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Bolstering Support for Living Donors, Telehealth Access, and Greater Federal Coordination of Kidney Policy Among ASN's 2025 Legislative Priorities

By Bridget M. Kuehn

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Expanding support and protections for living donors to help improve access to kidney transplants is among ASN's top legislative priorities for 2025.

In addition to championing bills to make living organ donation cost-neutral for donors, ASN's policy team is working to secure ongoing funding for the Health Resources and Services Administration's modernization of the Organ Procurement & Transplantation Network. Other policy priorities include an overhaul of the end-stage renal disease (ESRD) bundled payment system, the permanent expansion of COVID-19 pandemic-era telehealth rules, and a fix to pending cuts to Medicare reimbursements for physicians.

To support the society's goals to increase transplant access for all patients who would benefit, ASN formed a Transplant Policy Committee to help lead transplant advocacy across the federal government's legislative, regulatory, and executive branches. The new committee will continue coordinating with ASN's Policy and Advocacy Committee, Quality Committee, Health Care Justice Committee, and Workforce and Training Committee.

"[Creating the Transplant Policy Committee] solidifies ASN's deep commitment to improving access to kidney transplant," said Roslyn Mannon, MD, FASN, chair of the ASN Transplant Policy Committee and professor of internal medicine and vice chair of research in the Department of Internal Medicine at the University of Nebraska Medical Center, Omaha.

Wins and losses in 2024

The new policy agenda builds on several key policy developments in 2024 (1). These included finalizing the Increasing Organ Transplant Access model and the HIV Organ Policy Equity Act, which expands access to kidney allografts from donors who are HIV-positive. Before the

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Faster Declines in Kidney Function After COVID-19 Versus Pneumonia

By Timothy O'Brien

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Patients diagnosed with COVID-19 may be at risk of accelerated decline in estimated glomerular filtration rate (eGFR) compared with patients with pneumonia, reports an observational cohort study in *JAMA Network Open* (1).

The decline in kidney function occurs even though patients with COVID-19 tend to be younger and initially healthier than those with pneumonia, according to a study by Viyaasan Mahalingasivam, MPhil, London School of Hygiene and Tropical Medicine, United Kingdom, and colleagues. They write, "These findings help inform decisions regarding the need to monitor kidney function in survivors of COVID-19 and could have implications for policymakers."

New data on COVID-19-related kidney risks

Previous studies suggest that COVID-19 can affect kidney function, whether directly or indirectly. A 2020 meta-analysis suggested nearly a 30% rate of acute kidney injury among patients hospitalized for COVID-19 (2). Although histopathologic studies have documented a risk of irreversible kidney damage after COVID-19 (3), there are few epidemiologic data on long-term outcomes.

There are conflicting data as to the risks associated with COVID-19 versus pneumonia (4, 5). Also, previous studies have not accounted for the potential impact of the kidney function trajectory before respiratory infection.

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Inside

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(tenapanor) tablets

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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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Bolstering Support for Living Donors, Telehealth Access, and Greater Federal Coordination

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act's implementation, such donations were limited to research programs. The new policy will allow such donations within all organ transplant programs that have the capacity to secure them, improving access to this organ pool for eligible patients.

Several bipartisan pieces of legislation, aimed at further increasing transplant access and protecting Medicare reimbursements for nephrologists and other physicians, almost made it through as part of an end-of-year federal funding bill. However, the bill's passage was scuttled at the last minute due to objections to parts of the package, including comments from Elon Musk made on the social media platform X, which may have precipitated the collapse of a bipartisan-negotiated spending package (2). Legislation to protect living donors and legislation to ward off a scheduled cut to Medicare payments for physicians were casualties of the last-minute shake-up.

Suzanne Watnick, MD, FASN, chair of ASN's Policy and Advocacy Committee, ASN Health Policy Scholar-in-Residence, and professor of medicine in the Division of Nephrology at the University of Washington, Seattle, explained that a lack of adjustments to the physician fee schedule for inflation and a cut to the schedules have led to an approximately 30% to 40% reduction in physician Medicare reimbursement over the past decade. She said that until a fix passes, physicians will face an additional nearly 3% cut in Medicare reimbursements. However, there is strong support for a fix across medical associations. "We've advocated strongly on Capitol Hill to do away with the physician fee schedule cuts and make sure that there's a system in place [for cost-of-living increases], so there are physicians who can take care of patients covered by Medicare because that's becoming more challenging," Watnick said.

One critical piece of legislation that passed as part of a smaller compromise end-of-year spending package was a temporary extension of pandemic-era telehealth rules through March 2025. Passing a more permanent extension of the telehealth rules that have enabled greater access to care is a pressing priority for ASN and many other physician organizations at the start of this year.

Telehealth care has long been available for patients undergoing home dialysis and will continue to be, explained Watnick. During the COVID-19 pandemic, legislation extended access for patients on dialysis in centers and for transplant patients. Mannon said the telehealth expansion helped patients on dialysis and transplant patients to access care during the pandemic and is a critical tool in helping patients with limited resources or transportation access or those who may live in rural areas who have to travel long distances for in-person care. "As we continue to improve health care in this country, access to a physician is really critical," Mannon said.

Mannon was also optimistic that some legislative proposals that did not make it into the end-of-year package might pass in 2025 due to their broad bipartisan support. "We had a huge focus and a lot of momentum going into the end of the session with living-donor protections," she said. "We're back dealing with that issue again this year, and I think the bills will pass. It's just about getting the right [legislators] together."

Payment priorities

Another priority this year will be championing a reimagining of the Centers for Medicare & Medicaid Service's (CMS's) ESRD payment bundle. "It's important for the kidney community to come together to try to address payment for care to make sure it's done in an updated way to best benefit the patients," Watnick said. "It all starts with making sure that the value we're providing for the patients is front and center."

Watnick explained that the current ESRD prospective payment bundle is based on "2008 health care," as outlined in the Medicare Improvements for Patients and Providers Act of 2008. It focused on erythropoietin-stimulating agents, which at the time were extremely expensive and were a major driver of dialysis costs. The comparative costs of these drugs have come down, and many new drugs have become available. However, physicians may not receive a separate payment for other drugs in the bundle, hampering the use of newer medications for patients on dialysis. For example, approximately 15% to 40% of patients on dialysis experience moderate-to-severe uremic pruritis (severe itching). However, only about 1% receive difelikefalin, which became the first US Food and Drug Administration (FDA)-approved therapy for the condition in 2021, a reflection of the limitations of the current ESRD bundle in allowing patients to access beneficial new products that have been developed since 2008. Low uptake of new drugs for patients undergoing dialysis has squelched innovation, as pharmaceutical companies have little incentive to develop new drugs with low use. "The pipeline [for drugs for patients on dialysis] is not that robust," Watnick said. CMS tried to address this problem with transitional drug add-on payment adjustments. However, the payments are temporary, leaving some nephrologists hesitant to use them, as they worry about the potential for nonreimbursable costs in the long term that could affect a dialysis center's financial viability. "We need to update the prospective payment system. We need to think about how to do better to incorporate new treatments," Watnick said.

Watnick explained that kidney care advocates do not want to go back to individually paying for drugs, which can incentivize overuse. Still, there is a need for a system that provides reasonable reimbursement for indicated medications over the longer term. She suggested that a panel made up of patients, patient advocates, nephrologists, and federal representatives may be able to develop reasonable solutions that incentivize innovation and quality of care with appropriate guardrails. She noted that there are also challenges with medication coverage for approximately half of the patients on dialysis who are covered by Medicare Advantage plans. Both payment issues require legislation to fix. ASN's Policy and Advocacy Committee is working to advocate for bicameral, bipartisan legislative solutions—solutions that the ASN Quality Committee is also actively working on designing. "The nice thing is that kidney care is on the minds of our champions in the House and the Senate [more] than it ever has been before," she said. "We've educated people, and now we have to use that lever to move forward."

Transplant legislation

Among the transplant-related bills for which ASN advocates is the Living Donor Protection Act. The bill helps protect living donors by prohibiting health, life, disability, or long-term care insurance companies from charging higher premiums for living donors. It makes clear that living donors are eligible to take time off from work under the Family and Medical Leave Act (FMLA). Mannon explained that not all donors are family members, and some may not have been previously eligible to take time off under FMLA. She clarified that while some living donors may be able to take paid time off from their job through FMLA, many frontline workers and other workers who are paid hourly may not have access to paid time off or may even risk losing their job to take time off, creating financial barriers to donation.

The Living Donor Protection Act is also part of a larger slate of bills that aims to make living donation cost-neutral for donors. The Honor Our Living Donors Act, which ASN was instrumental in helping shape, aims to simplify access to reimbursement for living donors' transplant-related expenses. Currently, eligibility for expense reimbursement is determined by the recipient's income, a holdover from an era when donors were most likely family members.

Another bill that ASN worked closely on crafting—the Expanding Support for Living Donors Act—would reauthorize the National Living Donor Assistance Center program; increase the cap on reimbursement for donor expenses from $6000 to $10,000; and increase the income eligibility threshold for reimbursement to help cover donation-related travel, child care, or lost wages from just 350% of the federal poverty level to 700%. This bill proposes that an estimated 80% of all Americans could be eligible for reimbursement for donation-related costs if enacted. "The National Living Donor Assistance Center provides financial assistance so donors aren't losing money and make it budget-neutral for them to donate," Mannon said.

Beyond legislation

In addition to advocating for legislation in partnership with the ASN Policy and Advocacy Committee, the Transplant Policy Committee will also be working with the federal agencies to regulate kidney care and administer kidney policies, in collaboration with the ASN Quality Committee. For example, Mannon noted ongoing work to promote new endpoints for studies on transplant medications. She said that patients, patient organizations, and societies have been lobbying FDA to update transplant medication trial endpoints to spur much-needed innovation. These groups also plan to work with FDA on xenotransplantation and organ perfusion. These two technologies have the potential to further expand transplant access by increasing the number of usable organs.

The Transplant Policy Committee will also closely monitor the ongoing overhaul of the US transplant system, including the Health Resources and Services Administration's modernization of the US Organ Procurement & Transplantation Network and CMS's new Increasing Organ Transplant Access payment model. Mannon explained that many things are changing at once, and it will be critical to ensure sufficient organ procurement organization and transplant center capacity to meet growing demand and to troubleshoot unexpected hiccups that may arise during implementation.

ASN is also championing changes in the executive branch to better support kidney care. For example, the society is advocating for the creation of an Office of Kidney Health at the US Department of Health and Human Services to better coordinate kidney policy across the federal government. The ASN policy team will also be working with the new presidential administration to advance the goals outlined in the 2019 Advancing American Kidney Health initiative (3), enacted during President Trump's first term, and to spur the innovation and private investments needed to help achieve better patient outcomes and recoup investments in innovation and care. "We can move this forward and not just improve the care in terms of innovation but move the needle and hopefully get the best care for our patients," Watnick said. ■

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Faster Declines in Kidney Function After COVID-19 Versus Pneumonia

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The cohort study (1) used linked data from Karolinska Institutet's Stockholm Creatinine Measurements (SCREAM) Project in collaboration with Juan Jesús Carrero, PharmD, PhD, and his team. The researchers identified a cohort of 134,565 patients diagnosed with COVID-19 in 2020–2021 and a prepandemic pneumonia cohort of 35,987 patients diagnosed with pneumonia in 2018–2019. All patients had at least one eGFR measurement in the 2 years before diagnosis. The mean annual change in eGFR before versus after infection was estimated in a linear regression model.

"Accelerated eGFR decline" after COVID-19 diagnosis

Key patient characteristics differed between the COVID-19 and pneumonia cohorts. Patients with COVID-19 were younger (median age, 51 versus 71 years), had a higher baseline eGFR (94 versus 79 mL/min/1.73 m^2), and had a lower hospitalization rate (13.3% versus 46.5%). At a median follow-up of 10.8 months, mortality was 1.5% versus 16.9%, respectively.

Yet patients with COVID-19 had a faster eGFR decline compared with baseline (4.1 mL/min/1.73 m^2) compared with those with pneumonia (0.9 mL/min/1.73 m^2). Within the COVID-19 cohort, hospitalized patients had a more pronounced decline: 5.0 versus 3.2 mL/min/1.73 m^2. In the pneumonia cohort, only hospitalized patients had an accelerated eGFR decline: 2.4 mL/min/1.73 m^2.

A secondary dataset included patients with postdiagnosis eGFR measurements: 59,267 with COVID-19 and 20,138 with pneumonia. On adjusted analysis, the mean annual reduction was 3.5% in the overall COVID-19 cohort and 5.5% among hospitalized patients compared with 2.3% in the pneumonia cohort.

For patients who were hospitalized with COVID-19, annual decline in the eGFR was 2.6 mL/min/1.73 m^2 faster compared with the pneumonia group. After covariate adjustment, patients in the COVID-19 cohort were more likely to experience a 25% reduction in eGFR (hazard ratio, 1.19), increasing to 1.42 for patients who were hospitalized.

Implications for protecting kidney function after COVID-19

The analysis finds "an accelerated eGFR decline of a larger magnitude among survivors of COVID-19 than survivors of pneumonia due to other infections," Mahalingasivam and coauthors write. They note that the COVID-19-related declines are comparable to those in previous studies of COVID-19 versus pneumonia (6), as well as long COVID (7).

The researchers highlight some limitations of their study, including the possibility that eGFR declines among hospitalized patients with COVID-19 might reflect the occurrence of acute kidney injury. In addition, about half of the patients had no eGFR measurements after diagnosis of COVID-19 or pneumonia and thus might have experienced similar declines in kidney function. "If this difference imposed residual confounding, it would likely mean that we have underestimated the magnitude of faster eGFR decline after COVID-19," the researchers add.

Mahalingasivam and colleagues emphasize the need for studies from other health systems and with longer-term follow-up. The authors propose that "people who were hospitalized for COVID-19 should receive closer monitoring of kidney function to ensure prompt diagnosis and optimized management of chronic kidney disease to effectively prevent complications and further decline." ■

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KidneyX Prize Incentivizes Innovation in Dialysis Sustainability

https://doi.org/10.62716/kn.000152025

The KidneyX Sustainability Prize was awarded in January to seven winners in support of solutions to reduce water or power usage during dialysis care. The competition is the latest initiative from KidneyX (Kidney Innovation Accelerator), a public-private partnership between ASN and the US Department of Health and Human Services (HHS) to accelerate the prevention, diagnosis, and treatment of kidney diseases.

"Now through the KidneyX Sustainability Prize, we're seizing the opportunity to transform outcomes for patients—by identifying and supporting solutions to reduce the resource demands of dialysis," said Assistant Secretary for Health Admiral Rachel L. Levine, MD, in a press release from HHS (1). The KidneyX Steering Committee, led by John R. Sedor, MD, FASN, identified this topic in response to ASN's Statement on Climate Change (2).

More than half a million Americans require maintenance hemodialysis or peritoneal dialysis, and over 100,000 Americans begin dialysis every year (3). Globally, current hemodialysis technology requires 265 billion liters of water and uses 1.62 billion kW/hour of power annually (4). With a growing patient population, increasing frequency and persistence of water and power shortages, and intensifying acute disasters, the KidneyX Sustainability Prize aims to support innovative solutions to reduce resource demands and promote sustainable care for those who need this life-sustaining treatment.

A multidisciplinary selection committee evaluated submissions based on six equally weighted criteria: sustainability impact, equitable access, feasibility, technical innovation, patient engagement, and scalability and impact.

