascular disease that may be exacerbated by immunosuppression. She argued that artificial intelligence or other tools could be used to identify the best deceased donor organ matches, assess patients' risk profile post-transplant, and help optimize medication regimens.

Egbuna noted that dramatic advances have been made in HIV care that improve patients' quality of life, such as long-acting injectables that reduce the frequency of drug administration. We need similar advances in the transplant field, he suggested. "It is not just a new drug that gets approved but something that makes a difference in [patient] quality of life," he said. ■

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More Frequent Dialysis in SNFs Hastens Home Discharge

Among patients with kidney failure in skilled nursing facilities (SNFs), performing on-site more frequent dialysis (MFD) may lead to faster discharge to home, suggests a study in the open-access journal *Kidney360*.

The retrospective-prospective observational study included all patients with kidney failure newly admitted to an on-site dialysis service at 195 SNFs across 12 states. Analyses focused on the outcomes of MFD— targeting 14 hours of treatment over five sessions per week— compared with conventional, three-times-weekly dialysis. A 90-day cumulative incidence of home discharge was compared between groups, along with safety issues related to competing risks of hospitalization and death.

The analysis included 10,246 MFD episodes and 3451 conventional dialysis episodes. Patients receiving MFD had a higher mean age and were "consistently sicker" than those receiving conventional dialysis, with a first systolic blood pressure in more patients; lower hemoglobin and iron saturation; increased comorbidity; and higher rates of complicated diabetes, cerebrovascular disease, and congestive heart failure.

Despite these adverse characteristics, patients receiving MFD were more likely to be discharged to home within 42 days: 17.5% compared with 14% for those receiving conventional dialysis. Safety outcomes were similar between groups, with no increase in hospitalization or mortality.

The authors previously reported beneficial effects of MFD among patients with kidney failure at SNFs within a national service organization. The new study is the first, to our knowledge, to assess "hard outcomes" of MFD in SNF settings, focusing on early home discharge.

The observational data suggest an increase in timely home discharge among patients receiving MFD, despite their poorer health status, compared with those receiving conventional dialysis. If the findings are borne out by further study, the researchers conclude: "MFD in the SNF in coordination with hospital information transfer [may allow] for acceptance of [patients who are sicker] into the SNF, presumably permitting earlier hospital discharge, while also hastening SNF discharge to home" [Bellin EY, et al. On-site more frequent dialysis may hasten return home for nursing home end-stage renal disease patients. *Kidney360*, published online June 7, 2024. doi: 10.34067/KID.0000000000000487].

High Rates and Impact of Acute Kidney Damage in the Community

Episodes of acute kidney damage (AKD) are common in the community and may contribute to the development of chronic kidney disease (CKD), reports a study in *Nephrology Dialysis Transplantation*.

Using health care data from the Valencian Community in Spain from 2012 through 2016, the researchers identified more than 1.8 million community-dwelling adults (older than 23 years) with at least two serum creatinine measurements. Harmonized Kidney Disease: Improving Global Outcomes criteria were used to identify episodes of AKD, acute kidney injury (AKI), and CKD. AKD was defined as abnormalities of kidney structure and function present for less than 3 months. Changes in renal function and mortality were assessed, including the risk of developing CKD after recovery from AKD or AKI and the risk of declining kidney function in patients with previous CKD.

During 4.8 years of follow-up, 47,972 patients experienced a total of 56,850 episodes of AKD. The annual incidence rate was 4.3 per 1000 patients in patients without CKD and 12.56 per 1000 patients in those with previous CKD. Second episodes of AKD occurred in 10.3% of the group without CKD and in 18.4% of patients with CKD. Among patients with AKD, an annual incidence of AKI was 0.41 in patients without CKD versus 2.81 per 1000 patients with CKD.

CKD developed in 43.8% of patients with AKD who were initially free of CKD.

Among those with previous CKD, 63.1% had disease progression (greater than 50% decline in estimated glomerular filtration rate). Factors associated with progression to CKD included the following: female sex, older age, overweight or obesity, and heart failure. The same factors were associated with progression of previous CKD, with a further effect of number of AKD episodes.

Of patients with episodes of AKI, 12.7% progressed to CKD, whereas 43.2% of those with previous CKD had disease progression (greater than 20% decline in estimated glomerular filtration rate). Overall, death occurred within 3 months of an episode of AKD in 7% of patients and within 3 months of an episode of AKI in 30.1%.

AKD is a recognized concern in hospitalized patients or among those who require hospitalization for various causes. Less is known about the occurrence and consequences of AKD in the community.

These data from Spain suggest that based on acute elevations of serum creatinine, AKD is common among community-dwelling adults and may contribute to the development or progression of CKD. "Patients meeting criteria for AKD in the community may not always require hospital admission, but a careful review of clinical circumstances, avoidable risk factors, and follow-up is still warranted," the researchers write [Diaz J, et al. The impact of acute kidney damage in the community. *Nephrol Dial Transpl*, published online July 24, 2024. doi: 10.1093/ndt/gfae175]. ■

Hemodiafiltration Shows HRQoL Benefit Compared With Hemodialysis

High-dose hemodiafiltration (HDF) compared with hemodialysis slows the decline in several domains of health-related quality of life (HRQoL) in patients with end stage chronic kidney disease, reports a paper in *Kidney International*.

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Hemodiafiltration Shows HRQoL Benefit

Continued from page 23

The researchers present data from the CONVINCE (the comparison of high-dose HDF with high-flux HD [hemodialysis]) trial, a randomized, open-label clinical trial comparing the outcomes of high-dose HDF versus high-flux hemodialysis. In a study from last year, a significant reduction in all-cause mortality among patients assigned to HDF (17.3%) compared with those receiving hemodialysis (21.9%) was found.

The secondary analysis included state-of-the-art HRQoL assessment, drawn from the Patient-Reported Outcomes Measurement Information System. Responses were received from 541 patients with dialysis-dependent chronic kidney disease. Patients were observed for a median of 30 months.

