ASN American Society of Nephrology

Kidney News

June 2026 | Vol. 18, Number 6

NephroEconomics 2026: Costs and Innovation Pivotal for Kidney Care

By Bridget M. Kuehn

https://doi.org/10.62716/kn.003752026

Initiatives designed to rein in the costs of kidney care and increase care quality and innovation were the focus of the speakers at ASN's NephroEconomics 2026: Keeping Up With Changes in Kidney Care.

The virtual webinar was held on April 17th, as part of a collaboration between ASN and Columbia University's Irving Medical Center Division of Nephrology. Speakers at the event reviewed evolving federal payment models and the growing pressure to constrain kidney care costs. They also emphasized the impact of innovations in the transplant space and the challenges of balancing the need for care innovation with growing financial pressures on patients and the health system. In addition, speakers highlighted ASN's "Transforming Kidney Health Research" (TKHR) initiative's goal of tripling federal funding for kidney research to meet the urgent need to shift spending toward interventions that can preserve kidney health and patient quality of life (1).

"There are just so many opportunities where research or the creation of more knowledge could help catalyze our ability to get patients off this path from kidney disease detection and chronic kidney disease care through kidney failure and then to kidney replacement transplantation," said ASN President Samir M. Parikh, MD, FASN.

Finding value

Since the advent of the End-Stage Renal Disease (ESRD) Program benefit in 1973, which ensured Medicare coverage for kidney failure, the federal government has grappled with the challenge of paying for kidney care, noted Suzanne Watnick, MD, FASN, the inaugural ASN Health Policy Scholar, chair of the ASN Policy and Advocacy Committee, and a professor of medicine at the University of Washington, Seattle. Those pressures have only grown, as people with kidney failure, who make up 1% of Medicare beneficiaries, account for 7% of the costs. Yet, efforts to reduce costs have led to payments to nephrologists that have not kept pace with inflation, have stymied innovation, and, in some cases, have negatively impacted patient care, Watnick explained. "We really do need an act of Congress to overhaul the current system," she added.

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The Kidney-Heart-Brain Connection: Interactions Linked With Brain Symptoms in People With Kidney Diseases

By Bridget M. Kuehn

https://doi.org/10.62716/kn.003822026

The risk of cognitive impairment increases as kidney function declines, and as many as three-quarters of individuals on dialysis experience deficits in thinking, memory, and decision-making as their condition progresses, making it a pressing concern for nephrologists and people with kidney diseases (1).

"It is a major challenge," said Zeid Khitan, MD, FASN, professor of medicine and chief of the Renal Division at Marshall University Joan C. Edwards School of Medicine in Huntington, WV. "Cognitive impairment can affect medication adherence, dialysis decision-making, diet and fluid restriction, transplant education, home dialysis training, and informed consent," he continued.

Khitan explained that patients may struggle to recall information, process instructions, or make complex decisions. "This is especially important in advanced CKD [chronic kidney disease], where treatment choices are already technically and emotionally demanding," he said.

Some recent studies are helping shed light on the underlying mechanisms driving complex interactions

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ASN American Society of Nephrology

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074.

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $20 for *ASN Kidney News* subscription.

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NephroEconomics 2026

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Mallika Mendu, MD, MBA, FASN, a nephrologist at Brigham and Women's Hospital, Chief Population Health Officer at Mass General Brigham, and an associate professor at Harvard Medical School in Boston, MA, and chair of ASN's Quality Committee, highlighted the evolution of federal value-based payment models that have tried to control costs while boosting quality and patient outcomes. She noted that some past payment models, such as the Comprehensive ESRD Care Initiative, have not yielded cost savings for Medicare, so the government has increasingly focused on models that will yield savings—a focus that she expects will continue.

Improving quality and patient experience was also emphasized in President Donald J. Trump's 2019 Advancing American Kidney Health Initiative. The initiative set three ambitious goals for 2023: reducing kidney failure incidence by 25%, doubling the number of kidneys available for transplant, and ensuring that 80% of new patients with kidney failure receive home dialysis or a transplant.

Some recent models have made progress toward those goals, Mendu said; however, they have not necessarily achieved cost savings for Medicare. For example, Mendu noted that the mandatory ESRD Treatment Choices Model was recently sunsetted early because it did not increase the proportion of patients on home dialysis or wait-listed for transplant, and it led to increased Medicare costs. More recent models, such as Kidney Care First (KCF) and Kidney Care Choices (KCC), have achieved greater success in improving patient outcomes. She cited an evaluation report that found peritoneal dialysis increased by 26% in the KCF model and by 8% in KCC (2). Optimal dialysis starts increased 16%. There was also an increase in patients who were wait-listed for a transplant but no increase in transplants. Hospitalizations, emergency department visits, and readmissions did not change in the model. "The results were truly impactful in terms of improving clinical outcomes and quality for our patients," she said.

However, changes are coming to the programs, with a 1% discount in KCC starting in 2026, which will require greater improvements in patient outcomes for participating organizations to receive financial incentives, Mendu said. KCF quarterly payments have also been cut 50%, and a $15,000 bonus for patient transplants has been eliminated. The KCF model will also end in 2026. The changes will mean that participating clinicians and organizations will have to achieve better outcomes to achieve shared savings, and they may have to make up-front investments on their own to do so, Mendu said. She noted, however, that this may reduce participation in these voluntary programs. "CMS [Centers for Medicare & Medicaid Services] has stated very clearly in all of its value-based care models that when we have these models now moving forward, the way they will be designed is to ensure that CMS appreciates savings," she explained.