The diverse slate of winners will each receive an equal share of the $7.25 million prize pool (1):

- **Kuleana Technology Inc**. *Advancing Hemodialysis Sustainability: Dialysate Regeneration via Uremic Toxin Photo-Oxidation*. "Kuleana Technology's Dialysate Regeneration Module enables hemodialysis with just 2 liters of water per treatment, making dialysis portable and accessible while saving 300 billion liters of water per year worldwide."
- **Micro Nano Technologies Inc**. *Handheld Water-Free and Battery-Powered Renal Replacement System*. "The proposed technology mimics kidney filtration, eliminating the need for water and operating on a laptop-sized battery for 8 hours, ensuring dialysis access during disasters without traditional infrastructure."
- **Particle4X**. *SMART-PD: Sustainable Home Dialysis Revolution*. "SMART-PD is an advanced home dialysis system that produces sterile PD [peritoneal dialysis] fluid from tap water, reclaims effluent, and employs AI [artificial intelligence]-powered monitoring to enhance sustainability and patient safety."
- **Qidni Labs Inc**. *Qidni/D: A Novel Sorbent Platform for Dialysis*. "The Qidni/D is a portable and nearly waterless hemodialysis system that can offer accessible and sustainable access to care anywhere."
- **Stephen Ash, MD**. *Sorbent Regeneration of Dialysate With Improved Ammonium Capacity*. "[The recipient has] developed a sorbent with high capacity for NH_4^+ (from urea) and minimal binding of Ca^{2+} and Mg^{2+}, which should make regeneration of dialysate simpler, smaller, and more practical."
- **University of Minnesota**. *Decentralized Dialysis Fluid Production: Enhancing the Sustainability of Dialysis Care*. "[The] innovation enables decentralized production of peritoneal dialysis fluids, reducing dialysis energy and water consumption by 48% and 66%, respectively; increasing supply chain resilience; and improving patient outcomes worldwide."
- **Wearable Artificial Organs Inc**. *Green Dialysis on Batteries Using Only 300 mL of Water*. "A 2-pound miniaturized Wearable Artificial Kidney powered by rechargeable batteries, continuously regenerates dialysate water and delivers continuous dialysis 24 hours a day, 7 days a week."

Since its inception in 2018, KidneyX has awarded approximately $25 million to support more than 80 innovations. For more information on the KidneyX Sustainability Prize and KidneyX, visit kidneyx.org. ■

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The Pediatric Nephrology Match: A Fellow's Perspective on a Subspecialty Under Pressure

By Jordy Salcedo-Giraldo

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The results of the 2024 Pediatric Nephrology Fellowship Match have once again highlighted an ongoing concern in the field. This year, 45 fellowship programs offered a total of 73 positions, yet only 39 of these positions were filled across 20 programs (1). This continues the current trend in pediatric nephrology seen over recent years (1):

- **2023**: 42 programs, 67 spots offered, 36 filled in 17 programs
- **2022**: 43 programs, 60 spots offered, 33 filled in 18 programs
- **2021**: 44 programs, 69 spots offered, 51 filled in 28 programs (outlier year)
- **2020**: 41 programs, 64 spots offered, 38 filled in 19 programs

Decreasing workforce amid rising demand

This steady decline in fellowship match numbers comes at a time when the demand for pediatric nephrologists continues to increase. A 2018 analysis of referral patterns demonstrated a significant rise in consultations for conditions such as acute kidney injury, hypertension, chronic kidney disease, and kidney failure, among others (2).

Despite this, a workforce survey conducted in 2013 highlighted that one-third of pediatric nephrologists who responded planned to reduce their clinical practice, and nearly half intended to partially or fully retire in the coming years (3). As of June 2023, there were only an estimated 709 board-certified pediatric nephrologists under the age of 70 years in the United States. On average, this equates to just 13.3 pediatric nephrologists per state, although this number highly varies, with a range of 0 to 73 per state (4). This shortage is reflective in findings of increased faculty and trainee burnout rates associated with significantly lower quality of life, higher perceived stress, and lower satisfaction with career choice and work–life balance (5).

The question that remains is simple: Can the current trends keep up with the rising demand for pediatric nephrologists? A microsimulation model conducted by the American Board of Pediatrics in partnership with the Carolina Health Workforce Research Center estimated that in 2020, there were only 0.5 pediatric nephrologists per 100,000 children in the United States. Even if the current match rate persists, the model predicts only a 26% increase by 2040, reaching 0.63 pediatric nephrologists per 100,000 children, which only equates to an average rise of one physician per state (4).

Potential solutions: How can we reverse the trend?

Increasing interest in pediatric nephrology

Pediatric nephrology has consistently been one of the least competitive pediatric subspecialties. To address this, we must continue to explore ways to engage trainees early. By identifying programs that successfully generate pediatric nephrology applicants, other programs may be able to replicate their strategies in increasing interest among residents to the field. Other strategies can include expanding elective rotations and research opportunities in nephrology to spark interest among residents.

Shortening the training pathway

The current length of the 3-year pediatric nephrology fellowship has been a highly debated topic in the field of pediatric nephrology over the past several years. A 2016 American Academy of Pediatrics survey of pediatric nephrologists found that 49% supported reducing fellowship to 2 years, whereas 34% opposed, and 17% were undecided. The primary concern about shortening training lies in research, with opponents arguing that research is essential for academic centers and fearing that loss of research would lead to a decrease in pediatric research findings (6).

However, workforce data from 2018 to 2022 found that only 15% of pediatric nephrologists spent more than 25% of their work time on research, whereas 75% focused primarily on clinical care. Offering a 2-year clinical track alongside a 3-year research track could attract more applicants while maintaining research opportunities for those interested. This in turn could open the opportunity for pediatric nephrology to expand from being primarily affiliated with academic programs to small, private practices, which could allow for easier access to pediatric nephrology physicians, particularly in regions currently without physicians.

Pediatric nephrology could consider restructuring its training pathway to resemble pediatric neurology, in which trainees complete 2 years of general pediatrics followed by 3 years of subspecialty training, streamlining the process while maintaining clinical and research competency.

Advocating for higher compensation

Financial concerns remain a major barrier. Pediatric nephrology is one of the lower-paid pediatric subspecialties, and, on average, pediatric nephrologists earn significantly less than adult nephrologists. Given the current economic climate, requiring trainees to undergo 6 years of training with minimal compensation—only to enter a field with relatively lower pay—is increasingly unsustainable. Addressing salary disparities and advocating for increased compensation could help attract more trainees.

The ongoing challenges in the pediatric nephrology match highlight the need for thoughtful solutions to strengthen the workforce. Encouraging interest in the field, exploring flexible training pathways, and addressing compensation concerns could help attract more trainees. A collaborative effort will be essential in ensuring that children with kidney diseases continue to receive the specialized care they need. ■

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

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

Business Round-Up: Q3–Q4 2024 Activity in the Nephrology Industry

By Melissa West

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In August 2024, *Kidney News* published "Business Round-up: Q1–Q2 2024 Activity in the Nephrology Industry" as the inaugural report to the community of ASN's efforts to track commercial activities (accessible here: bit.ly/KN160808). This report on Q3–Q4 2024 activity finishes out the year and was compiled in January 2025, when the J.P. Morgan Healthcare Conference was getting ready to convene.

Melissa West is the Senior Director, Strategic Relations and Patient Engagement, at ASN. She previously was the Project Director for the Kidney Health Initiative. With over 20 years' experience working in the kidney community, Ms. West tracks the trends in business and kidney care for ASN Council and staff. Please contact Ms. West at mwest@asn-online.org to share publicly available information that may have been missed in this article.

Summary: Biologic, drug, and device approvals and label extensions

Approval	Type	Product	Company	Reference
510K Clearance	Device	Moda-flx Hemodialysis System	Diality	Diality Secures FDA Clearance for Hemodialysis System (August 7, 2024). https://www.fiercebiotech.com/medtech/diality-secures-fda-clearance-hemodialysis-system
Accelerated approval	Drug, new indication	Fabhalta (iptacopan)	Novartis	Novartis Receives FDA Accelerated Approval for Fabhalta (Iptacopan), the First and Only Complement Inhibitor for the Reduction of Proteinuria in Primary IgA Nephropathy (IgAN) (August 8, 2024). https://www.novartis.com/news/media-releases/novartis-receives-fda-accelerated-approval-fabhalta-iptacopan-first-and-only-complement-inhibitor-reduction-proteinuria-primary-iga-nephropathy-igan
Full approval	Drug	FILSPARI (sparsentan)	Travere Therapeutics	Travere Therapeutics Announces Full FDA Approval of FILSPARI (Sparsentan), the Only Non-Immunosuppressive Treatment That Significantly Slows Kidney Function Decline in IgA Nephropathy (September 5, 2024). https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-full-fda-approval-filsparir
Label extension, European Commission	Drug	Ozempic (semaglutide)	Novo Nordisk	Europe Allows Novo to Include Reduction of Kidney Disease in Ozempic Label (December 12, 2024). https://www.reuters.com/business/healthcare-pharmaceuticals/european-drug-regulator-allows-novo-include-reduction-kidney-disease-ozempic-2024-12-12/

FDA, US Food and Drug Administration.

Summary: Biologic, drug, and device development

Activity	Type: Category	Product	Company	Reference
Release of phase 3 data	Drug: Heart failure	KERENDIA	Bayer	Bayer Announces Primary Endpoint Achieved in Phase III FINEARTS-HF Cardiovascular Outcomes Study Investigating KERENDIA (Finerenone) in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction (August 5, 2024). https://www.bayer.com/en/us/news-stories/study-investigating-kerendiar-in-patients-with-heart-failure
Rare pediatric disease designation	Drug: Primary hyperoxaluria	META-001-PH	Meta Pharmaceuticals	Meta Pharmaceuticals Receives FDA Rare Pediatric Disease Designation for META-001-PH (August 7, 2024). https://www.healio.com/news/nephrology/20240807/meta-pharmaceuticals-receives-fda-rare-pediatric-disease-designation-for-meta001ph
Release of phase 3 data	Drug: C3G and IC-MPGN	Pegcetacoplan	Apellis Pharmaceuticals	Apellis and Sobi Announce Positive Topline Results From Phase 3 VALIANT Study of Pegcetacoplan in C3G and Primary IC-MPGN (August 8, 2024). https://investors.apellis.com/news-releases/news-release-details/apellis-and-sobi-announce-positive-topline-results-phase-3
FDA hold lifted	Gene therapy: Fabry disease	4D-310	4D Molecular Therapeutics (4DMT)	FDA Lifts Hold on 4DMT's Fabry Gene Therapy (August 9, 2024). https://endpts.com/fda-lifts-hold-on-4dmts-fabry-gene-therapy/
Release of safety data	CAR-T cell therapy: Lupus nephritis	KYV-101	Kyverna Therapeutics	Kyverna Shares Safety Data for CAR-T; Evotec Gets $75M Milestone (August 13, 2024). https://endpts.com/kyverna-shares-safety-data-for-car-t-evotec-gets-75m-milestone/
Strategic update	Cell therapy: Chronic kidney disease with diabetes	Rilparencel	ProKidney	ProKidney Announces Strategic Updates to Its Phase 3 Program to Accelerate Rilparencel's Registrational Path to Potential Approval in the U.S. (September 3, 2024). https://finance.yahoo.com/news/prokidney-announces-strategic-updates-phase-113000700.html
Release of phase 3 data	Drug: IgAN	Sibeprenlimab	Otsuka Pharmaceutical	Otsuka's Cytokine-Targeting Drug for IgAN Clears Phase 3 Hurdle (October 22, 2024). https://endpts.com/otsukas-cytokine-targeting-drug-for-igan-clears-phase-3-hurdle/
Rare pediatric disease designation	Drug: C3G	Zaltenibart	Omeros	FDA Grants Rare Pediatric Disease Designation to Zaltenibart for C3 Glomerulopathy (October 24, 2024). https://www.healio.com/news/nephrology/20241024/fda-grants-rare-pediatric-disease-designation-to-zaltenibart-for-c3-glomerulopathy
Breakthrough device designation	Chronic systemic inflammation: Dialysis	Selective Cytopheretic Device (SCD)	SeaStar Medical	FDA Grants Breakthrough Device Designation for SeaStar Medical's Selective Cytopheretic Device for Adults Undergoing Chronic Dialysis (November 6, 2024). https://investors.seastarmedical.com/news/news-details/2024/FDA-Grants-Breakthrough-Device-Designation-for-SeaStar-Medicals-Selective-Cytopheretic-Device-for-Adults-Undergoing-Chronic-Dialysis/default.aspx
Breakthrough device designation	Device: Dialysis access	STARgraft	Healionics	Healionics' STARgraft Receives FDA Breakthrough Device Designation (November 14, 2024). https://www.einpresswire.com/article/760408590/healionics-stargraft-receives-fda-breakthrough-device-designation

C3G, complement 3 glomerulopathy; CAR-T, chimeric antigen receptor T cell; IC-MPGN, immune complex membranoproliferative glomerulonephritis; IgAN, immunoglobulin A nephropathy.

Summary: Investments

Company	Amount, $	Type	Reference
Renalys	37.8 Million	Series A	Renalys Raises $37.8M to Take Travere's Kidney Disease Drug Into Phase 3 Trial in Japan (July 17, 2024). https://endpts.com/renalys-raises-37-8m-to-take-traveres-kidney-disease-drug-into-phase-3-trial-in-japan/
Baxter/Vantive Kidney Care	3.8 Billion	Private equity	Baxter Announces Definitive Agreement to Divest Its Vantive Kidney Care Segment to Carlyle for $3.8 Billion (August 13, 2024). https://www.baxter.com/baxter-newsroom/baxter-announces-definitive-agreement-divest-its-vantive-kidney-care-segment
Borealis Biosciences	150 Million	Series A	Versant and Novartis Build "Chinook 2.0" for RNA Therapies in Kidney Diseases (August 22, 2024). https://endpts.com/versant-novartis-launch-borealis-biosciences-for-rna-therapies-in-kidney-diseases/
eGenesis	191 Million	Series D	eGenesis Raises $191 Million Series D Financing to Advance Lead Program for Kidney Transplant (September 4, 2024). https://www.businesswire.com/news/home/20240904466099/en/eGenesis-Raises-191-Million-Series-D-Financing-to-Advance-Lead-Program-for-Kidney-Transplant
34 Lives	44.2 Million maximum	ARPA-H	ARPA-H Project Awardees. No Kidney Left Behind (September 23, 2024). https://arpa-h.gov/research-and-funding/mission-office-iso/awardees
Judo Bio	100 Million	Seed and series A	Judo Bio Launches With $100M for Kidney-Targeted siRNA Therapies (October 7, 2024). https://endpts.com/judo-bio-launches-with-100m-for-kidney-targeted-sirna-therapies/
Purespring Therapeutics	105 Million	Series B	Purespring Nabs $105M to Take Gene Therapy Into the Clinic as IgAN Field Matures (October 9, 2024). https://endpts.com/purespring-nabs-105m-to-take-gene-therapy-into-the-clinic-as-igan-field-matures/
Revalia Bio	Undisclosed	NKF Innovation Fund investment	National Kidney Foundation Innovation Fund Invests in Revalia Bio to Advance Innovative Kidney Disease Therapeutics (October 17, 2024). https://www.kidney.org/press-room/national-kidney-foundation-innovation-fund-invests-revalia-bio-to-advance-innovative
Quanta Dialysis Technologies	60 Million	Series E	Quanta Dialysis Technologies Raises $60M for Its Dialysis Tech (November 19, 2024). https://www.massdevice.com/quanta-dialysis-technologies-raises-60m-for-its-dialysis-tech/
Maze Therapeutics	115 Million	Series D	Maze Therapeutics Looks to Steer Lead Kidney Disease Assets Through the Clinic With $115M Series D (December 3, 2024). https://www.fiercebiotech.com/biotech/maze-therapeutics-set-steer-lead-kidney-disease-assets-through-clinic-115m-series-d

ARPA-H, Advanced Research Projects Agency for Health; NKF, National Kidney Foundation; siRNA, small interfering RNA.