The HDF and hemodialysis groups both showed a "small to modest" deterioration in HRQoL. Across all eight domains, patients receiving HDF had a slower rate of decline in HRQoL. The strongest effect was noted in the domain of cognitive function, with a score difference of 2.95. Social participation and physical function showed score differences of 1.65 and 1.20, respectively.

Estimated change in overall physical health was −1.19 with HDF versus −1.65 with hemodialysis. High-dose HDF was associated with a slower decline in cognitive function compared with hemodialysis: −0.49 versus −1.05. Trends in anxiety and depression scores were similar between groups.

Previous studies of the HRQoL effects of HDF versus hemodialysis have yielded inconclusive results. This secondary analysis of CONVINCE data finds "a consistent pattern of positive effects" for patients assigned to HDF. The findings suggest that HDF slows the rate of decline in physical and social components of HRQoL—particularly on cognitive function—and that these effects become more prominent over time. The authors discuss their findings in light of the previous mixed results on HRQoL outcomes with HDF [Rose M, et al. The CONVINCE randomized trial found positive effects on quality of life for patients with chronic kidney disease treated with hemodiafiltration. *Kidney Int*, published online July 30, 2024. doi: 10.1016/j.kint.2024.07.014]. ■

Pruritus Linked to Increases in Adverse Outcomes for Patients on Dialysis

Pruritus is present in one-third of patients receiving maintenance dialysis and is associated with increased rates of several adverse health outcomes, reports a study in the *American Journal of Kidney Diseases*.

The researchers assessed the burden of pruritus in 3281 patients receiving hemodialysis or peritoneal dialysis in Stockholm, Sweden, between 2005 and 2021. Two-thirds of patients were men; the median age was 64 years. Rates of clinically recognized pruritus were assessed, based on diagnostic codes or prescription of pruritus treatments, including ultraviolet therapy. Patient factors associated with prevalent or incident pruritus were analyzed. The study also examined associations with clinical outcomes including mortality, severe infections, anxiety or depression, and sleep disorders.

Pruritus was present at baseline in 13.9% of patients and developed during follow-up (median, 3.3 years) in an additional 19.1%. Period prevalence was higher in patients receiving hemodialysis (36.0%) compared with peritoneal dialysis (26.4%). Most cases were identified through initiation of pruritus treatments rather than diagnostic codes.

A wide rate of patient and clinical factors was linked to pruritus, including older age; female sex; lower serum albumin; and higher C-reactive protein, serum calcium, and serum phosphorus. Patients with pruritus were more likely to have sleep disorders (hazard ratio [HR], 1.96) and anxiety or depression (HR, 1.56). Pruritus was also associated with a significant increase in hospitalizations for severe infections (HR, 1.36), mainly reflecting higher rates of sepsis and peritonitis in patients undergoing peritoneal dialysis. There was no association with all-cause mortality.

Although pruritus is common in patients on dialysis, the overall burden of this complication and its impact on clinical outcomes remain unclear. The new analysis finds evidence of pruritus in 33% of patients on maintenance dialysis, consistent with the range reported in previous studies.

The study identifies clinical risk factors associated with pruritus and associations with certain adverse outcomes, although not with mortality. The researchers conclude, "Individualized clinical management to prevent and to treat this burdensome uremic symptom might significantly improve patients' quality of life and potentially health outcomes" [Faucon A-L, et al. Burden of CKD-associated pruritus and adverse clinical outcomes in patients receiving dialysis: The Stockholm CREAtinine Measurements (SCREAM) project. *Am J Kidney Dis*, published online July 25, 2024. doi: 10.1053/j.ajkd.2024.05.013]. ■

Does Saving the Kidneys Mean Risking the Eyes?

By Cindy X. Cai, Ian C. Han, and Jia Hwei Ng

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) such as semaglutide have been a breakthrough therapy for many patients with type 2 diabetes and/or obesity. Beyond weight loss and improved glucose control, GLP-1 RAs can lower the rate of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (1). Moreover, a recent study has shown that semaglutide reduced the risk of adverse kidney outcomes and death from cardiovascular causes in patients with chronic kidney disease, with outcome events being 24% lower in the semaglutide group than in the placebo group (2). Additionally, the mean annual estimated glomerular filtration rate decrease was slower by 1.16 mL/min/1.73 m^2 in the semaglutide group.

Recently, however, concern has arisen regarding the negative consequences of GLP-1 RAs for the eyes. For example, in SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes), those receiving semaglutide had significantly higher rates of retinopathy-related complications, including vitreous hemorrhage and diabetes-related blindness, and were more likely to require ocular treatment such as intravitreal injections or pan-retinal photocoagulation (1). A recent study linked semaglutide with a rare and potentially blinding eye condition known as nonarteritic anterior ischemic optic neuropathy (NAION) (3).

In the ophthalmic community, there is ongoing debate regarding the best response to these emerging data. The increased rates of diabetic retinopathy complications are not surprising. For example, the phenomenon of initial worsening of retinopathy with intense glucose control has been known since the 1980s from the landmark Diabetes Control and Complications Trial among patients with type 1 diabetes mellitus (4). Also, the paradoxical worsening with improved glucose control may not be overly concerning given the effectiveness of available treatments—appropriate and timely treatment of vision-threatening diabetic retinopathy reduces the risk of blindness by more than 90% (5). Furthermore, the finding of an increased rate of diabetic retinopathy complications has not been replicated in larger retrospective studies of semaglutide (6).

More worrisome, perhaps, is the recent article suggesting a potential association with semaglutide and NAION (3). NAION is a rare ischemic injury to the optic nerve affecting 2–10 per 100,000 people per year and resulting in blindness in nearly one-quarter of affected patients (7, 8). Unlike complications of diabetic retinopathy, there are no reliable treatments to restore vision loss from NAION (9). The potential association between semaglutide and NAION, however, requires more investigation. Notably, the recent study had many limitations, including its potential for inclusion bias (i.e., only patients referred to a subspecialty neuro-ophthalmology clinic at a tertiary care hospital were analyzed) and its use of relatively small numbers for comparison (17 patients with NAION on semaglutide versus 6 in the comparison group). The authors are also quick to note that demonstrating a potential association does not prove causality, especially in the absence of a clear mechanism. A larger, retrospective, multicenter population-based cohort study, for example, via the Observational Health Data Sciences and Informatics network (10), is needed to provide further clarity on this controversy.