Summary: Mergers, acquisitions, and partnerships

Company	Amount, million $	Type	Reference
Biogen	1.15	Acquisition of Human Immunology Biosciences (HI-Bio)	Biogen Completes Acquisition of Human Immunology Biosciences (July 2, 2024). https://investors.biogen.com/news-releases/news-release-details/biogen-completes-acquisition-human-immunology-biosciences
Crosswalk Therapeutics	Undisclosed	Acquisition from Codexis/ Takeda	Crosswalk Picks Up Fabry, Pompe Compounds From Abandoned Takeda, Codexis Collab (July 2, 2024). https://www.fiercebiotech.com/biotech/crosswalk-picks-fabry-pompe-compounds-abandoned-takeda-codexis-collab
Pfizer	N/A	Partnership	Flagship Pioneering and Quotient Therapeutics Announce Agreement to Identify Potential Novel Targets for the Treatment of Cardiovascular and Renal Diseases Under Strategic Partnership With Pfizer (August 28, 2024). https://www.prnewswire.com/news-releases/flagship-pioneering-and-quotient-therapeutics-announce-agreement-to-identify-potential-novel-targets-for-the-treatment-of-cardiovascular-and-renal-diseases-under-strategic-partnership-with-pfizer-302230763.html
University of Cambridge and GSK Pharmaceuticals	65	Collaboration	Cambridge and GSK Announce New Five-Year Collaboration Aiming for Improved Outcomes for Patients With Hard-to-Treat Kidney and Respiratory Diseases (October 21, 2024). https://www.cam.ac.uk/news/cambridge-and-gsk-announce-new-five-year-collaboration-aiming-for-improved-outcomes-for-patients
GSK Pharmaceuticals	300	Acquisition from Chimagen Biosciences	GSK Aims to Extend Lupus Dominance via $300M Upfront Deal for Clinical-Stage T-Cell Engager (October 29, 2024). https://www.fiercebiotech.com/biotech/gsk-aims-extend-lupus-dominance-300m-upfront-deal-clinical-stage-t-cell-engager
Tvardi Therapeutics	To be determined	Merger with Cara Therapeutics	Fibrosis-Focused Tvardi to Go Public via Merger With Cash-Strapped Cara (December 18, 2024). https://www.fiercebiotech.com/biotech/fibrosis-focused-tvardi-go-public-merger-cash-strapped-cara

N/A, not applicable.

Summary: Value-based kidney care

Organization	Type	VBC relationship	Reference
Arizona Complete Health, a Centene subsidiary (Medicare Advantage plan)	Insurer	Duo Health	Duo Health Partners on Value-Based Kidney Disease Care With Ariz. MA Plan (July 17, 2024). https://www.hcinnovationgroup.com/population-health-management/chronic-illness/news/55126682/duo-health-partners-on-value-based-kidney-disease-care-with-ariz-ma-plan
Cigna Healthcare	Insurer	Healthmap Solutions Chronic Kidney Disease Program	Healthmap Solutions Chronic Kidney Disease Program Will Reach Customers in 27 Additional Markets (July 25, 2024). https://providernewsroom.com/cigna-healthcare/healthmap-solutions-chronic-kidney-disease-program-will-reach-customers-in-27-additional-markets/
Cigna Healthcare	Insurer	Interwell Health	Expansion of Interwell Health Value-Based End-Stage Renal Disease Condition Management Program (July 25, 2024). https://providernewsroom.com/cigna-healthcare/expansion-of-interwell-health-value-based-end-stage-renal-disease-condition-management-program/
Humana	Insurer	Evergreen Nephrology	Humana and Evergreen Nephrology Introduce a New Specialized Kidney Care Program (August 29, 2024). https://press.humana.com/news/news-details/2024/Humana-and-Evergreen-Nephrology-Introduce-New-Specialized-Care-Program-for-Patients-Living-with-Kidney-Disease/
Gold Kidney Health Plan, Medicare Advantage plan in Arizona and Florida	Insurer	N/A	Gold Kidney Health Plan Expands in Florida and Arizona in 2025 (September 20, 2024). https://www.goldkidney.com/gold-kidney-health-plan-expands-in-florida-and-arizona-in-2025/
Humana	Insurer	Interwell Health	Humana and Interwell Health Announce Addition of State of Florida to Value-Based Kidney Care Program (September 24, 2024). https://www.interwellhealth.com/who-we-are/news/humana-and-interwell-health-announce-addition-of-state-of-florida-to-value-based-kidney-care-program

MA, Medicare Advantage; VBC, value-based care.

Grief Counseling for People Living With Kidney Diseases: A Nonclinical Perspective

By Rachael Nolan and Prakash Gudsoorkar

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The emotional and psychological impacts of kidney diseases are often overlooked in nephrology practice (1). Chronic kidney disease (CKD) and kidney failure, including their treatment through dialysis or kidney transplantation, represent profound, life-altering experiences for patients (2). Beyond the physical demands of these conditions, the emotional and psychological impacts are often substantial and pervasive. One of the most common responses stemming from patients while grappling with their condition is grief. Described as the normal and natural reaction to loss, grief encompasses both anticipatory and actual responses to a wide range of experienced or perceived losses, which can be social, physical, emotional, spiritual, or financial in nature (3, 4).

Beyond the rising global threat of kidney diseases (5, 6), grief itself is an important public health issue that can lead to significant health problems (7). Grief has been associated with depression, anxiety, and reduced quality of life (3–7). The emotional burden of grief can activate the hypothalamic-pituitary-adrenal axis, leading to increased cortisol and stress hormones, which in turn suppress the immune system, promote chronic inflammation, and elevate the risk of cardiovascular issues (8). Unresolved grief in patients undergoing dialysis can intensify the already elevated risk of complications, further reducing treatment adherence and adversely affecting patient survival and overall health outcomes (9).

Addressing grief through psychodynamic support and nonclinical grief counseling (NCGC) can enhance the well-being of patients with CKD and kidney failure (10–13). As a crucial aspect of holistic care in chronic disease management, effective NCGC has been shown to help patients process their emotions, find meaning in their experiences, and develop positive coping strategies (10, 12, 13). More importantly, NCGC can provide a strong sense of community and support, alleviating feelings of isolation and loneliness—making the integration of grief health professionals into nephrology practice a vital step toward meeting the comprehensive, emotional, and psychological needs of these patients (11).

By prioritizing emotional and psychological health alongside physical treatment, nephrologists can enhance the overall quality of life for individuals with kidney diseases. Because NCGC focuses specifically on the emotional process of mourning and loss, rather than diagnosis and treatment of mental health conditions, it is distinct from clinically based approaches like psychological counseling (12). Whereas psychological counseling addresses a broad range of mental health issues, NCGC hones in on helping patients process and cope with specific feelings of loss associated with their condition (12, 13).

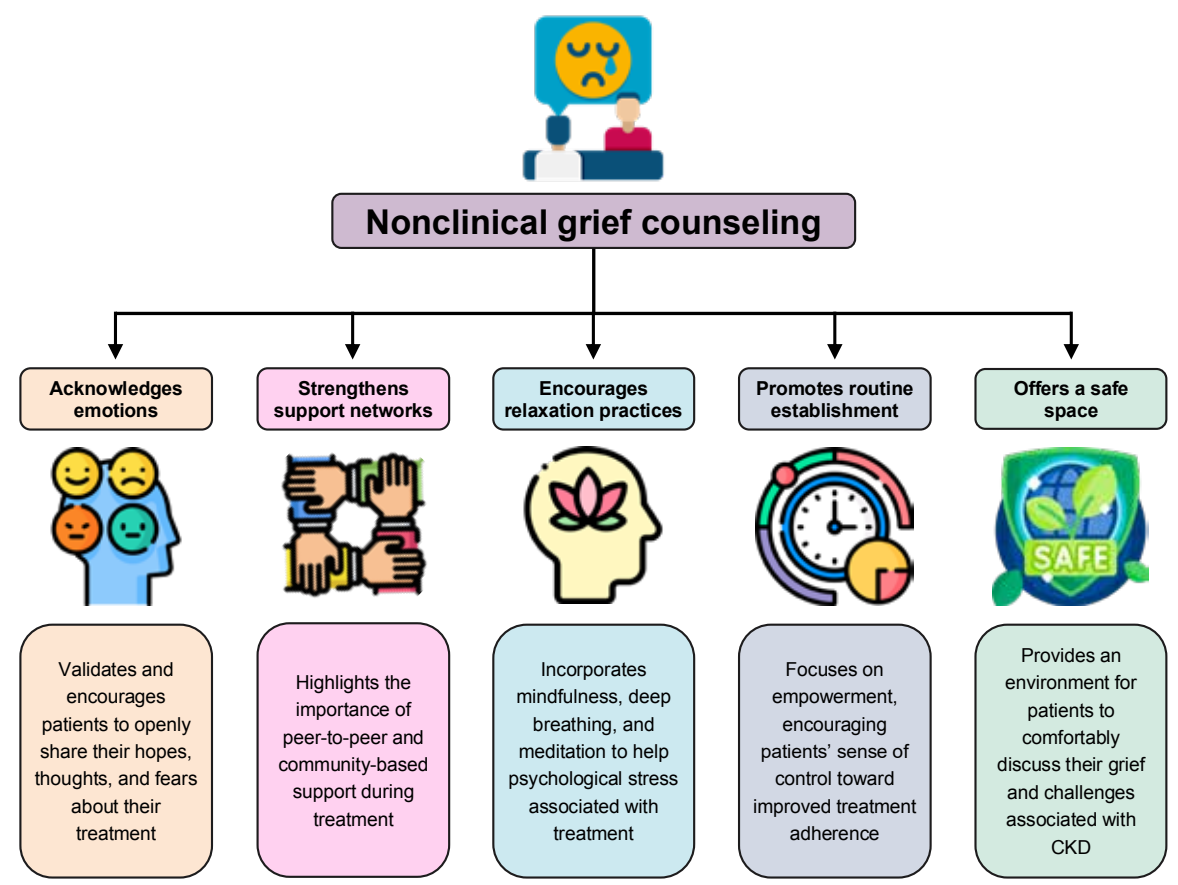
Effective components of NCGC include emotional expression, validation, and the development of coping strategies in a safe, nonjudgmental environment, in which patients share their experiences (Figure) (12–14). This expression is crucial, as patients may feel isolated in their grief, believing that others may not understand their pain. By unburdening their emotion, patients can alleviate the weight of unspoken grief by using strategies that have been shown to help patients manage emotional aspects of their disease such as mindfulness, relaxation techniques, journaling, and creativity (15).

Although the benefits of NCGC are well-established (8–11), several challenges remain. Access to NCGC may be limited, especially in rural or underserved areas. Stigma surrounding mental health support can deter some patients, particularly older individuals and those from cultures in which mental health issues are taboo. Addressing these barriers requires collaboration among nephrologists, community organizations, and patients' families and friends to ensure that individuals with kidney diseases receive the emotional support they need.

Often as primary care practitioners for patients on dialysis, nephrologists must recognize and address grief to truly provide holistic care that extends beyond physical symptoms. By integrating NCGC into nephrology practice, practitioners can better support patients' emotional needs, which can lead to improved treatment adherence and overall health outcomes. Equally important is training nephrologists to identify early signs of grief, which would enable timely referrals to NCGC and other psychological services.

By equipping patients with the tools and support needed to navigate their journey with resilience and hope, nephrologists can greatly enhance patients' quality of life. It is essential for nephrologists to recognize the importance of integrating NCGC into routine care for patients living with kidney diseases, ensuring that patients' emotional well-being receives the attention it deserves. ■

Figure. Components of nonclinical grief counseling



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FDA Paternalism Versus Patient Choice:
The Case of HIF-PHIs

By Jay B. Wish

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During the last 2 decades, the Nobel Prize-winning discovery of the hypoxia-inducible factor (HIF) pathway led to the development of a new class of pharmaceutical agents for the treatment of anemia in patients with chronic kidney disease (CKD). These agents, which are small molecules administered orally, inhibit the prolyl hydroxylase (PH) enzymes responsible for the degradation of the HIF-α subunit, thereby increasing transcription of erythropoietin and erythropoietin receptor genes, as well as transcription of a variety of genes that code for proteins involved in gastrointestinal absorption and internal transport of iron (1).

Six HIF-PH inhibitors (HIF-PHIs) have been developed worldwide, and three have been submitted for US Food and Drug Administration (FDA) approval. Currently there is no HIF-PHI approved in the United States for treatment of anemia in patients with nondialysis-dependent CKD (NDD-CKD), and only one HIF-PHI is available in the United States for treatment of anemia in patients with dialysis-dependent CKD (DD-CKD).

Roxadustat, which has been approved in China, the European Union, Japan, the United Kingdom, and numerous other countries for both patients with NDD-CKD and DD-CKD, was rejected by FDA for both patient populations in 2021 due to concerns regarding thrombotic events, seizures, and infections in patients with NDD-CKD (placebo control) and deep venous and vascular access thrombosis in patients on dialysis (erythropoiesis-stimulating agent [ESA] control) (2). Daprodustat, which was approved in Japan for patients with NDD-CKD and DD-CKD, was rejected by FDA in 2023 for patients with NDD-CKD, primarily due to concerns regarding readmissions for heart failure (HF) among those with a prior history of HF. Major adverse cardiovascular events (MACE) for daprodustat met the prespecified confidence interval upper bound compared with ESAs in the intention-to-treat analysis. It is not clear why the HF issue could not have been addressed with a label warning to use daprodustat with caution or to avoid its use in patients with prior history of HF. FDA approved daprodustat for patients on dialysis for at least 4 months (3). Daprodustat was voluntarily withdrawn from the US market in November 2024. Vadadustat, which has been approved in 35 countries for patients with DD-CKD, without restriction as to duration of dialysis therapy, was approved by FDA in 2024 for patients on dialysis for at least 3 months (4). It should be noted that postmarketing reports from other countries, in which HIF-PHIs have been approved, have not revealed any safety issues in up to 5 years of data collection.

The *NEJM Evidence* meta-analysis suggests that, on balance, HIF-PHIs are as safe as ESAs...

In August 2024, *NEJM Evidence* published a systematic review and meta-analysis assessing the long-term safety of HIF-PHIs; the primary outcome was MACE (5). A total of 25 trials involving 26,478 participants were analyzed. The MACE results and the only outcomes with statistically significant risk ratios are summarized in the Table. Adverse events leading to drug discontinuation were higher among patients treated with HIF-PHIs than ESAs (patients with NDD-CKD and DD-CKD) or placebo (NDD-CKD); this could be attributed to patients being more likely to associate side effects with a new oral drug, when compared with ESAs, particularly in the absence of double-dummy trials (the Weber effect). Most of these adverse events were gastrointestinal symptoms, including nausea, vomiting, and diarrhea. All studies of HIF-PHI versus placebo were with roxadustat.

The *NEJM Evidence* meta-analysis suggests that, on balance, HIF-PHIs are as safe as ESAs, especially with regard to MACE, which has traditionally been the litmus test for the safety of anemia treatments in patients with CKD. Given the risks of red blood cell transfusion and allosensitization for future transplant, which may result from untreated or inadequately treated anemia, many patients with NDD-CKD may be willing to accept some incremental risk from an HIF-PHI versus an ESA, which is difficult to obtain and administer. Proper labeling of HIF-PHIs to inform patients and practitioners of risk and to promote informed decision-making among a minimal number of therapeutic options is more consistent with the culture that we espouse than denying these agents to all patents with NDD-CKD, particularly those who are unwilling to receive a subcutaneous ESA injection on a regular basis.