Nephrologists should be aware of these potential eye issues with GLP-1 RAs. Until further data are available, nephrologists should continue prescribing GLP-1 RAs, but cautiously, and also should ensure that their patients are up to date with recommended ophthalmic screenings and have proper access to ophthalmic care. ■

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The authors report no conflicts of interest.

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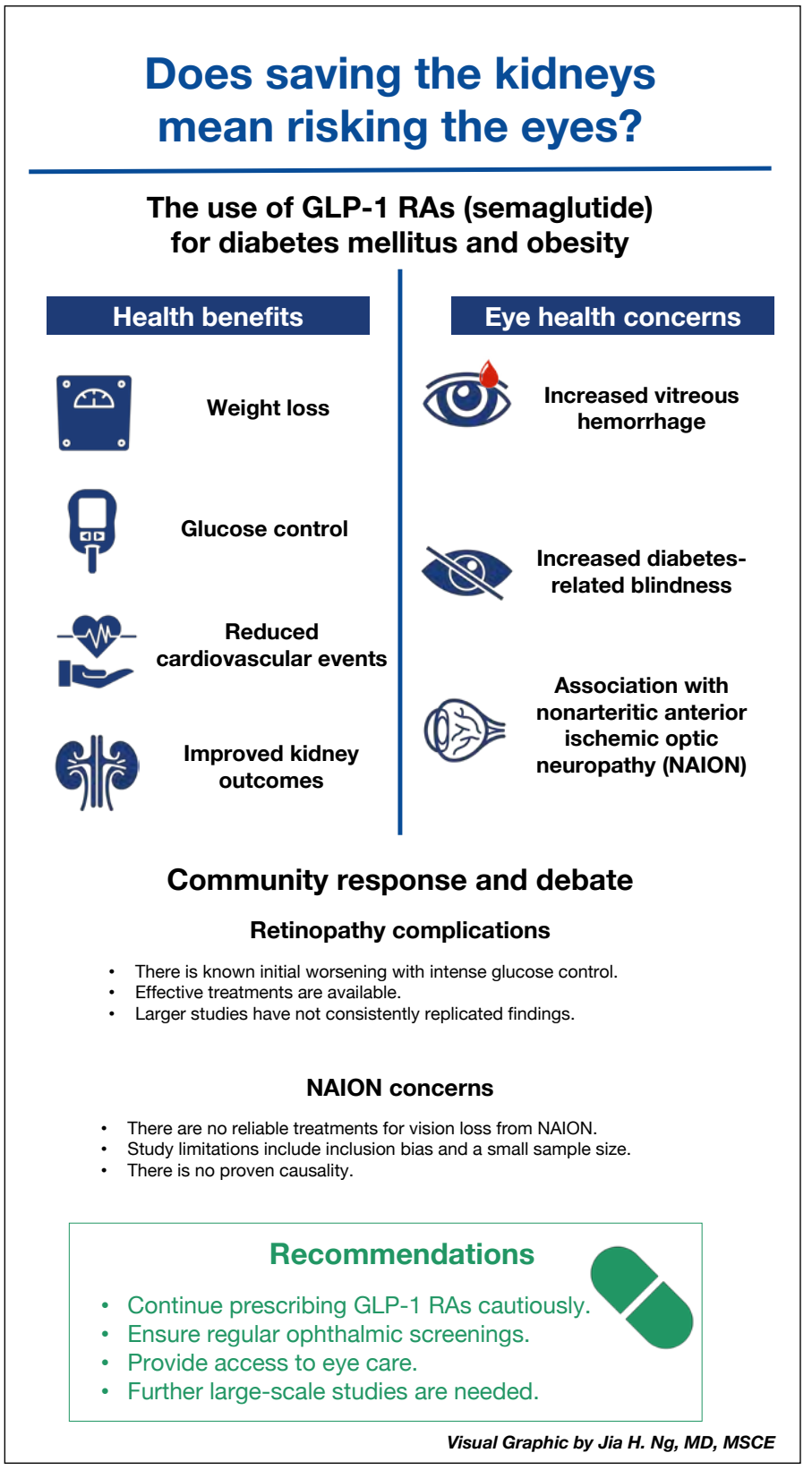

Targeting the PI3Kα Pathway to Treat Proliferative Glomerulonephritis

By Abbal Koirala, Bryan Chang, and Duvuru Geetha

Glomerular diseases cause 15% of kidney failure, disproportionately affecting African American and Hispanic populations (1). Effective therapies to slow disease progression are urgently needed.

Phosphoinositide 3-kinase (PI3K)α, a lipid kinase, is stimulated by various signals such as cytokines, growth factors, and immune signals (2). This activation leads to the recruitment of 3-phosphoinositide-dependent protein kinase 1, which phosphorylates AKT at the T308 residue (3). Consequently, the mammalian target of rapamycin (mTOR) is activated, initiating signaling pathways in cell proliferation, motility, survival, and metabolism in podocytes and lymphocytes (4). Dysregulation of this pathway has been linked to glomerular diseases in both human and mouse models (5).

Recently published in *The Journal of Clinical Investigation*, Yamaguchi and colleagues reported a significant discovery related to glomerular disease and its progression to kidney failure (6). Researchers found that a somatic PI3Kα mutation causes proliferative glomerulonephritis. Using mouse models, single-cell RNA sequencing, and spatial transcriptomics, they showed that this mutation promotes podocyte proliferation, dedifferentiation, and inflammation through the activation of the AKT/mTOR pathway (Figure). These findings suggest that this pathway is a potential therapeutic target for proliferative glomerulonephritis.

Researchers demonstrated that alpelisib, a PI3Kα inhibitor, can ameliorate glomerular lesions and improve kidney function in mouse models of proliferative glomerulonephritis and lupus nephritis by targeting podocytes. Interestingly, alpelisib modulates T and B lymphocytes, reducing proinflammatory cytokines, autoantibodies, and glomerular complement deposition in lupus nephritis models. These findings are significant because PI3Kδ, not PI3Kα, is predominantly expressed in lymphocytes. Similar effects were observed in human lymphocytes from patients with lupus nephritis.

Besides apolipoprotein L1 (*APOL1*) high-risk variants, collapsing glomerulopathy can be caused by other factors, such as idiopathic causes, ischemia, and bisphosphonate toxicity. Given the unique nature of *APOL1*-associated collapsing glomerulopathy and the emergence of promising therapeutic interventions (7), the authors of a recent article have uncovered the potential role of alpelisib in reversing glomerular lesions in non-*APOL1*-mediated collapsing glomerulopathy. This should be further tested in a clinical trial setting.

This research by Yamaguchi et al. (6) suggests that PI3Kα inhibition is a potential therapeutic strategy for glomerular disease. Further investigations are warranted to validate these findings in clinical trials and to assess the long-term efficacy and safety of PI3Kα inhibitors in patients with glomerular disease. ■

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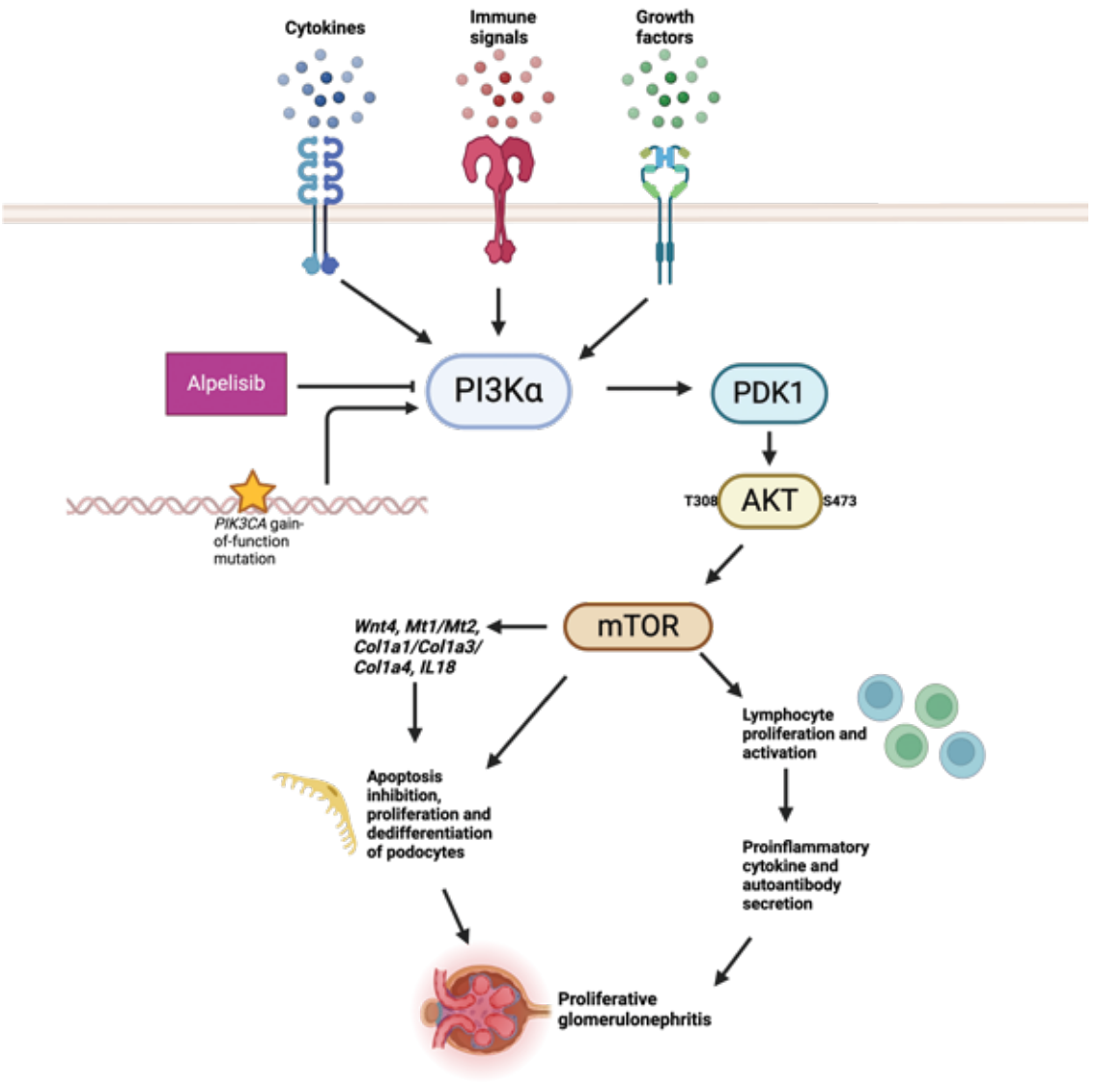
Drs. Koirala and Chang report no conflicts of interest. Dr. Geetha reports serving as a consultant to Amgen, Calliditas, Vera Therapeutics, GSK, and Sana Biotechnology.

Figure. PI3Kα pathway



Activation of PI3Kα has multiple downstream effects contributing to proliferative glomerulonephritis. These effects may be inhibited by alpelisib, a PI3Kα inhibitor.
PDK1, 3-phosphoinositide-dependent protein kinase 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha. Figure created with BioRender.com.