This paternalistic approach by the FDA seems to be greater in nephrology than in other specialty areas, in which new drugs, such as monoclonal antibodies, with very serious potential side effects are approved on a regular basis. The exceptionally high bar for drug approval in nephrology denies patients new therapies—the risks of which they may make an informed decision to accept—stifles innovation, and discourages trainees from joining our profession. ■

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Table. Summary of meta-analysis

Comparison	Population	Outcome	Risk ratio	95% CI	Certainty of evidence
HIF-PHI vs. ESA	DD-CKD	MACE	0.99	0.92–1.08	N/A
HIF-PHI vs. ESA	NDD-CKD	MACE	1.08	0.95–1.22	N/A
HIF-PHI vs. placebo	NDD-CKD	MACE	1.10	0.96–1.27	N/A
HIF-PHI vs. ESA	DD-CKD	Atrial fibrillation	0.69	0.58–0.83	Moderate
HIF-PHI vs. placebo	NDD-CKD	Dialysis access thrombosis	1.86	1.20–2.88	Very low
HIF-PHI vs. placebo	NDD-CKD	Venous thromboembolism	3.07	1.48–6.37	Very low
HIF-PHI vs. ESA	DD-CKD	Adverse event leading to drug discontinuation	1.81	1.32–2.49	Moderate
HIF-PHI vs. ESA	NDD-CKD	Adverse event leading to drug discontinuation	1.49	1.18–1.88	Moderate
HIF-PHI vs. placebo	NDD-CKD	Adverse event leading to drug discontinuation	1.39	1.07–1.82	Moderate
HIF-PHI vs. placebo	NDD-CKD	Systemic hypertension	1.45	1.16–1.81	Moderate
HIF-PHI vs. placebo	NDD-CKD	Infections	1.24	1.16–1.56	High
HIF-PHI vs. placebo	NDD-CKD	Hyperkalemia	1.29	1.06–1.59	Moderate
HIF-PHI vs. ESA	NDD-CKD	Esophageal or gastric erosions	1.72	1.20–2.49	Low
HIF-PHI vs. placebo	NDD-CKD	Seizures	5.13	1.79–14.68	Very low

Source: Ha et al. (5). CI, confidence interval; N/A, not applicable.

Clinical Trials Show Promise for Novel Treatments for IgA Nephropathy

By Bhadran Bose

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Immunoglobulin A nephropathy (IgAN) is recognized as the most common primary glomerular disease. Although its incidence varies geographically, a systematic review of biopsy-based studies indicates an incidence of at least 2.5 per 100,000 (1). Ten-year kidney survival rates range from 57% to 91% (2). Prognosis is influenced by factors such as pathological findings, hypertension, proteinuria, and estimated glomerular filtration rate (eGFR) at diagnosis.

Renin-angiotensin-aldosterone system blockade has been the cornerstone of IgAN treatment. However, in patients at high risk of progression to kidney failure, various therapeutic approaches have been explored over the years with mixed results.

Recent clinical trials in high-risk patients with IgAN have investigated the role of sodium-glucose cotransporter-2 inhibitors (3, 4), complement inhibitors (5, 6), endothelin receptor antagonists (7, 8), and inhibitors of B cell-activating factor and a proliferation-inducing ligand (9). The findings from some of these trials were presented at ASN Kidney Week 2024 (Table). Many of these studies are only in phase 2, with small sample sizes, short follow-ups, and limited racial and ethnic diversity.

One recently published, notable phase 2 trial, ENVISION (Safety and Efficacy Study of VIS649 for IgA Nephropathy), demonstrated promising results. It suggested that sibeprenlimab, an anti-a proliferation-inducing ligand monoclonal antibody, blocks a key initiating step in the immune pathogenic cascade of IgAN by limiting aberrant IgA1 (galactose-deficient IgA1) production and immune complex formation (10). This trial served as the foundation for the phase 3 VISIONARY trial (Visionary Study, Phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy), a multicenter, randomized, double-blind, placebo-controlled study (11). Approximately 530 adult patients with IgAN receiving standard-of-care therapy were enrolled to evaluate the efficacy and safety of sibeprenlimab, 400 mg administered subcutaneously every 4 weeks, compared with placebo.

The interim results of the VISIONARY trial were announced in October 2024. The study met its primary endpoint, showing a statistically significant and clinically meaningful reduction in proteinuria after 9 months of treatment, alongside a favorable safety profile. The trial continues in a blinded manner to evaluate the change in kidney function over 24 months and is expected to be completed in 2026. Based on the interim analysis, Otsuka Pharmaceuticals intends to review these results with the US Food and Drug Administration for regulatory submission.

In summary, the exploration of multiple therapies represents a significant advancement for a condition that has long lacked specific treatments beyond the renin-angiotensin-aldosterone system blockade. The final results of these ongoing trials are highly anticipated. ■

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The author reports no conflicts of interest.

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Table. IgAN trials presented at ASN Kidney Week 2024

Study description, authors, year	Study design	Participants	Intervention	Primary outcome	Secondary outcomes	Safety	Limitations	Conclusion
Ravulizumab, Lafayette et al. 2024 (5)	Phase 2, randomized, double-blind, placebo-controlled trial	66 Adults with IgAN, proteinuria ≥1 g/day, eGFR ≥30 mL/min/1.73 m²	Ravulizumab versus placebo (26 weeks) + open-label ravulizumab (24 weeks)	30.1% Reduction in proteinuria at 26 weeks (p = 0.005)	Sustained proteinuria reduction (44.8% at 50 weeks) and eGFR stabilization	Well-tolerated; mild adverse events; no meningococcal infections or significant immunogenicity	Small sample size; limited racial and ethnic diversity; phase 2 trial	Promising therapy with meaningful proteinuria reduction and eGFR stabilization
Iptacopan, Perkovic et al. 2024 (6)	Phase 3, double-blind, placebo-controlled trial	443 Patients with biopsy-proven IgAN, UPCR ≥1 g/g, eGFR ≥30 mL/min/1.73 m²	Oral iptacopan 200 mg twice daily	38.3% Reduction in 24-hour UPCR at 9 months (p < 0.001)	UPCR <1 g/g achieved without kidney replacement or rescue therapy	No unexpected safety concerns; mild to moderate reversible adverse events	Interim analysis only; long-term eGFR outcomes not reported	Promising alternative pathway inhibitor; ongoing studies for long-term impact
Selective endothelin receptor antagonist SC0062, Heerspink et al. 2024 (7)	Phase 2, double-blind, placebo-controlled trial	131 Adults with IgAN, eGFR ≥30 mL/min/1.73 m², UPCR ≥0.75 g/g	SC0062 (5, 10, and 20 mg) versus placebo for 24 weeks	Dose-dependent UPCR reduction: −38.1% (20 mg; p = 0.0002) at 12 weeks	UPCR reduction up to −51.6% (20 mg) at 24 weeks; no significant eGFR changes	Similar adverse events across doses; mild peripheral edema (6%–3% versus 15% in placebo)	Short follow-up; conducted only in China; limited long-term safety assessment	Effective in reducing proteinuria with good safety; further studies needed for long-term data
Atrasentan, Heerspink et al. 2024 (8)	Phase 3, double-blind, placebo-controlled trial (ALIGN)	404 Patients with biopsy-proven IgAN, UPCR ≥1 g/day, and eGFR ≥30 mL/min/1.73 m²	Atrasentan (0.75 mg/day) versus placebo for 36 weeks	36.1% Reduction in 24-hour UPCR compared with placebo (p < 0.001)	Long-term effects on eGFR under investigation; exploratory outcomes with SGLT2 inhibitors	Similar adverse events across groups; mild fluid retention (11.2% versus 8.2%)	Limited diversity; interim results only; long-term outcomes pending	Potential therapy for high-risk IgAN with substantial proteinuria reduction
Atacicept, Barratt et al. 2024 (9)	Open-label extension of a 96-week phase 2b trial	113 Patients with eGFR ≥30 mL/min/1.73 m², UPCR ≥0.75 g/g	Weekly atacicept 150 mg subcutaneous injections	Sustained reductions in proteinuria (UPCR ↓52%) and stabilization of eGFR	Reduction in biomarkers: galactose-deficient IgA1 ↓66%, hematuria ↓75% over 96 weeks	77% Had mild, nonserious treatment-emergent adverse events	Small sample size; open-label design; no placebo control in the extension	Reduces key biomarkers with sustained efficacy and safety

ALIGN, Atrasentan in Patients With IgA Nephropathy; SGLT2, sodium-glucose cotransporter-2; UPCR, urine protein-to-creatinine ratio.

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Prioritizing Frailty in the Assessment of People With Kidney Diseases

By Karen Blum

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With older adults constituting an increasing proportion of kidney transplant candidates and people with kidney failure, it behooves clinicians to factor in frailty when evaluating patients and planning treatment, speakers said at Kidney Week 2024.

Frailty is characterized by muscle loss, slow gait speed, low energy levels, reduced mobility, and difficulty performing daily activities, said Krista Lentine, MD, PhD, FASN, associate division director of nephrology at SSM Health Saint Louis University Hospital in Missouri. The condition—which coincides with but is not synonymous with age—can be marked by immune system dysregulation and decreased physiologic reserve to adapt to stressors such as surgical procedures and infections, she said. Compared with non-frail counterparts, patients with frailty undergoing kidney transplantation are more likely to suffer surgical complications and delayed graft function, require longer hospital stays, be discharged to settings other than home, and have reduced survival rates (1). However, some patients with reversible frailty can improve with transplantation versus remaining on dialysis.

Frailty is increasingly recognized as an important risk factor in kidney transplant evaluation, especially for patients who are older and medically complex, she said. Evaluation of frailty is essential to guide counseling and decision-making in kidney transplantation. Accurately identifying frailty enables weighing risks and benefits of therapies and supports tailored management strategies including whether someone should undergo a transplant, whether prehabilitation is needed, what types of organs will be appropriate, and what type of immunosuppression regimen is optimal.

"Risk prediction is challenging because for our patients, often chronologic age is not equivalent to physiologic age," said Dorry Segev, MD, PhD, director of the Center for Surgical and Transplant Applied Research at NYU Langone Health in New York City. "Even the younger adults sometimes look like older adults. How many of us see somebody in clinic who's 42 going on 92?"

About 10% of all people over age 65 undergoing elective surgery have frailty, and an additional 31% can be considered to have intermediate frailty, as classified using a validated scoring scale from 0 to 5 (2), Segev said. Even among much younger patients on dialysis, almost 30% have frailty, he said. A longitudinal study by his group has found the prevalence of frailty in patients experiencing kidney failure to be 42%. These patients had a 40% 3-year mortality compared with 16% in those without frailty, as well as a higher risk of falls (3).

Frailty also has a cognitive component, Segev said, with a "pretty high" rate of developing dementia within 10 years of undergoing a transplant. It is associated with twice the risk of developing post-transplant delirium (4). Related adverse outcomes include increased length of hospitalizations and higher risk of graft loss and mortality. "When [a patient receives a kidney transplant], their cognition improves because they're off of dialysis and living more normal lives," he said. "However, while those who are frail get an initial improvement, soon thereafter their cognition continues to deteriorate."

Transplant centers that consistently assess frailty as part of their clinical practice have been shown to have 10%–15% better outcomes than centers that do not assess frailty, Segev said (5), although that connection may be correlative.

Clinicians can evaluate their older patients for frailty using the Fried frailty phenotype (6), which assesses patients for factors such as unintentional weight loss, physical activity, exhaustion, strength, and walking time. Performing these assessments can take time, Segev said, so his team has been working on an abridged, "light-touch" clinical measure of frailty that incorporates some of the same measures but can be done faster (7). Clinicians also can get hints of a patient's frailty by looking at inflammatory markers such as interleukin-6 and C-reactive protein, as well as computed tomography to review sarcopenia of the psoas muscle, he explained.

Additional measures for frailty used by clinical practices include the FRAIL [Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight] Scale, the Timed Up and Go test, and other tests of walk speed or mobility, Lentine said. However, there is significant heterogeneity in practice, and the best measure for kidney transplant recipients is currently unclear.

It is also unclear when to measure frailty in kidney transplant candidates to be most effective, she noted. Assessments could be done during an initial evaluation, prior to surgery to gauge perioperative risk and establish a baseline for recovery, and after transplant to guide rehabilitation needs and frequency of clinical follow-up.

The importance of prehabilitation

A trial of prehabilitation before kidney transplantation may be useful in distinguishing those with reversible versus irreversible frailty (8), Lentine said. Prehabilitation typically includes an exercise-based intervention to improve cardiopulmonary fitness and muscle strength. It also may include nutritional support to achieve optimal weight before surgery and psychosocial interventions to address mental health and reduce anxiety and depression.

Prehabilitation should be completed prior to transplantation with the goal of improving tolerance to physiologic stressors and enabling patients with more frailty to become kidney transplant recipients, Lentine said. "Although the benefits seem intuitive, the evidence for prehabilitation in the transplant population is at a relatively nascent stage," she said.

Approximately 20% of candidates become more frail between their first evaluation and their transplant, Segev noted. In a pilot study (9) that provided patients with weekly physical therapy sessions and at-home exercises, participants improved physical activity by 64% over a 2-month period, and their hospital length of stay following the transplant was halved—an average of 5 days for patients with the physical therapy sessions versus 10 days for similar patients who did not receive the therapy. Researchers are now conducting a larger randomized trial. The European Society for Organ Transplantation published a consensus statement (10) in 2023 on prehabilitation for solid organ transplant candidates, but its recommendations focused on the need for more research, including identification of an optimal prehabilitation modality, specific components, feasibility, and core outcome measures to assess impact, Lentine said.

A subsequent perspective in *JASN* (11) emphasized some of the key questions facing practitioners, including who should be referred for prehabilitation, when patients should be referred, what type of intervention should be prescribed, and how programs should be implemented. To successfully integrate prehabilitation requires building a team, including physical therapists and dietitians, guidelines to streamline referrals, funding to support equipment and infrastructure, and appropriate reimbursement strategies, the authors wrote.

Management of frailty should continue after transplantation, Lentine said. There may be an ongoing need for rehabilitation, modifications to immunosuppression regimens, and targeted efforts to prevent and treat delirium, as well as medication safety and adherence modifications to institute as necessary (8).

Prehabilitation also may be able to reduce cognitive frailty, Segev said. In a pilot study (12), he and his colleagues gave a group of patients who were undergoing hemodialysis either iPad-based brain games to play at dialysis sessions or a foot peddler that they could use for exercise during their treatment. Patients who participated in these activities did not experience the deterioration in cognition seen in similar patients not presented with these opportunities.

To maximize kidney transplantation for older adults, consider strategies such as timely listing and expediting transplantation to reduce their risk of frailty deterioration while on a waiting list, Lentine said (13). This can include considering both living donor transplants and nonstandard deceased donor organs. "Time is essential for our older [patients with frailty] to avoid declining on the list and becoming too sick for transplantation," she said. "We [also] need to be vigilant to immunosuppression complications, preventing infection, and avoiding delayed graft function." ■

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The Missing Piece? Spirituality and Religion in CKD

By Rakhi Khanna

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For many of us, spirituality, religion, and faith are essential parts of our lives. Forty-seven percent of Americans identify as religious, 33% identify as spiritual, and 18% identify as neither religious or spiritual (1). Yet, these core aspects of identity are rarely discussed within the kidney community. Is it because we as physicians are unsure of how to define these terms in a medical setting? Or is it because we are not convinced of their role? Perhaps there is fear, discomfort, or concerns of unintentionally discriminating against a patient's individual faith or belief system.

Of the over 333 million people who live in the United States, more than 35.5 million experience chronic kidney disease (CKD). Of those individuals, approximately 500,000 are undergoing some form of dialysis (2–4).

CKD impacts every aspect of a person's well-being. It affects the physical condition of the body by causing fatigue, weakness, lack of appetite, and poor sense of taste, among other symptoms. CKD also affects a person's mental wellness. Depression rates in patients undergoing dialysis vary from 25% up to 85%. Depression and anxiety are known to reduce quality of life and increase the burden of disease, resulting in higher mortality and morbidity (5). Nephrologists are increasingly aware of how CKD affects mental health, and social workers routinely screen for depression in people undergoing dialysis. However, this assessment only scratches the surface of a person's whole well-being and emotional experience living with CKD.

A 2022 MITRE-Harris poll (6) found that 52% of patients in the United States feel that they are not heard when seeking medical treatment. This sentiment is even more prevalent in patients from the Hispanic community. Rates of nonadherence across all populations are similar—approximately 50% (6). Furthermore, various studies have shown patient dissatisfaction with the time that their physician spends with them during dialysis sessions. Nephrologists are faced with the challenge of alleviating the burden of kidney diseases for their patients, while many themselves experience poor job satisfaction and burnout (7).

Perhaps the common thread is a lack of meaning, purpose, and connection to our work as nephrologists. Have we been so focused on treating the physical and physiologic aspects of CKD that we overlooked the emotional, spiritual, and religious components?

As a community nephrologist with over 20 years of experience, I have witnessed my patients face challenges such as heart disease and amputations, as well as undergoing kidney transplants, all in their fight to sustain their lives. I have treated patients who have lost both of their legs and continue to have a positive outlook with the will to keep going. Their stories of determination and faith, many of which are grounded in their religion or spirituality, are inspiring.

Spiritual care resources and counseling are often reserved for patients in end-of-life care, but it is imperative that we find ways to extend spiritual care to all patients, including those with CKD. To treat patients holistically, the nephrology community must conduct its own evaluation and research to determine how best to assess and meet the spiritual care needs of its patients. For example, physicians and spiritual care teams can conduct a brief spiritual care history, including questions about their patients' faith and support system and what gives meaning to their life. Spiritual care assessments may help people with kidney diseases cope with their illness, influence their response and adherence to treatment, and provide a crucial support network (Figure). Other potential areas of action include engaging with patients on their spiritual beliefs, involving patients' faith-based communities as support systems, and incorporating spirituality and religion in transplant education for living donors.

The kidney community must do more to study and evaluate the emotional, religious, and spiritual needs of our patients. Perhaps the spiritual component is the missing piece of kidney care. ■

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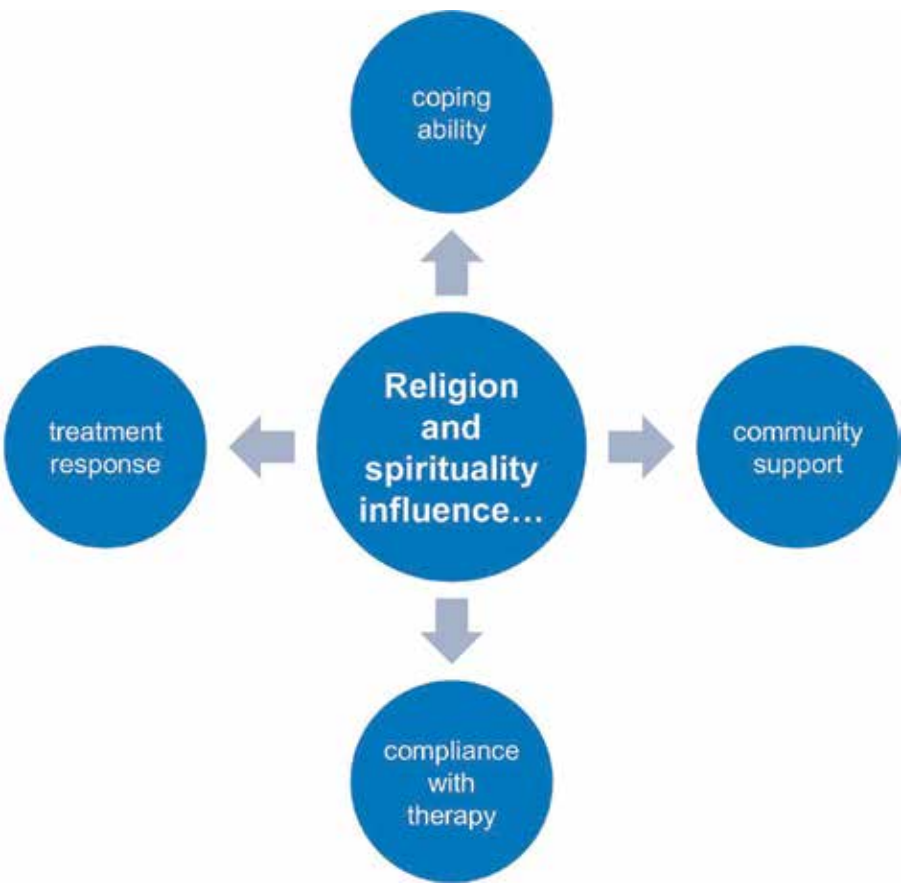
Figure. Influence of religion and spirituality on people with kidney diseases



Adapted from Koenig (8).

Exploring Tirzepatide's Dual Agonism in Kidney Diseases: GLP-1 Agonist With Potential GIP-Mediated Benefits

By Fatima Ali and Marwa Farzand

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The success of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in diabetes management—and, more recently, weight loss—is well established in both clinical guidelines and practice. Tirzepatide is a first-in-class dual gastric inhibitory polypeptide (GIP) and GLP-1RA approved for the same indications. By activating the GLP and GIP receptors, tirzepatide enhances insulin secretion, reduces glucagon release, slows gastric emptying, and promotes satiety to improve glucose control and support weight loss. Its dual mechanism of action may also influence kidney outcomes, although further studies are needed to substantiate this claim. While current clinical guidelines recommend GLP-1RAs for patients with type 2 diabetes and chronic kidney disease (CKD), more evidence is required to determine the specific role of dual GLP-1/GIP receptor agonists. This review aims to examine the current evidence regarding kidney benefits of GLP-1 and GLP-1/GIP receptor agonists as well as how tirzepatide compares with existing GLP-1RAs.

Kidney disease is the most prevalent complication of type 2 diabetes, and traditional therapies focus on managing risk factors with medications that target the renin-angiotensin-aldosterone system, sodium-glucose cotransporter-2 inhibitors, and finerenone (1). Recent cardiovascular outcome trials indicate that new glucose-lowering agents offer kidney benefits in addition to cardiovascular advantage (2). Accordingly, in the FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial, published in *The New England Journal of Medicine*, patients with type 2 diabetes and CKD were randomized to receive 1.0 mg weekly semaglutide or placebo (1). The primary outcome—a composite of major kidney events (including kidney failure, a ≥50% decline in estimated glomerular filtration rate [eGFR], or death from kidney or cardiovascular causes)—showed a 24% lower relative risk with semaglutide compared with placebo (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.66–0.88; p = 0.0003) after 3.4 years. This trial demonstrated that semaglutide, a GLP-1RA, significantly reduces kidney disease progression, major cardiovascular events, and mortality, expanding its established benefits in glycemic control and weight loss to include kidney outcomes.

The FLOW study's authors suggest that semaglutide's nephroprotective effects are likely "multifactorial." GLP-1 receptors are found on kidney tissues and vasculature, and while improvements in glycemia, weight, blood pressure, and cholesterol contribute modestly, nephroprotection is primarily linked to anti-inflammatory, antioxidative effects and reduced fibrosis (1). Evidence continues to suggest the organ-protective effects of GLP-1RAs, as well as tirzepatide, although the exact mechanisms underlying kidney benefits remain an active area of investigation.

Tirzepatide functions as a multi-agonist, and its selectivity for GIP potentiates the anti-inflammatory and antioxidant effects that GLP-1RAs offer on their own. The dual GLP/GIP agonism offers substantial reduction in CKD risk factors such as blood pressure, weight, and glycemic control (3). In terms of how tirzepatide compares with semaglutide, an international, randomized, open-label, phase 3 noninferiority trial comparing the two agents in adults with type 2 diabetes concluded that all three doses of tirzepatide (5, 10, and 15 mg) were noninferior and superior to 1.0 mg semaglutide, with respect to change in the glycated hemoglobin level from baseline. At 40 weeks, tirzepatide reduced glycated hemoglobin by –2.01%, –2.24%, and –2.30%, respectively, compared with –1.86% with semaglutide. Tirzepatide also demonstrated dose-dependent reductions in body weight, with mean reductions of –7.6 kg, –9.3 kg, and –11.2 kg for tirzepatide doses of 5, 10, and 15 mg, respectively, compared with –5.7 kg with semaglutide (4). Furthermore, a post hoc analysis of the five SURPASS studies revealed that significant reductions in systolic blood pressure with tirzepatide (ranging from –2.8 to –12.6 mm Hg) were largely attributed to weight loss, and tirzepatide at 10 mg and 15 mg doses demonstrated greater reductions in systolic blood pressure compared with semaglutide at a 1-mg dose (5).

Although a dedicated trial evaluating tirzepatide's kidney outcomes is underway, a post hoc analysis of the completed SURPASS-4 (A Study of Tirzepatide [LY3298176] Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes and Increased Cardiovascular Risk) trial reported that when compared with insulin glargine, tirzepatide use was associated with a slower rate of eGFR decline, lower albuminuria, and lower incidence of the composite kidney outcome of an eGFR decline ≥40% from baseline, kidney failure, death due to kidney failure, or new-onset macroalbuminuria (HR, 0.58; 95% CI, 0.43–0.80) (Table) (6). Such findings are by no means conclusive and should be interpreted as hypothesis-generating. Ongoing analyses continue to shed light on the role of dual GLP-1/GIP receptor agonists in people with kidney diseases. To provide further clarity on the clinical role of tirzepatide in kidney diseases, the TREASURE-CKD (A Study of Tirzepatide [LY3298176] in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes) trial is currently recruiting participants (3). Results derived from studies that are powered for analysis of kidney parameters will provide further insight.

Overall, the novel drug tirzepatide has established its use in diabetes management and as a weight-loss aid. Meanwhile, GLP-1RAs are widely recommended by major guidelines (7, 8) in patients with underlying conditions, including, but not limited to, CKD. For the time being, the clinical role of tirzepatide remains under investigation, as ongoing research will define its effects in populations with kidney diseases. ■

Table. SURPASS-4 trial: eGFR changes between baseline and end of treatment for both groups of drugs

	Patients, No. (N = 1995)	eGFR decline per year, mL/min/1.73 m² (SE)	
		Tirzepatide	Insulin glargine
Sex			
Female	747	–1.4 (0.4)	–4.1 (0.4)
Male	1242	–1.5 (0.3)	–3.4 (0.3)
eGFR, CKD-Epidemiology Collaboration, mL/min/1.73 m²			
<60	338	0.5 (0.5)	–3.2 (0.5)
≥60 to <90	794	–1.4 (0.4)	–4.0 (0.4)
≥90	857	–2.2 (0.3)	–3.5 (0.3)
Urine albumin-to-creatinine ratio			
Normoalbuminuria	1246	–1.1 (0.3)	–3.8 (0.3)
Microalbuminuria	545	–1.7 (0.4)	–2.9 (0.5)
Macroalbuminuria	161	–2.7 (0.9)	–4.3 (0.9)

Adapted from Heerspink et al. (6).

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Will Patients With Acute Interstitial Nephritis Recover? Insights From a New Biopsy Series

By Long Qian and Dennis G. Moledina

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Acute interstitial nephritis (AIN) is a common cause of unexplained acute kidney injury and is noted in one in five patients who undergo a kidney biopsy for acute kidney injury (1, 2). AIN is typically treated by drug withdrawal in those with drug-induced AIN and is sometimes supplemented with immunosuppressive therapy (3). AIN often results in some degree of permanent kidney damage, and many patients with AIN do not recover their kidney function completely (4). Prognostication of AIN remains a significant challenge, as nephrologists currently lack reliable methods to predict which patients are likely to recover and which are not.

In a recent study, Miao et al. provide data to assess prognosis after AIN (5) (Figure). The authors examined 166 patients with biopsy-proven AIN at the Mayo Clinic from 2012 to 2023. They tested the association of 15 selected factors with a 6-month outcome of kidney function recovery—either complete recovery (defined as achieving serum creatinine within 25% of pre-AIN baseline or below 1.4 mg/dL) or partial recovery (defined as 50% reduction in creatinine without returning to within 25% of baseline). Complete and partial recovery was observed in 51% and 25% of patients, respectively. In multivariable analysis, recovery was more likely in those with lower severity of interstitial fibrosis and tubular atrophy (IFTA), those who did not require dialysis, and those in whom AIN was suspected before the biopsy. This study also updates a prior study from the same center (6), providing valuable insights into trends in AIN etiology, particularly noting the increased occurrence of immune checkpoint inhibitor (ICI)-associated AIN, which accounted for 18% of drug-AIN cases compared with 0% in the previous study. Since first reports of ICI-AIN were published in 2016 (7, 8), the proportion of cases of AIN from ICI is likely to increase.

Whereas over 80% of patients in the Miao et al. study (5) were prescribed steroids, this group did not have greater kidney function recovery, although this analysis was limited by significant baseline differences in steroid-treated and untreated participants and lack of power. The authors state that "it is difficult to definitively conclude that steroids have no potential benefit in AIN" due to these limitations. Other limitations of the study include retrospective data collection and use of single-center data.

Understanding factors associated with kidney function recovery in patients with AIN is of high clinical and scientific interest. Previously, factors associated with nonrecovery included a higher degree of IFTA and being on dialysis (9), which were also noted in this study. A higher severity of interstitial infiltrate, which was associated with greater recovery of kidney function in prior studies (4, 10), could not be evaluated in this study due to lack of reliable quantification. Finally, the issue of whether steroids are effective in treating AIN remains unresolved, as studies testing steroid use with kidney function recovery have yielded conflicting results. The authors appropriately conclude that randomized controlled trials are needed to evaluate the role of steroids in AIN.

In conclusion, this study shows that greater kidney function recovery is noted in those with lower fibrosis and when AIN was suspected before biopsy, highlighting the role that early diagnosis plays in improving outcomes in AIN. ■

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Dr. Qian reports no conflicts of interest. Dr. Moledina reports being a named coinventor on a pending patent, "Methods and Systems for Diagnosis of Acute Interstitial Nephritis"; a cofounder of the diagnostics company Predict AIN, LLC; and a consultant for BioHaven, Ltd.

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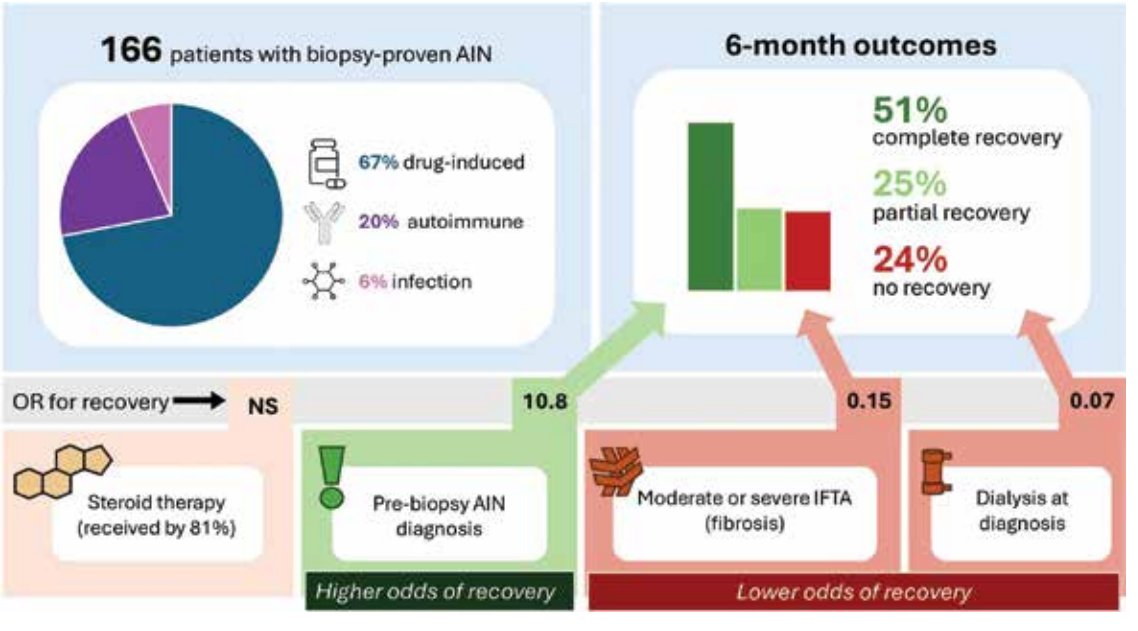
Figure. Predictors of kidney function recovery in patients with AIN



Complete recovery is defined as achieving serum creatinine within 25% of pre-AIN baseline or below 1.4 mg/dL; partial recovery is defined as a 50% reduction in creatinine without returning to within 25% of baseline. Factors significantly associated with any recovery (complete or partial) on multivariable analysis are shown. NS, nonsignificant; OR, odds ratio.