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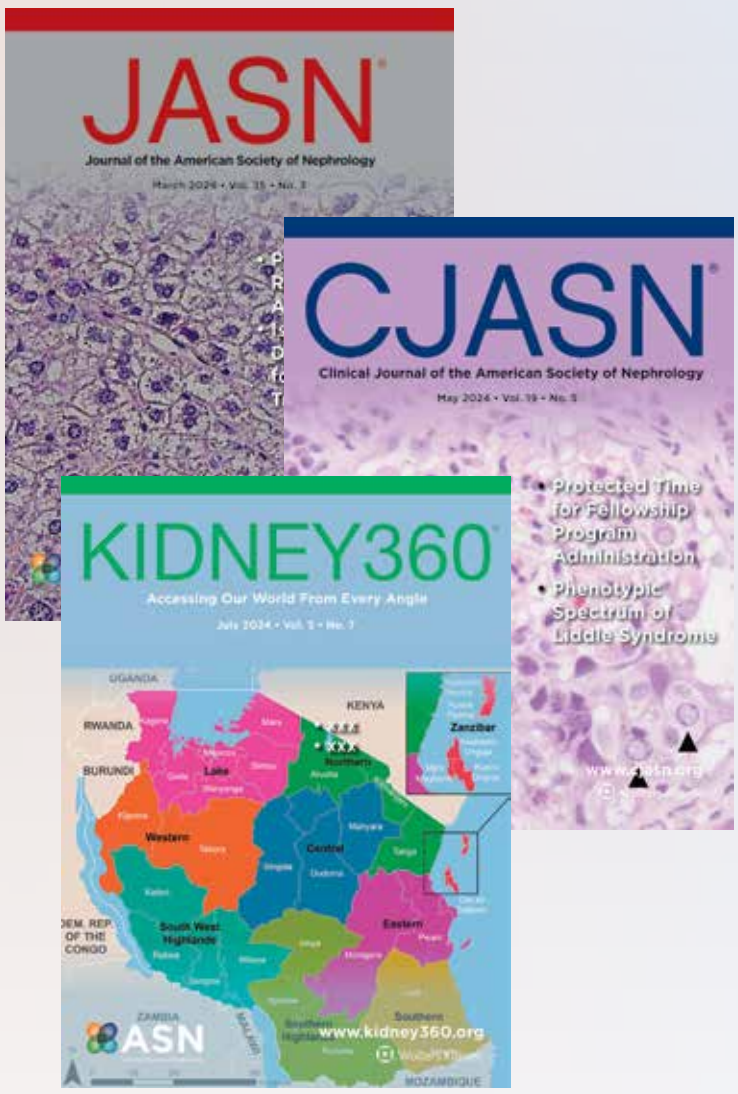

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Increasing Access to Innovation

ASN President Crews Outlines Path to Equity in Kidney Research

By Bridget M. Kuehn

To achieve equity in kidney care, the field of nephrology must help remove barriers to research participation and improve access to care innovations for those who are disproportionately affected by kidney diseases, said ASN President Deidra C. Crews, MD, ScM, MS, FASN, at the Kidney Innovation Conference in June.

The meeting, hosted by the Kidney Health Initiative, the Kidney Innovation Accelerator (KidneyX), and KidneyCure, brought together nephrologists, researchers, patients, industry representatives, and regulators to help advance innovation in kidney care. Crews, a professor of medicine at Johns Hopkins University School of Medicine in Baltimore, MD, and deputy director of the Johns Hopkins Center for Healthy Equity, shared her experience as a researcher focused on addressing the adverse social determinants of health that drive disparities in hypertension and kidney health.

Approximately 9 in 10 people with kidney diseases are unaware of their condition, and awareness tends to be lowest among some populations who have a high risk of poor outcomes, Crews explained during her talk. The groups that are impacted by health disparities, including kidney health disparities, are "individuals who systematically have experienced greater obstacles to their health based on things like their racial or ethnic group, their socioeconomic status, their gender identity, their physical ability status, their sexual orientation, or any other characteristic that has been historically linked to either discrimination or exclusion," she said.

"These are the very same ones [who] tend to face barriers to accessing health-related innovations," Crews continued. For example, they may miss out on the opportunity to participate in research or to benefit from the latest therapies due to a range of barriers.

Breaking down barriers

Crews expressed that health disparities are both inhumane and costly. Health disparities in the United States are on track to cost the nation an estimated $1.2 trillion annually by 2040 (1). Advanced kidney disease is a major contributor to those costs. "There is a great need for innovation, both for the health benefits [to individuals affected by health disparities] and because of cost considerations," she explained.

She noted that the roots of those disparities often begin early in care. For example, Asian, Black, and Hispanic individuals are more likely to have delayed referrals to nephrologists. That denies individuals early identification and treatment of their condition. This behavior also cuts off these communities' access to clinical trial participation and newer therapies, which may only be available through a nephrologist.

Groups disproportionately affected by kidney diseases may also have competing responsibilities like childcare or work schedules or physical challenges that make getting to a nephrology clinic or participating in study visits difficult, Crews noted.

Mistrust of researchers or health professionals is often cited as another barrier to research participation. However, Crews suggested reframing that discussion by recognizing that people's experiences with health care and other institutions are a driving factor. "It is really fear of unfair treatment," she said. "In many cases, [individuals from populations underrepresented in research] have had negative, unfair, and unjust experiences with various institutions. They may carry over that experience into research settings, which may inform their willingness even to accept an invitation to be a part of research."

Another challenge that often stems from poor access to specialist care or to primary care for kidney diseases is a lack of access to information about research or care innovations. "These [groups that are socially marginalized] may have not received that sort of information," she said. "It may not have been presented to them in a way [that] they can understand and interpret."

Too often, researchers wait until late in the study development process to engage the patients who are most likely to benefit from the intervention, Crews reflected. "We should begin with [patients from populations that are socially marginalized] because they are going to be most likely to benefit because they are the ones most likely to have progression of their disease," she said.

She described how investigators from groups that are socially marginalized are more likely to understand the concerns faced by people in their communities and be motivated and skilled in engaging those populations. However, the limited number of investigators from these groups is a real barrier. "Programs that work to support and expand the pool of these investigators are critically important," she said.