Gene Therapy Is Slowly Gaining Traction in Nephrology

By Karen Blum

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The kidney's multiple cell types, unique tissue architecture, and a glomerular filtration barrier that can restrict particles by size and charge are among the reasons gene therapy has been lagging in nephrology. However, ongoing research in animal and cell models suggests that there is hope for these treatments in the future.

"We as scientists need to garner more interest in cell and gene therapy for our patients," said Matthew Wilson, MD, PhD, a nephrologist at Vanderbilt University Medical Center in Nashville, TN, during a presentation at Kidney Week 2024. About 30% of chronic kidney disease cases have an underlying monogenic cause (1), "so there are multiple possible targets for kidney gene therapy," Wilson said.

In some studies of note, researchers were able to induce re-expression of an inactivated polycystic kidney disease gene in mice to reverse autosomal-dominant polycystic kidney disease (ADPKD) (2) and induce expression of nephrin in nephrin-deficient mice, preventing perinatal death (3), he explained. "If delivery can be achieved in each one of these diseases, then gene therapy can become a reality," Wilson said. However, there are barriers to overcome.

The kidney is a complicated organ, he said, and diseases that occur along the nephron—from glomerular diseases such as Alport syndrome to proximal tubule diseases such as cystinuria and polycystic kidney disease—each come with a unique phenotype and different cell types involved. "This just proves that there's not going to be a one-size-fits-all approach for kidney gene therapy," he said. "It's going to have to be tailored for each individual disease state."

Kidney gene therapy "is definitely in its infancy," according to the literature, Wilson said. During the past 25 years, the number of publications about gene therapy averaged between 500 and 1000 per year, he explained, but when looking specifically for those related to kidney diseases, the most in a given year has been 12. "There is a lot of availability in this space," he said. "New approaches need to be made…new diseases need to be targeted."

Trying to interest pharmaceutical companies in the topic is another challenge to overcome, said Wilson. It takes time for research, and a vector that may work for one kidney disease may not work for another. Finding enough study participants for rare diseases and funding also are concerns. Additionally, the long-term effects of gene therapies are unknown.

Still, a few recent advances in gene therapy were highlighted at Kidney Week, including in a preliminary program on RNA gene editing and gene therapy. Several abstracts were presented on adeno-associated viruses (AAVs) and nanoparticles as potential delivery methods for gene therapies, ultrasound technologies, gene transfer in vivo in mice and pigs, and gene transfer in human kidney organoids, Wilson said.

A review (4) on the current status and prospects of viral vector-based gene therapy for kidney diseases covered antisense therapy (the use of antisense oligonucleotides to target messenger RNA) for ADPKD, small interfering RNA (the use of a double-stranded RNA molecule to silence genes by cleaving mRNA) for primary hyperoxaluria, lentivirus vectors to deliver gene therapy for cystinosis, and AAV or lentivirus vectors to deliver gene therapy for Fabry disease. However, none of these involved gene transfer to the kidney directly, which is where the field needs to advance, Wilson pointed out.

Wilson highlighted some of the latest articles in the following areas of gene therapy:

- **Nanoparticles for gene transfer to the kidney.** Two reviews (5, 6) showcase efforts to improve the use of this technology to target the kidney.
- **Use of lentivirus vectors to deliver gene therapy.** In a recently published article (7), investigators retargeted lentiviruses to the kidney in mice using a Zika virus envelope glycoprotein for Dent disease, in which they were able to rescue expression of the chloride channel ClC-5.
- **Use of AAV vectors to deliver gene therapy.** One study in this area (8) used an AAV-based gene therapy to target the defects in the podocyte gene *NPHS2* in human and mouse models of childhood genetic nephrotic syndrome, leading to improvements in urinary albuminuria. In 2024, Purespring Therapeutics, a London, United Kingdom, company with which two of the authors are affiliated, raised $105 million to further develop AAV gene therapy for kidney diseases. In other advances, researchers developed a new AAV vector (9) for prophylactic and therapeutic treatment of anti-glomerular basement membrane disease.

Numerous questions remain for the future of kidney gene therapy, said Wilson, including whether nanoparticles and other methods can be used for nonviral delivery of gene therapy, whether other viruses can be engineered to target the kidney, whether vectors can be produced that target the kidney alone instead of also involving the liver, and whether gene editing can be done in the kidney in vivo. An abstract presented at Kidney Week (10) from a team at the Mayo Clinic demonstrated use of CRISPR/Cas9 editing to correct a variant in a mouse model of ADPKD.

Additional presentations in the session covered gene therapy targeting podocytes, targeting microRNA for the treatment of polycystic kidney disease, and gene-targeted therapy for hyperoxaluria. ■

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A New Step Forward in Gene Therapy Research for Kidney Diseases

By Mohamed G. Atta

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Gene therapy is increasingly studied and has shown success in treating several diseases. Among the studied replication-defective viral vector platforms—of adenovirus, lentivirus, and adeno-associated virus (AAV)—the most widely used gene therapy vehicle has been AAV. Its small size (20–25 nm in diameter), linear single-stranded DNA genome (4.7 kb), and low immunogenic potential have made it an attractive packaging system. Furthermore, modifications of its capsid have generated AAV capsid libraries with randomly generated variations that were passaged serially over cultured cells for specific capsid selection that confers more effective and tissue tropism. Examples of US Food and Drug Administration-approved AAV gene therapy for monogenic diseases include the treatment of inherited blindness in 2017 (1), spinal muscular atrophy in 2019 (2), and hemophilia in 2023 (3).

Despite the increasing spectrum of application of gene therapy using both therapeutic viral and nonviral vector platforms in many organs such as the liver, the eye, blood, and the central nervous system, gene therapy for kidney diseases has been lagging. The restrictive filtering apparatus of the kidney has made it challenging to deliver the large mass of available vectors to kidney cells. Other challenges include inefficient trafficking to a specific kidney cell because of the diverse number of cell types in the kidney and vector tropism with sequestration by the liver after systemic vector infusion. Efforts have been made in animal models over the past few years to overcome some of these challenges, such as delivering vectors directly via antegrade administration into the renal artery, direct subcapsular intraparenchymal injections, and retrograde administration.

Recently, Ding and colleagues used AAV-based gene therapy to rescue a genetic defect caused by mutations in the podocyte gene *NPHS2*, encoding podocin and resulting in congenital nephrotic syndrome (4). They identified the AAV-LK03 serotype as a highly efficient transducer of human podocytes. The authors demonstrated that AAV-LK03 mediated the transduction of podocin in mutant human podocytes, resulting in functional rescue in vitro. However, AAV-LK03 was a poor transducer of mouse podocytes in vitro. Instead, the use of AAV2/9 gene transfer, both before induction of disease in conditional knockout mice or 2 weeks after induction disease in proteinuric conditional knockin mice, resulted in successful amelioration of kidney diseases, offering both therapeutic and prophylactic benefits of gene therapy.

In a more recent study, Wu and colleagues identified a new AAV vector that specifically targets glomerular cells (5). To select kidney-specific AAV capsids, the authors sequentially screened a random AAV2 display peptide library in vivo and identified a sequence with higher tropism to kidney tissue, particularly to the glomeruli. Applying luciferase reporter gene activity, they demonstrated that this vector was specifically transduced in glomerular endothelial cells (GECs) but not in human podocytes or mesangial cells. The new vector, AAV2-GEC, was subsequently packaged with the gene encoding *IdeS* (AAV2-GEC-*IdeS*), the *Streptococcus pyogenes* protease that specifically cleaves immunoglobulin G in the hinge region. To test its prophylactic and therapeutic potential in a mouse model of anti-glomerular basement membrane (anti-GBM) disease, treatment with AAV2-GEC-*IdeS*, 2 weeks before or 1 day after induction of anti-GBM glomerulonephritis, was protective (Figure). Compared with control mice injected with AAV2-GEC without *IdeS*, treated mice had lower and less persistent albuminuria and had weaker deposition of immunoglobulin G on the GBM.

The study is a step forward in providing proof of concept that gene therapy might be a viable treatment strategy for kidney diseases and may further support evaluation of its translational potential in the future.

Research and new methodologies are key in this journey of discovery to answer many questions such as determining the lowest therapeutic vector dose that prevents potential toxicities, overcoming the development of anti-AAV neutralizing antibodies that will likely prevent vector readministration, and restricting the number of patients eligible for AAV gene therapy. Hepatoxicity remains a primary safety consideration in any systemic AAV delivery, as most AAV serotypes efficiently traffic to the liver, irrespective of the target cell. Despite the low-frequency AAV integration events, long-term safety concerns of genotoxicity after systemic AAV vector administration will require close monitoring.

The study by Wu et al. (5) presents welcome progress in AAV-based gene therapy of kidney diseases. More work is needed to develop the next generation of gene-based treatment that addresses existing challenges before applying this treatment to human trials. ■

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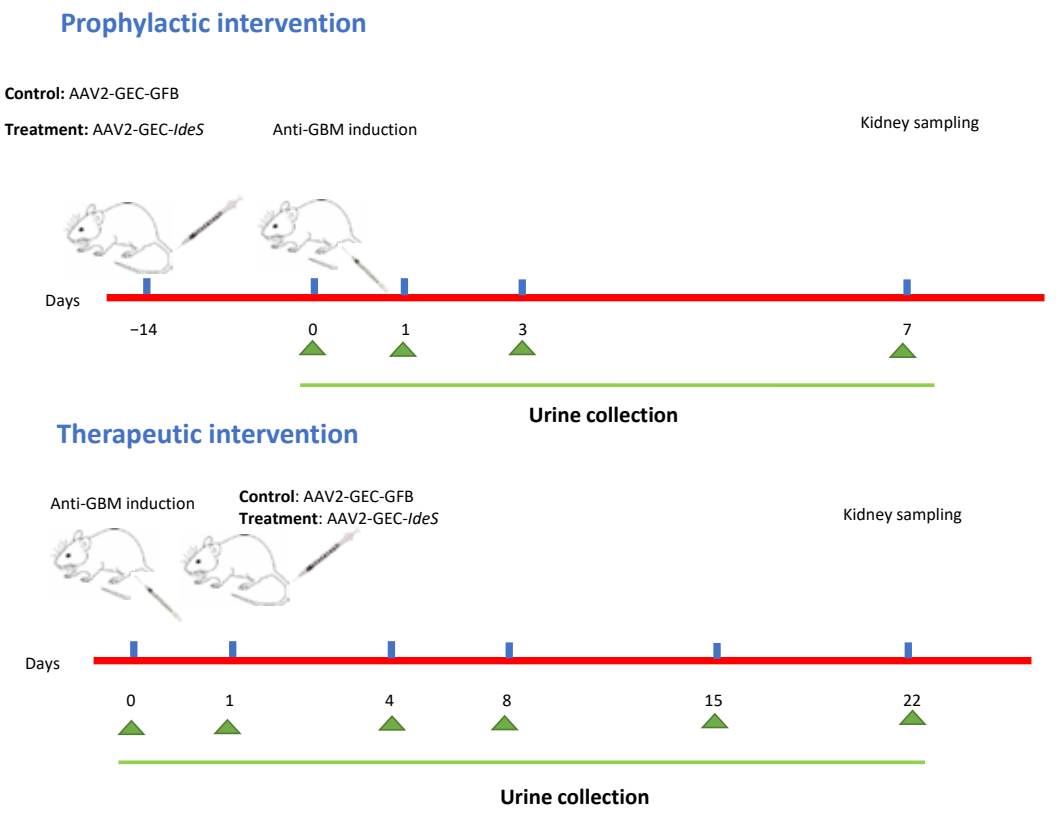
Figure. Treatment with AAV2-GEC-*IdeS*



AAV2-GEC delivery of *Ide*S, at a dose of 1×10^{13} vg/kg, prevented and successfully treated anti-GBM glomerulonephritis. GFB, glomerular filtration barrier.

Palliative Care Underused in Children With CKD

By Karen Blum

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One of the first requests Taylor House, MD, received during her pediatric nephrology fellowship at Seattle Children's Hospital was to counsel a young adult patient wanting to discontinue dialysis. House, feeling underequipped to assess the patient's goals for care, asked the person who paged her if the palliative care team was working with the patient. Their response suggested that children on dialysis do not typically die, so why would they need palliative care?

It was this experience that shaped House's efforts to improve the quality of life and care for children and adolescents with chronic kidney disease (CKD) by integrating palliative care. The relatively high survival rate among this patient population is "all the more reason why we need palliative care because the goal is not just to make what's bad less bad, but it's also to make what's good better, stronger," said House, now a pediatric nephrologist with University of Wisconsin Health, in an interview.

There is a lot of confusion over what constitutes palliative care in this population, said pediatric nephrologist Aaron Wightman, MD, in a presentation at Kidney Week 2024. Wightman is codirector of education at Seattle Children's Hospital's Treuman Katz Center for Pediatric Bioethics and Palliative Care. To their knowledge, he and House are the only pediatric nephrologists in the country who have completed certificate training in palliative care, an indication of the developing nature of this field.

"We in pediatric nephrology are very much at the beginning of our journey," Wightman reflected. Although there have been "incredible advances" in the understanding and treatment of kidney diseases in the past 50 years that have significantly improved children's survival, a life with CKD is burdensome, he said.

"Patients with CKD on dialysis report higher levels of pain, nausea, pruritus, fatigue, poor growth or sleep, ... depression, anxiety, trauma, and post-traumatic stress symptoms relative to healthy children and, frankly, relative to other children with chronic disease," Wightman said (1). They frequently miss school, social interactions, and life opportunities due to their disease.

Palliative care—not to be confused with end-of-life or hospice care—is a needs-based approach focused on providing relief from the stress and symptoms of serious illness, he said, with the goal of improving the quality of life for the child and their family. The goal is to add life to the child's years, not simply years to the child's life, according to an American Academy of Pediatrics description (2). High-quality palliative care addresses four domains: physical symptoms, psychosocial distress, open communications about serious illness, and care coordination.

"There's an under-recognition of how significant some of the burdens are for [children] who have kidney disease and their families and how palliative care can help to address those," House said. "We've made so many strides in the clinical medicine of pediatric kidney disease…and I worry that sometimes that has maybe outpaced the emphasis that we've put on [patients'] quality of life." Pediatric nephrology patients make up fewer than 3% of those seen by specialty palliative care teams, she noted (3).

Palliative care is rarely used or written about in pediatric nephrology, Wightman said. If it is addressed, it is typically an afterthought when active treatments did not work or mentioned at the end of ethics chapters in nephrology textbooks.

Embracing and integrating palliative care presents an opportunity for nephrologists, Wightman and House said. In surveys, their group and others have found that 80%–100% of pediatric nephrologists, nephrology nurses, and nephrology fellows believe that palliative care services for children with advanced kidney disease must be further developed (4). However, several barriers exist.

Despite support behind studying palliative care in children, the surveys show less comfort among nephrologists with providing primary palliative care (4). More than half of the survey respondents misconstrue palliative care as giving up or diminishing hope, and some worry that patients share these misconceptions, said Wightman. But parents and patients "actually hold very few preconceived notions of what palliative care is, and when explained to them, they desire it," he continued.