Early engagement is key

According to Crews, it is vital to engage people from groups that are marginalized in research early in the development of research protocols. Such engagement increases transparency in the research process. "It helps to build trust with those individuals when they've been invited to be part of the process," she said. "It may lead them to feel [that] they can trust both the process and the findings of that work on the back end." Crews took it a step further, emphasizing that it is essential to treat these individuals as true partners. "They have knowledge; they have experience that is going to help us shape the work we are doing," she said.

It is important to engage study team members who share identities with the populations participating in the study. "That really does help to foster trust," she said. Also key are good communication and meeting people where they are.

"It's important to ensure we partner with various individuals to help us format the information that we are sharing in a way that people with low health literacy or limited English proficiency can actually understand," she said. Helping patients overcome barriers to transportation, or providing flexible scheduling for study visits is also essential.

Additionally, untraditional recruitment venues such as community screenings or social media should be used to identify individuals who may not currently be receiving care for their conditions. Crews recommended providing diagnostic and educational information to prospective participants who discover through the study screening process that they have kidney diseases.

Crews also recommended outreach to community members and organizations to identify potential study participants and leveraging peer networks for recruitment. For example, Crews and her colleagues designed the Five, Plus Nuts and Beans for Kidneys trial to address real-world obstacles to healthy eating, such as poor neighborhood access to healthy food options, among Black people with early stages of chronic kidney disease (2). The researchers wanted to test whether nutritional advice on the Dietary Approaches to Stop Hypertension diet plus $30 per week worth of potassium-rich foods would reduce albuminuria and improve participants' blood pressure compared with a control group that received only a gift card for groceries.

Early in the trial development, Crews and her colleagues engaged with a local grocer and community-based groups for input on study design. They also established a community advisory board. In addition to working with the board while preparing the grant application and protocol development, the board recommended tactics to encourage participation such as the gift card for the control group. They also recruited participants from primary care clinics serving patients with limited incomes, provided participants with information on chronic kidney disease, and provided flexible scheduling and transportation to study visits. The study team sent frequent communications, holiday cards, and COVID-19 information with their community partners during the study, which overlapped with the pandemic.

"We had several Black or African American investigators as well as staff, which likely played a role in our ability to engender trust with our participants," she said. As the study progressed, the researchers collected stories from participants and shared them with new study recruits, which Crews also found very helpful.

Identifying opportunities

Crews also highlighted opportunities for developers creating innovative kidney treatments, study funders, and policymakers to help support equitable access to innovation and study participation. For instance, she suggested that developers of wearable kidneys include individuals who may work long days or juggle multiple jobs early in their development process so that the resulting devices would work under those conditions.

She also recommended that policymakers consider equity in policy design, implementation, and testing. For example, she suggested that the kidney health awareness campaigns developed under the Advancing American Kidney Health initiative ensure that they reach populations that are socially disadvantaged. Crews also proposed creating services to address social determinants of health into new payment models for kidney failure or transplant care. Finally, she urged study funders and policymakers to provide guidance on best practices for engaging groups that are socially marginalized in research and to support programs to train investigators from groups that are underrepresented in biomedical research. She noted that she benefited from participation in the Robert Wood Johnson Foundation's Harold Amos Medical Faculty Development Program (3).

"Disparities in kidney health are profound, and examination of the root causes of disparities in kidney research participation point[s] us to different opportunities for enhancing inclusion of [groups that are socially marginalized] and integrating health equity considerations in all the aspects of research and innovation processes," Crews encouraged. ■

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Kenya Rising: Advancements in Kidney Care

By Khalida B. Soki

The path to becoming a nephrologist in Kenya involves 3 years of internal medicine training, followed by a 2-year nephrology clinical fellowship. Prior to 2018, nephrology training was not available locally, which meant that trainees, like me, needed to seek fellowships elsewhere. So, in 2017, I went to England on a scholarship from the International Society of Nephrology (ISN).

When I left for my clinical fellowship, Kenya had only 30 nephrologists serving a population of 50 million. We lacked precise data on the prevalence of chronic kidney disease (CKD), and there were approximately 300 patients undergoing hemodialysis (HD) and an even smaller number of patients undergoing peritoneal dialysis.

During my time in England, the nephrology landscape in Kenya started changing. In 2016 to address the major increase in patients receiving HD, the president of Kenya decreed that each of the country's 47 counties would have a functioning dialysis unit. The National Health Insurance Fund (NHIF) began reimbursing hospitals for twice-weekly HD sessions, which had previously been an out-of-pocket expense for those with kidney failure. Although patients and physicians welcomed this change, the kidney community was ill-prepared for such an abrupt rise in patients receiving HD.

Since then, the Kenya Renal Association (KRA) registry has recorded an annual increase of approximately 1500 patients on HD, reaching a peak of over 5000 patients in 2022 (according to unpublished data from the KRA registry). When I returned to Kenya in 2019, I found an overwhelmed and struggling medical workforce and NHIF.

Consequences of inadequate dialysis

The increase in patients undergoing HD plateaued in 2022, partially because NHIF tightened the criteria for dialysis eligibility but additionally because we started seeing that the long-term consequences of inadequate HD had started catching up with patients.

Without universal health care coverage or screening systems, patients with CKD in Kenya often "crash into" dialysis, presenting in crises with fluid overload or arrythmias. If they do survive this critical state, they are maintained on twice-weekly HD.

Twice-weekly HD without residual renal reserve results in inadequate dialysis. Our patients with kidney failure experience acidosis, uremia, fluid overload, malnourishment, hypertension, and chronic hyperkalemia. Ultrafiltration rates are often >1 L/hour, and intradialytic hypertension or hypotension is the norm. The use of a 210H dialysis membrane is routine, and many patients will opt to have low-efficacy dialysis rather than experience the disequilibrium that inevitably follows. Due to the lack of trained doctors in creation of dialysis vascular accesses and the fact that NHIF does not pay for vascular access creation or intervention, many patients develop vascular access failure within a short time, with superior vena cava syndromes and nonfunctional arteriovenous fistula. Arteriovenous grafts are too expensive to create and present another out-of-pocket expense.

Our culture is not one of palliation. NHIF does not pay for medication or transplant. The patients are trapped on dialysis, and it is often a socially, financially, and emotionally exhausting experience for them. The incidence of depression among patients on HD in public hospitals in Kenya has been documented at 72.5% (1); fatigue was reported in 77.9% (2).

Varied causes of kidney diseases

In one study (3), diabetic nephropathy was the leading cause of CKD (31.3%) in urban Kenya followed by glomerulonephritis (18.5%). In rural Kenya, however, more than two-thirds of those with CKD did not have HIV, diabetes, or hypertension (4). Hypertensive nephrosclerosis is often a default diagnosis for patients with a late presentation whose diagnosis is unknown.

The average age for CKD is relatively young in urban areas, averaging 42.5 years old (3). In the assessment of patients biopsied for CKD (5), the mean age was 27.3 years, and the most common cause of nephrotic syndrome was focal segmental glomerulosclerosis (30%). Idiopathic glomerulonephritis accounted for more than 20% of the cases.

Small but growing workforce

The number of nephrologists serving sub-Saharan Africa is low compared with the population, with some countries recording no nephrology physician presence (Table). Feedback indicates that many nephrologists are leaving their home countries in search of better working conditions and higher standards of living.

With more patients on HD and more dialysis units, Kenya has required more trained nephrologists and care teams. While the workforce is still low, there has been a vast improvement driven by the East African Kidney Institute (EAKI), a project funded by the African Development Bank. EAKI set up a preceptorship program consisting of a 3-month training for the internists, medical officers, and nurses responsible for Kenya's dialysis units. As a result of EAKI's efforts and much goodwill from the international community and ISN, Kenya has seen a 50% increase in its workforce in the last 5 years, adding 15 nephrologists. All nephrologists in Kenya are also honorary lecturers at EAKI. We commit to teaching and training the EAKI fellows who have come from Kenya, Uganda, Somalia, Southern Sudan, Tanzania, and the Democratic Republic of Congo.

KRA Conference (KRACon)

KRACon, Kenya's annual kidney conference, had always been a small meeting. However, in 2019, KRA hosted the African Association of Nephrology (AFRAN) conference and has since maintained strong ties with AFRAN.

KRACon has now transformed into a regional learning and networking hub for the multidisciplinary teams involved in nephrology care. Held every September, it attracts over 500 attendees from across Eastern Africa, consisting of doctors, nurses, dieticians, and physiotherapists. In 2023, the conference featured partnerships with AFRAN, ISN, the Declaration of Istanbul Custodian Group, and the American Society of Onconephrology.

Making progress

The nephrology field in Kenya has matured since I began my clinical fellowship 7 years ago. Although progress can still be made, we have seen major improvements to better serve our community of patients on dialysis, including increased trained personnel, advanced technology, and enhanced systems. Additionally, Kenya is setting up the infrastructure and laws to initiate a deceased organ donation program and CKD registry, as well as establish mentorship programs for trainees.

There have been many challenges for nephrologists and patients with kidney diseases in Kenya, but our kidney community has been resilient. Courage is the little voice at the end of the day that tells us to keep making progress. ■

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The author reports no conflicts of interest.

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Table. Number of nephrologists per country per million population—Africa

Country	2024 Number of nephrologists	2021 Population, million	2024 Number of nephrologists, per million population
Angola	0	34.50	0
Botswana	9	2.58	3.49
Burundi	4	12.50	0.32
Cameroon	35	27.19	1.28
Chad	4	17.17	0.23
Cote d'Ivoire	42	27.47	1.52
Democratic Republic of Congo	36	95.89	0.37
Djibouti	0	1.11	0
Ethiopia	35	120.30	0.29
Ghana	15	32.83	0.45
Kenya	45	53.00	0.84
Liberia	0	5.19	0
Mauritius	11	1.26	8.73
Mozambique	3	32.08	0.09
Namibia	3	2.53	1.18
Nigeria	200	213.40	0.93
Republic of the Congo	10	5.83	1.71
Rwanda	10	13.46	0.74
Senegal	53	16.88	3.13
Somalia	4	17.07	0.23
Tanzania	39	63.59	0.61
Uganda	14	45.85	0.30
Zambia	6	19.47	0.30
Zimbabwe	6	15.99	0.37

Based on unpublished data from the African Renal Registry.

Comprehensive Kidney Disease Management: Multidisciplinary Approaches and the Transition to Dialysis and Transplant

By Stephanie L. Donahue, Daniil Shimonov, Andrew Bohmart, and Sri Lekha Tummalapalli

Chronic kidney disease (CKD) causes multisystem complications. This complexity, which includes both mental and physical manifestations, makes it challenging for one practitioner to take care of all of a patient's needs, especially given increasing constraints on time and stagnant reimbursement. One answer to this challenge is a multidisciplinary care (MDC) approach. MDC clinics are increasingly being implemented by health systems, payers, and nephrology practices participating in value-based payment models, such as the Centers for Medicare & Medicaid Services' Kidney Care Choices Model.

Several programs that incorporate MDC approaches to CKD have been implemented and report positive outcomes. One such program, the Healthy Transitions Program in Late Stage Kidney Disease at Northwell Health in New York, used nurses who partner with nephrologists and an informatics system for tracking. They reported fewer hospitalizations, increased peritoneal dialysis and pre-emptive transplantation, and improved optimal starts (1). Another MDC program is the Program for Education in Advanced Kidney Disease (PEAK) at the Rogosin Institute in New York City, which includes nurse practitioners, a nurse educator, a dietitian, a social worker, a psychologist, and peer mentors to assist the primary nephrologist in caring for patients with CKD stages 4 and 5. Initial PEAK appointments are made with a nurse practitioner and a social worker, and appointments with the other disciplines are scheduled on an individualized basis (Figure). When compared with national averages, both Healthy Transitions and PEAK consistently outperform in several patient outcomes (Table) (2). Given the importance of optimal dialysis starts, pre-emptive transplantation, and preventing hospitalizations, an MDC approach seems to be our best chance to improve the well-being and lives of a vulnerable patient population.