Ideally, palliative care should be discussed at the time of diagnosis. But it is never too late to integrate it, House said, noting that she has never had a patient and family decline palliative care services. She asks colleagues, "Is there ever *not* a good time to emphasize someone's quality of life?"

Another challenge is determining which children with kidney diseases would benefit from palliative care. The World Health Organization (5) and the American Academy of Pediatrics (6) recommend early palliative care for all children with life-limiting conditions, Wightman explained. "I would make the case [that] this includes nearly all children with advanced kidney disease and some children with conditions such as nephrotic syndrome that can be particularly burdensome," he said. However, this could amount to 200,000 patients in the United States alone (7), so referrals to existing palliative care clinics could overwhelm the system, Wightman noted.

Additionally, there are no suitable palliative care models available for adaptation to pediatric nephrology. In adult nephrology, patients referred to a kidney supportive-care clinic are typically at a decision point of initiating dialysis or pursuing exclusively conservative measures, House said. "That rarely happens in [pediatric] nephrology, because patients and families want both. They want to start dialysis *and* they want somebody to focus on their quality of life."

Pediatric oncology is not an exact match either; for example, cancer is typically a high-intensity disease over a shorter period, whereas kidney diseases are often long-term conditions with fluctuating levels of intensity.

Meanwhile, House and Wightman agreed that there is a need for more training for pediatric nephrologists in primary palliative care. "We need to leverage our community and its particular advantages," Wightman said, noting that pediatric nephrologists have continuity with patients and their families, following them for decades. "We are their medical home," he said. "We engage in holistic care models already and utilize interdisciplinary models with continuity nurses, social workers, or dietitians."

Approximately 97% of fellows expressed interest in this training during their fellowship (4). But palliative care is currently not offered among competencies for pediatric nephrologists by the American Board of Pediatrics or the Accreditation Council for Graduate Medical Education, Wightman highlighted. He and House have taken steps to address this, such as leading a workshop at the 2022 International Pediatric Nephrology Association Congress, which was attended by 175 pediatric nephrologists from around the world. House knows of two pediatric nephrology fellows, including one of her mentees, planning to pursue fellowships in palliative care.

Wightman and House are working to establish kidney supportive-care clinics at their institutions. At certain points in a patient's journey, such as when they start dialysis or are referred for transplant, they would automatically come to the clinic to have their psychosocial or other needs met. Meanwhile, Wightman and House promote palliative care to their patients and consult with colleagues as needed.

Pediatric nephrologists looking to get involved could engage patients in collaborative decision-making, they said. The PRO-Kid (patient-reported outcome measure for the assessment of symptom burden in pediatric chronic kidney disease) (8), a recently validated patient symptom assessment tool, can be used to cover patients' physical and psychosocial symptoms.

Table. Resources to support nephrologists' palliative care skills

Center to Advance Palliative Care (www.capc.org)
Courageous Parents Network (www.courageousparentsnetwork.org)
Graduate Certificate in Palliative Care, University of Washington (www.pctc.uw.edu)
International Children's Palliative Care Network (https://icpcn.org/resources/)
International Society of Nephrology Academy webinar (www.theisn.org/blog/event/isn-ipna-webinar-making-life-better-importance-of-palliative-care-in-pediatric-nephrology/)
NephroTalk (9)
Palliative Care Education and Practice, Harvard Medical School (https://pallcare.hms.harvard.edu/courses/pcep)
VitalTalk (www.vitaltalk.org)

Adapted from Thomas et al. (10).

A number of free resources exist to strengthen palliative care skills, including online trainings offered by VitalTalk, the Courageous Parents Network, and the Center to Advance Palliative Care (Table). In addition, House advised, "Get to know your local palliative care team to understand what their availability and bandwidth is, and discuss ways you could potentially collaborate." Harvard University and the University of Washington offer more formal certificate training programs.

"It's not feasible to think that every [child] who has CKD3 or higher is going to see a specialty palliative care physician," House said. "We have to find a way to meet that need among ourselves. We're uniquely positioned to do that because we have the most experience and understanding of kidney diseases." ■

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Symptom Management in CKD

By Areeba Jawed and Kunal Bailoor

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Patients with chronic kidney disease (CKD) and kidney failure continue to have high burdens of symptoms in multiple domains, which presents challenges for treating nephrologists. Here, we briefly review updates in some commonly reported symptom domains and treatments among those experiencing CKD and kidney failure (Table).

Pain

Pain affects approximately 70% of patients with CKD. Nociceptive pain, often described as sharp, cramping, or dull, can be treated with nonopioid analgesics if mild; however, caution needs to be exercised with nonsteroidal inflammatory drug use, given its adverse effects (1, 2). If the pain is severe, the preferred opioids are oxycodone or hydromorphone for short-acting pain relief and fentanyl, methadone, or buprenorphine for long-acting pain relief. The following medications should generally be avoided in patients with advanced CKD, given their adverse effects and impaired pharmacokinetics: codeine, tramadol, morphine, and meperidine or pethidine.

If the pain is neuropathic, described as shooting, stabbing, or burning, it is often treated with gabapentin, pregabalin, or tricyclic antidepressants. If none of these are effective, methadone may be considered.

Nausea and vomiting

Nausea and vomiting are common symptoms in patients with CKD regardless of stage or whether the patient is undergoing dialysis. Despite nausea and vomiting being common concerns among patients with CKD, there is a lack of effective interventions (3). Given the high frequency of adverse effects related to antiemetics, in particular, extrapyramidal reactions, nonpharmacologic measures such as smaller, frequent meals; avoiding strong aromas; and sitting up after a meal are recommended first. Relaxation techniques such as acupuncture may also be considered.

Pharmacologic management includes low-dose haloperidol (0.5 mg every 8 hours as needed), followed by ondansetron if there is no QTc (heart rate-corrected QT interval) prolongation. For patients with gastroparesis, also known as gastric stasis, metoclopramide dosed for kidney function should be considered.

Lack of appetite

Approximately 40%–50% of patients with CKD experience poor appetite, which may worsen with kidney disease progression. Yet, limited information is available regarding appetite management. Nonpharmacologic interventions, such as nutritional supplements, frequent meals, and physical activity as tolerated, are preferred to stimulate appetite. Appetite stimulants such as megestrol acetate have not proven to be effective in the population with CKD and are, therefore, not recommended (4).

Depression

The incidence of depression in patients with CKD ranges between 30% and 50% (5). Despite this prevalence, depression remains undertreated.

A recent systematic review (6) suggested that antidepressant therapy and group psychological therapy can reduce depression scores. Fluoxetine, sertraline, and escitalopram have been used in trials of patients experiencing kidney failure, as they are not dialyzable. There are fewer data available for patients with CKD not on dialysis. The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) in patients with advanced CKD not on dialysis did not show a change in depressive symptoms with sertraline relative to placebo, suggesting that starting with nonpharmacologic therapy may be a better initial strategy in these patients (7).

Itching

Uremic pruritus is reported in 60%–80% of all patients experiencing kidney failure at some point in their lifetime (8). Gabapentin and pregabalin have been shown to reduce itch. Hydroxyzine has been shown to have similar efficacy to gabapentin (8). Difelikefalin, an intravenous selective peripheral kappa opioid agonist, has also been shown to reduce itch intensity significantly (9).

In placebo-controlled trials, topical therapies such as capsaicin, gamma-linolenic acid, and cromolyn sodium have been shown to be efficacious. Interventions with less clear benefits include managing hyperphosphatemia (e.g., the Dialysis Outcomes and Practice Patterns Study [10] showed no relationship between phosphorus level and pruritus), ultraviolet therapy (efficacious but with a high discontinuation rate), or sedating antihistamines (in which adverse effects may be significant, particularly in older adults).

Insomnia and fatigue

Patients with advanced CKD and kidney failure often experience sleep disruption and fatigue, with exceptionally high rates of sleep apnea. A meta-analysis reported that the prevalence of insomnia was 46% in patients on hemodialysis and 61% in patients on peritoneal dialysis (11). Fatigue is generally multifactorial; however, an anemia evaluation is recommended. Patients with CKD are also at risk of developing restless leg syndrome, whether due to comorbid iron deficiency, type 2 diabetes, or increased estrogen levels in kidney failure. Nonpharmacologic strategies such as ensuring appropriate sleep hygiene and gentle exercise, as well as treatment of comorbid primary sleep disorders, are the mainstays of management (11).

A high symptom burden remains in patients with CKD, with or without dialysis therapy. Early recognition and management of these symptoms are essential aspects of patient-centered care. ■

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Table. Common symptoms and treatment measures for CKD and kidney failure

Symptom domain	Treatment measure
Nociceptive pain	Short acting: Oxycodone, hydromorphone Long acting: Fentanyl, methadone, buprenorphine
Neuropathic pain	Gabapentin, pregabalin, tricyclic antidepressants, methadone (if severe)
Nausea	Low-dose haloperidol, ondansetron, metoclopramide dosed for kidney function (if concurrent gastroparesis)
Lack of appetite	Nonpharmacologic measures preferred
Depression	Sertraline, fluoxetine, escitalopram
Pruritus	Oral: Gabapentin, pregabalin, hydroxyzine Intravenous: Difelikefalin Topical: Capsaicin, gamma-linolenic acid, cromolyn sodium
Insomnia and fatigue	Comorbid anemia evaluation, sleep apnea screening, sleep hygiene

Personalized Care Key to Kidney Allograft Longevity

By Bridget M. Kuehn

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Personalized care driven by advances in immunology, technology, and clinical care is the key to further extending the longevity of kidney allografts, according to speakers at the Kidney Week 2024 session, Improving Kidney Transplant Longevity: Advanced Technologies on the Horizon.

The immunosuppressive regimen used for patients undergoing kidney transplant has not changed much in over 12 years, said Gaurav Gupta, MD, division chief for nephrology and medical director of kidney transplantation at Virginia Commonwealth University in Richmond. Tacrolimus mycophenolate and low-dose steroids remain the treatments of choice for most patients after kidney transplant. Despite the lack of innovation, patient and kidney allograft survival has improved, owing to improved management techniques, with almost two-thirds of deceased donor kidney recipients surviving at 10 years post-transplant, according to 2008–2011 data (1). Yet kidney transplant survival rates in the United States still lag behind those in other countries. "There is still a lot of work to be done," Gupta said. "Up to a third of transplants will fail within the first 5 or so years."

Gupta and other speakers outlined how advances in clinical care, policy, immunology, and technological advances may help further extend the lifespans of kidney allografts and the patients who receive them.

Adherence is crucial

Adherence, limited by access to immunosuppressive drugs, may be one reason that the United States lags behind other nations. Gupta explained that nearly half of all allograft failures result from antibody rejection, with nonadherence driving half of them. However, Gupta noted that patients' nonadherence to immunosuppressive regimens is often not voluntary. He said that studies of US graft survival rates begin to diverge from other countries after 1 year; at this point, the duration of graft survival hinges largely on patient incomes (2).

Until recently, Medicare only covered immunosuppressive drugs for up to 1 year post-transplant, so patients without private insurance coverage or financial means were at risk of losing access. But starting in January 2023, Medicare extended that coverage longer term for eligible patients (3). "Access to immunosuppression probably is the most important thing we can do for our patients' long-term graft survival," he said.

New technologies are also helping to identify patients who are voluntarily nonadherent to their immunosuppressive drugs or who need extra support to keep up with their regimens. Gupta cited a study showing that patients who used pill bottles with wireless-enabled technology had better adherence than those receiving standard of care (4). The wireless technology monitored when patients opened their pill bottles and sent them automated text reminders to take their medication. Clinicians also followed up by telephone in some cases.

In addition to highlighting a promising tool, the study showcased how common nonadherence is. Gupta noted that adherence among transplant patients is likely only about 60% to 70% in the first 6 months after transplant, based on the data.

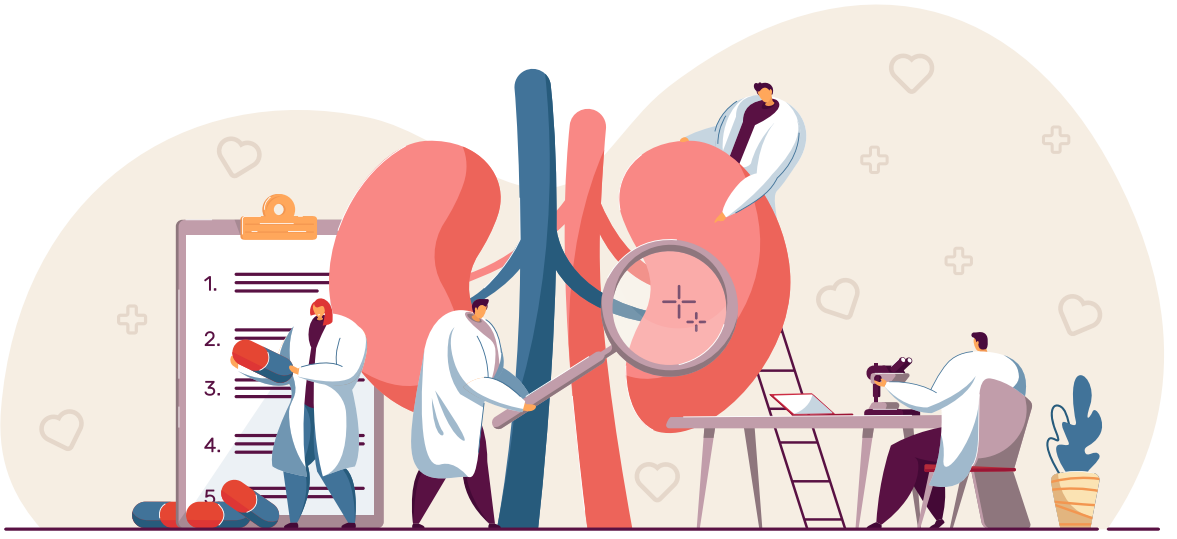
Gupta explained that other tools are available "over the counter," such as pill boxes that notify a patient's family member or caretaker of nonadherence. He said that several organizations also have mobile applications to help patients with adherence. Data on such an application, which may be available in about 1 year, suggest that it can reduce patient errors, adverse events, and hospitalization (5).

Personalized prescriptions

Monitoring patients' medication levels is also key to kidney longevity. Gupta noted that tacrolimus is metabolized in the liver by the CYP3A pathway and that mutations in the genes in this pathway may alter drug metabolism. For example, patients with the CYP3A4*22 mutation may need a lower tacrolimus dose, whereas those with CYP3A5*1 may need a higher one (6).

"Tacrolimus dosing is probably the most crucial [aspect] in terms of survival," he said. Gupta highlighted a study showing that a model taking into account genetic variants that affect tacrolimus, metabolism, age, and other factors to optimize dosing had a higher chance of meeting treatment targets (7). He suggested that incorporating such a model into electronic health records systems might help.

Another monitoring challenge is patients having frequent blood draws at a laboratory to measure drug trough levels. Gupta highlighted a promising approach using a home capillary blood draw and a blood spot that can be mailed to a laboratory, demonstrating comparable efficacy to laboratory-based approaches.



Managing drug side effects is also important. Gupta noted that tacrolimus can have neurotoxicity and chronic nephrotoxicity, whereas mycophenolate can cause bone marrow suppression and gastrointestinal disturbance. He shared a study showing that shifting patients to LCP tacrolimus improved motor function and tremors (7). Another trial showed that switching patients from tacrolimus to belatacept improved memory, executive function, and movement (8). A third study showed that switching patients with nephrotoxicity to belatacept led to better graft survival, lower rates of death, and better estimated glomerular filtration rates (9). Gupta said that clinicians should consider these options for patients having adverse effects.

Beyond preventing rejection, Gupta noted that it is essential to carefully dose medications to prevent overimmunosuppression, which can lead to deadly infections or cancer. He highlighted studies showing some infection-reduction benefits to reducing or eventually eliminating mycophenolate doses in patients taking tacrolimus (10). Gupta explained that belatacept, which has some short-term benefits, has risks of strong immunosuppression in the long term, including cytomegalovirus infections and exaggerated COVID-19 vaccine responses. He and others are studying less frequent dosing of belatacept as a way to mitigate these risks.

Gupta also emphasized the importance of adequately managing type 2 diabetes in transplant recipients. He noted that only 4%–8% of kidney transplant recipients with diabetes are receiving appropriate diabetes therapies, like metformin or sodium-glucose cotransporter-2 inhibitors. "We have a lot of ground to cover in terms of applying what we already know for these patients in a better way," he said.

Promising research and technology

Other speakers at the session highlighted research on better donor-recipient matching and potential technology-driven diagnostic tools in the research pipeline.

Rainer Oberbauer, MD, PhD, FASN, professor at the Medical University of Vienna, Austria, shared research on how genome-wide and eplet-based compatibility may improve donor-recipient matching. He explained that currently, transplant surgeons rely on the human leukocyte antigen (HLA) system for donor-recipient matching. He noted that the HLA system is one of the most genetically diverse systems in humans and that there are 30,000 alleles in class I alone, and more are identified daily. Eplets—sequences of amino acids on the surfaces of HLA antigens—have also been linked to compatibility, Oberbauer noted. He highlighted studies using software to assess the role of eplets in the risk of rejection. Oberbauer also mentioned studies assessing the roles of mismatched gene pairs beyond the HLA system in graft survival (11).

Mariam Alexander, MD, professor of pathology at the Mayo Clinic in Minneapolis, MN, shared data on the potential to use artificial intelligence (AI)-enhanced biopsy interpretation. She noted that AI can help simplify and streamline manual tasks for pathologists. Alexander and her colleagues participated in a study showing that AI could help annotate biopsies and identify tissue classes such as glomeruli, tubules, and blood vessels (12). Alternatively, it can help with larger-scale efforts. "For any pathologist, this [task] is mundane, can be boring, and it can be very challenging to be reproducible," she said. "Artificial intelligence and machine learning models help you to review data and gather information that's unscalable with conventional techniques."

AI may also help identify signs of chronic kidney disease or signs of graft loss and help to identify biomarkers. "Today with all [of] the improvements in allograft transplantation and improved immunosuppression, graft failure due to immune injury remains the most significant cause of graft failure," she said. "We need to improve on how we pick it up and diagnose it."

Lorenzo Gallon, MD, professor of medicine and surgery and director of the solid organ transplant program at the University of Illinois Chicago, highlighted research on biosensors and biomarkers for post-transplant graft assessment. He shared research looking at ways to identify genomic

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biomarkers and developing biosensor devices that could be implanted in a transplanted kidney to measure temperature and blood flow as biomarkers for rejection. He and his colleagues are currently studying a biosensor in large animals that, when implanted on a transplanted organ, could notify transplant teams of changes indicative of rejection.

Gallon said he expects that using biomarkers to assess rejection will become more common in nephrology despite the complexity, and he urges nephrologists to learn more about these advancements. "We have to embrace them and start learning how to use them," he said.

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Donor DNA Monitoring for Early Diagnosis of Kidney Transplant Rejection

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Donor-derived cell-free DNA (dd-cfDNA) monitoring may enable earlier diagnosis and treatment of antibody-mediated rejection (AMR) after kidney transplantation, suggests a preproof paper in *Nephrology Dialysis Transplantation*.

The open-label randomized clinical trial enrolled 40 kidney transplant recipients with anti-histocompatibility leukocyte antigen de novo donor-specific antibodies (dnDSAs) but no previous biopsy-confirmed diagnosis of AMR. All patients had an estimated glomerular filtration rate of 20 mL/min/1.73 m^2 or greater.

Patients in the intervention group received dd-cfDNA monitoring, with biopsy triggered by a dd-cfDNA level of greater than 50 copies/mL. Controls received standard care, with biopsy performed in response to clinical indications. In both groups, protocol biopsies were performed after 12 months. Time to diagnosis of chronic or active AMR was compared between groups.

Of 39 patients with functioning grafts at the time of study completion, 16 had increased absolute dd-cfDNA. Kidney biopsy was performed in 13 patients in the intervention group (all for increased dd-cfDNA) and 13 in the control group (all according to protocol). Of these 26 patients, 12 had confirmed AMR: seven in the intervention group and five in the control group.

The median time to AMR diagnosis was 2.8 months for patients assigned to donor DNA monitoring versus 14.5 months in the control group. In the study population of patients who were dnDSA-positive, longitudinal dd-cfDNA monitoring had a diagnostic sensitivity of 83%, specificity of 79%, and positive and negative predictive value of 77% and 85%, respectively. Several patients had increased absolute dd-cfDNA in association with subclinical AMR.

According to the authors, the study is the first randomized clinical trial to examine the possible benefit of dd-cfDNA monitoring in kidney transplant recipients. The findings suggest that dd-cfDNA-guided biopsy can shorten time to diagnosis compared with biopsy triggered by clinical events. The investigators conclude that "dd-cfDNA-guided early diagnosis may become increasingly important, since timely therapeutic intervention could significantly change the course of AMR by preventing chronic irreversible damage and thereby improve outcomes" [Akifova A, et al. Donor-derived cell-free DNA monitoring for early diagnosis of antibody-mediated rejection after kidney transplantation: A randomized trial. *Nephrol Dial Transpl*, published online November 29, 2024. doi: 10.1093/ndt/gfae282]. ■

Urine Ba Predicts Outcomes in Patients With AKI in the ICU

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In adults who are critically ill, levels of urine complement factor Ba (an activation fragment of factor B) reflect the presence and severity of acute kidney injury (AKI) as well as the likelihood of AKI recovery or persistence, according to a meta-analysis in *Kidney International Reports*.

The researchers analyzed data on 439 adults who were critically ill, drawn from a clinical trial of early erythropoietin therapy. Of these, 187 patients had AKI at the time of intensive care unit (ICU) admission (123 patients) or at 24 to 48 hours after (64 patients). The remaining 252 patients did not have AKI.

Urine Ba fragment levels were measured in samples collected at ICU admission and at 24 and 48 hours. Associations between urine Ba and patient outcomes were assessed, including the presence, persistence, and resolution of AKI. About one-half of patients had AKI recovery (serum creatinine reduction to <0.3 mg/dL above baseline) within 48 hours. The rest were classified as having persistent AKI.

Urine Ba levels rose with increasing AKI stage, after adjustment for age and critical illness severity (applying the APACHE II [acute physiology and chronic health evaluation II] score). Urine Ba was significantly higher in patients with persistent AKI versus recovery: odds ratio, 6.6 per doubling of urine Ba level.

Urine Ba effectively discriminated between patients with and without AKI. Higher urine Ba levels were also associated with worse organ failure outcomes, including reductions in days alive, ventilator-free days, inotrope-free days, and ICU-free days.

In adults who are critically ill, AKI is associated with high morbidity and mortality and has no specific treatment options. Previous reports have suggested that complement activation fragments might be useful biomarkers of AKI. "Our findings add to previous preliminary evidence demonstrating the association between urine Ba and AKI severity," the researchers write. The findings also suggest that higher urine Ba levels may be useful in identifying patients with AKI persistence or recovery. The authors discuss the implications for future studies of AKI treatment, including trials of factor B inhibition [Stenson EK, et al. Urine complement factor Ba identifies persistent acute kidney injury and organ failures in critically ill adults. *Kidney Int Rep*, published online November 24, 2024. https://doi.org/10.1016/j.ekir.2024.11.030]. ■

"Equivalent" Outcomes of Surgery for Cancer in Patients on Hemodialysis

https://doi.org/10.62716/kn.000062025

In patients undergoing hemodialysis with resectable cancers, surgery may provide clinical outcomes comparable to those of other patients with cancer, suggests a pre-proof paper in the *Clinical Kidney Journal*.

The multicenter Japan Cancer and Dialysis (J-CANDY) study analyzed 502 patients on hemodialysis diagnosed with primary cancers between 2010 and 2012. Kidney cancer was the most common diagnosis, followed by colorectal, stomach, lung, liver, bladder, pancreas, and breast cancers. Surgical practice patterns and patient outcomes were compared with those of general patients with cancer from the National Cancer Center database.

Fifty-seven percent of patients on hemodialysis were asymptomatic at the time of cancer diagnosis; most were diagnosed using routine screening tests. The median time from hemodialysis initiation to cancer diagnosis was 74 months. In patients with kidney and breast cancers, the intervals were 142 and 156 months, respectively.

Seventy-four percent of patients underwent surgery. Kidney cancer was the most common diagnosis in the surgically treated group, followed by colorectal and stomach cancer. Overall, 99% of patients undergoing surgery were considered to have resectable cancers compared with 23% in the nonsurgical group. Of those patients who did not undergo surgery, more than half (52%) had metastatic cancers.

Overall 3-year survival was 80% in patients undergoing surgery versus 32% in the nonsurgical group. Eighty percent of deaths among patients undergoing surgery were noncancer related, whereas 70% of deaths in the nonsurgical group were cancer related. Pancreatic cancer and anemia were risk factors for poor outcomes. Rates of surgical treatment and 3-year outcomes among patients on hemodialysis were similar to those of general patients with cancer.

Patients undergoing hemodialysis have an increased incidence and mortality of cancer. There is a lack of data on clinical management of cancers in patients on dialysis and whether surgical treatment leads to an improved prognosis. In appropriate cases, the "prognosis in [patients with cancer on hemodialysis] might be equivalent to that of general [patients with cancer]," the researchers write. "[P]hysicians should consider surgery a treatment option if [patients on dialysis] are diagnosed with resectable cancer." The authors highlight the need for further studies of cancer screening and treatment strategies for the population undergoing hemodialysis [Toriu N, et al. Cancer diagnosis and prognosis after initiation of hemodialysis: Multicenter Japan Cancer and DialYsis (J-CANDY) study. *Clin Kidney J*, published online December 20, 2024. https://doi.org/10.1093/ckj/sfae430]. ■

Intensive BP Strategy Reduces Cardiovascular Risks in Type 2 Diabetes

https://doi.org/10.62716/kn.000072025

For patients with type 2 diabetes and hypertension, intensive therapy with a systolic blood pressure (BP) target of less than 120 mm Hg leads to reduction in major cardiovascular events, reports a clinical trial in *The New England Journal of Medicine*.

The study included 12,821 patients aged 50 years or older with type 2 diabetes, elevated systolic blood pressure, and cardiovascular disease risk factors, enrolled at 145 clinical sites in China. Patients were assigned to intensive therapy targeting a systolic BP of less than 120 mm Hg or to standard treatment with a target of less than 140 mm Hg. The mean age was approximately 64 years; 45% of patients were women.

Patients continued their assigned treatment for up to 5 years. Major cardiovascular events—nonfatal stroke or myocardial infarction, heart failure treatment or hospitalization, or death from cardiovascular causes—were compared between groups.

At 1 year, mean systolic BP was 121.6 mm Hg in the intensive therapy group versus 133.2 mm Hg in the standard treatment group. The difference was sustained throughout the study period. At a median follow-up of 4.2 years, rates of primary outcome events were 1.65 per 100 person-years with intensive therapy versus 2.09 events per 100 person-years with standard treatment (hazard ratio [HR], 0.79).

Intensive BP control achieved significant reductions in fatal or nonfatal stroke (HR, 0.79) but not in myocardial infarction, heart failure, or cardiovascular mortality. Incidence of albuminuria was lower in the intervention group (HR, 0.87); there was no difference in the occurrence or progression of chronic kidney disease. The two groups had similar rates of serious adverse events, although symptomatic hypotension and hypokalemia were more frequent with intensive treatment.

Despite previous clinical trials, the optimal blood pressure target for patients with type 2 diabetes remains undefined. The new findings show a reduced risk of major cardiovascular events in patients receiving intensive therapy with a systolic BP target of less than 120 mm Hg compared with standard treatment. The researchers emphasize the need for further studies in populations with differing ethnicity and other characteristics [Bi Y, et al.; BPROAD Research Group. Intensive blood-pressure control in patients with type 2 diabetes. *N Engl J Med*, published online November 16, 2024. doi: 10.1056/NEJMoa2412006]. ■

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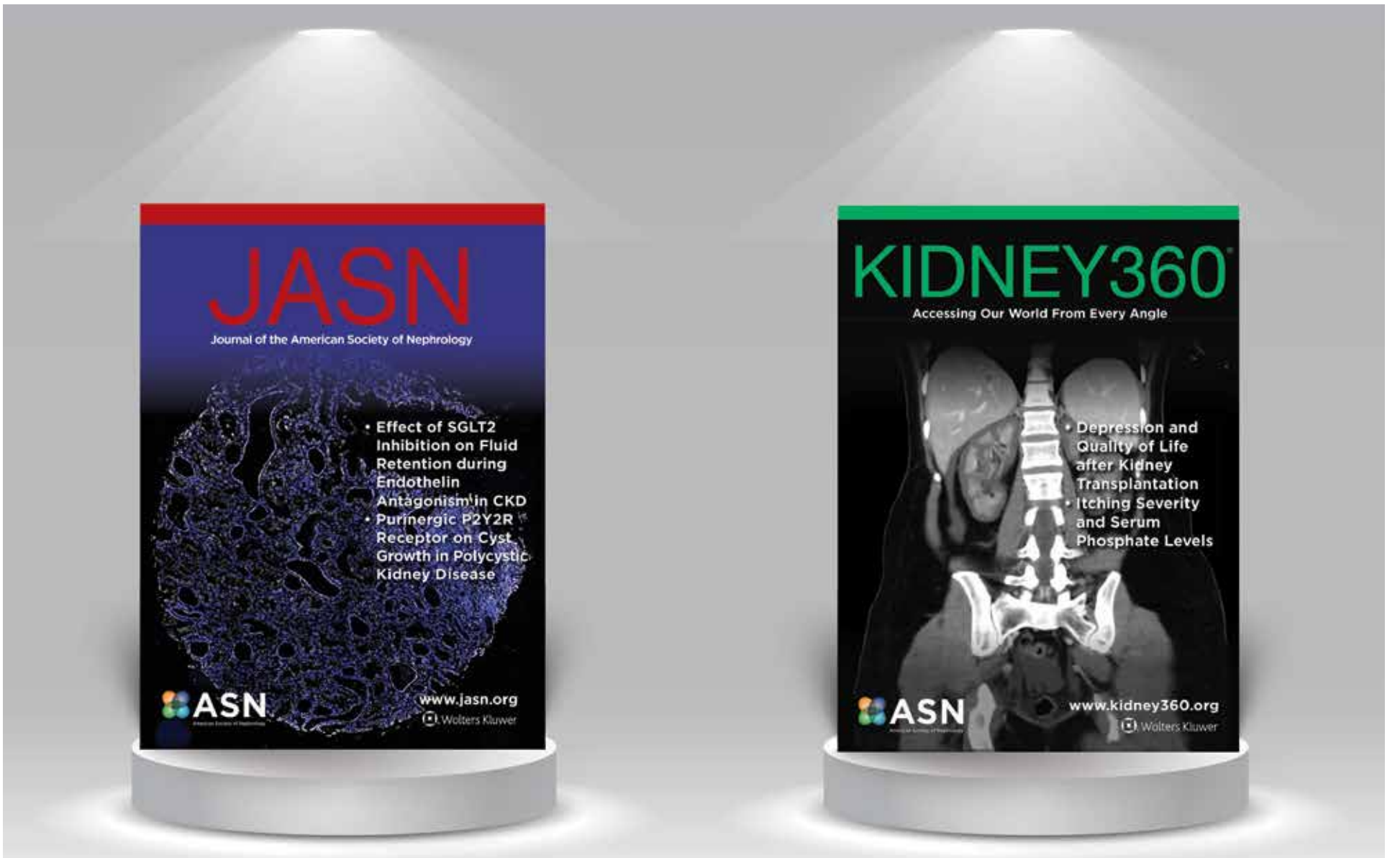

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