One question that has repeatedly come up is how to best compose an MDC team. A previous systematic review examined the staffing compositions of MDC clinics for CKD care. Among 38 MDC clinics reviewed, the average team size was 4.6 members, and 97.4% incorporated nephrologists, 86.8% nurses, 84.2% dietitians, 57.9% social workers, and 42.1% pharmacists (3). In some cases, different MDC teams have distinct staffing models but yield similar positive results. Part of the reason for this may be the complexity of the care rendered and/or the subtle, even unknown, contributions that are difficult to measure. For example, a nurse who checks in with a patient in between visits and before important appointments and a social worker who arranges transportation and delivery from a pharmacy are critical to care for patients with multimorbidity.

Although the optimal MDC model is unclear, it is also likely to vary for different patient populations and health care settings. Future studies could leverage pragmatic trial designs within large health care systems to understand which MDC staffing models may have the greatest improvement in clinical outcomes and which are cost-effective. MDC clinics have traditionally focused on patients with CKD stages 4 and 5, but modeling studies suggest that MDC may be cost-effective even in earlier stages of CKD (4). MDC clinics that engage with patients through multiple health care professionals may ultimately encourage patient engagement and lead to optimal outcomes and well-being.

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The authors are members of the PEAK program team and note that they are the coauthors of one of the references for this article.

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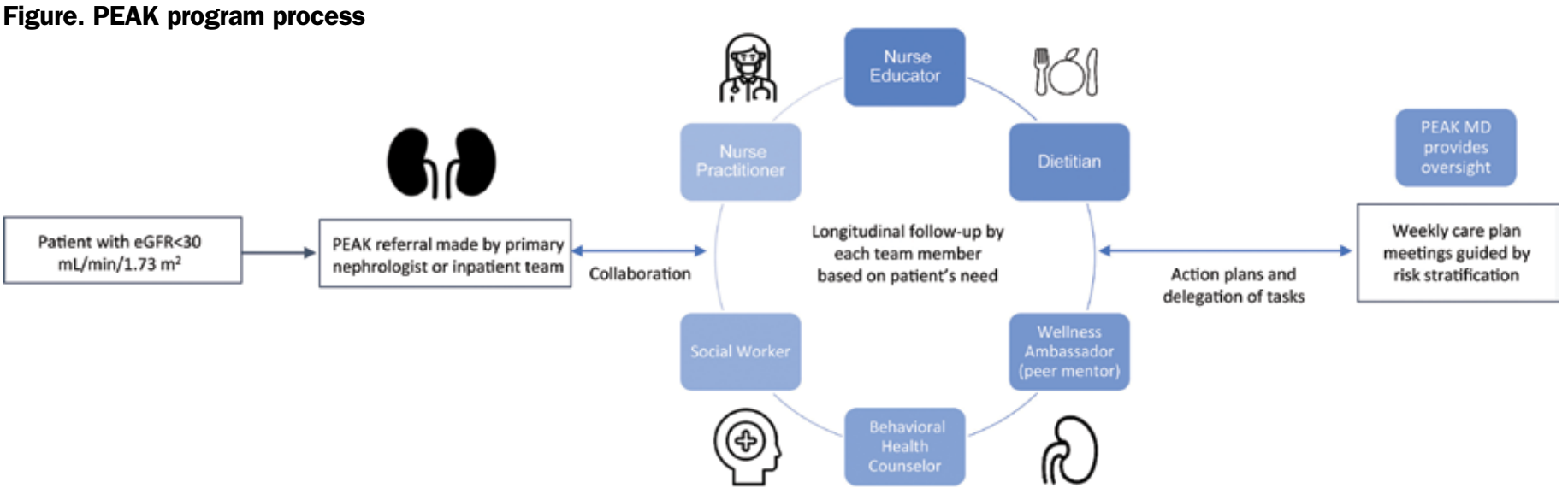
Table. Clinical outcomes in two New York-based MDC clinics for CKD

Outcomes	Healthy Transitions Program	PEAK	National average[a]
Optimal starts, %[b]	70	58	30
Home dialysis, %	23	23	11
Pre-emptive transplantation, %	13	12	2.7

[a]Results were calculated from prepandemic (2015–2019) US Renal Data System data.
[b]Optimal starts were defined as starting in-center hemodialysis with an arteriovenous fistula or graft, initiating home dialysis, or pre-emptive transplantation.

Figure. PEAK program process



eGFR, estimated glomerular filtration rate. Reproduced with permission from Shimonov et al. (2).

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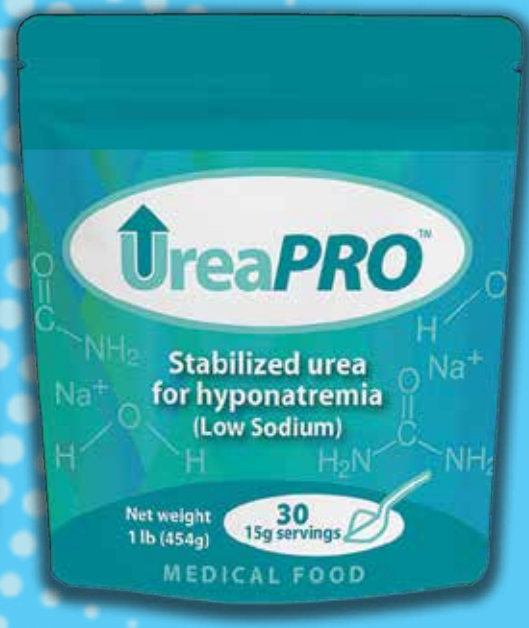

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