Mendu predicts that a new value-based kidney care model is coming and may be mandatory. "Because this is a condition that impacts patients who have [a] very high total cost of care, the federal government is particularly interested in managing costs and focused on outcomes and quality for this population," she said.

She also emphasized the importance of nephrologists' input in the design of new payment models to ensure that they benefit patients and offer realistic financial incentives for participating clinicians and organizations. "If we're successful there, we have the opportunity to slow the progression of conditions like chronic kidney disease," Mendu said. "If we do that, we're going to reduce the total cost of care; we're going to improve clinical outcomes."

Prioritizing innovation

Watnick, along with individuals living with kidney diseases and advocates, testified before the US House Ways and Means Subcommittee on Health during the "Improving Kidney Health Through Better Prevention and Innovative Treatment" hearing on March 18th. The hearing garnered bipartisan support for a greater focus on screening and diagnosis to prevent progression to kidney failure, on individualized care, and on ensuring patients' access to innovative therapies.

"Personalized patient care really is the future," Watnick said, "We need to address each person's kidney disease journey. If you're focusing only on dialysis, that becomes a siloed environment. We need to think about upstream care—that whole journey—and make sure that there are smooth transitions of care so our patients can land softly."

The hearing also highlighted that the United States invests only $20 annually in kidney disease research per patient with kidney disease, just a fraction of the $400 per patient spent on cancer research. Parikh noted that this strong investment in cancer research has yielded major advancements in care, as have investments in research on other diseases such as HIV and diabetes. To help boost investment in kidney research, ASN launched the TKHR initiative seeking an additional $1.8 billion per year for kidney research, starting with a $1 billion down payment. More than 35 organizations have signed onto a TKHR kickoff letter from ASN, the National Kidney Foundation, and other organizations (3). The initiative has also gained bipartisan and bicameral support, Parikh said.

Several speakers also discussed innovation occurring in the transplant space, including the modernization of the Organ Procurement and Transplantation Network and the implementation of the Increasing Organ Transplant Access Model, which are paired, matching initiatives. Other efforts to improve kidney allocation were also reviewed.

Financial pressures

The field of kidney care has already seen a flurry of innovative therapies, noted Sri Lekha Tummalapalli, MD, MA, MBA, FASN, a nephrologist and health services researcher at Weill Cornell Medicine in New York, NY. She mentioned sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1), new therapies for immunoglobulin A (IgA) nephropathy, and gene therapies on the horizon for some genetic forms of kidney disease. "We really have an embarrassment of riches in terms of novel therapeutics for kidney disease," Tummalapalli said.

However, the high costs of these therapies for patients and restrictions on their use, designed to limit costs for the health system, have created barriers to access. The list prices for SGLT2 inhibitors can range from $500 to $1000 per month, she explained, leading to high costs for payors and substantial out-of-pocket costs for patients. She postulated that "nobody pays the list price" because of rebates and discounts.

Some relief may be on the horizon. The 2022 Inflation Reduction Act (IRA) included a $2100 out-of-pocket drug price cap for Medicare beneficiaries that went into effect in 2025. IRA also allowed the government to negotiate drug prices with drug companies, and SGLT2 inhibitors and the GLP-1 semaglutide were part of the first two rounds of negotiations. For example, prior to negotiations, semaglutide was costing Medicare $15 billion per year, but the negotiations brought the list price down from almost $1000 per month to $274. Tummalapalli indicated that the US Food and Drug Administration has also approved a generic version of the SGLT2 dapagliflozin, and 18 companies already are approved to manufacture it. That may also lower costs and lead to fewer restrictions from payors, she noted. "This is going to be a huge boon to our patients," she said.

Tummalapalli also highlighted several other innovative policies. She noted that a recent executive order from President Trump called for most-favored-nation pricing for the United States and that 16 companies have agreed. A TrumpRx direct-to-consumer drug-purchasing platform has also been created; however, Tummalapalli said that it is unlikely to benefit most people with kidney diseases who access their medications through insurance. She explained that there are also several proposals at the Center for Medicare and Medicaid Innovation (CMMI) to implement international reference pricing or most-favored-nation pricing in Medicaid and Medicare Part B and Part D. There is also a proposal to have CMS negotiate GLP-1 prices on behalf of state Medicaid programs and Medicare Part D. "We'll see what gets implemented and what the impact is on affordability for our patients because most of our [patients with chronic kidney disease] are going to be on GLP-1s," she said.

Tummalapalli indicated that uptake of new IgA nephropathy therapies is also likely to be slow due to high costs and underdiagnoses of the condition. "Some patients will get these medications for free through copay assistance programs," she explained. "If they have commercial insurance, they can get coupons and work with the payor to get them for free, but the uptake is really going to be kind of variable due to these high prices."

She noted that the United States does not currently have a systematic approach to negotiating drug prices, unlike some countries. Concern about the potential of drug rationing or having a central decision-making body has led to that choice, she explained. However, she explained that insurance plans, pharmacy benefit managers, and prior authorization requirements still affect access. "We do place restrictions on the back end," Tummalapalli said. "We place restrictions for patients based on who can navigate the system, whether they can afford good insurance, and what their insurance looks like."

She highlighted a successful effort in Louisiana to negotiate a subscription payment model for hepatitis C medications that may be a model for other medications. She explained that the costs to the state's Medicaid program of treating patients with hepatitis C threatened to bankrupt the program. However, the state negotiated a flat fee of $58 million per year with the drugmaker for unlimited access to sofosbuvir and velpatasvir. To get the most value out of the payment, the state also ramped up screening for hepatitis C.

"This allowed five times the number of patients to receive hepatitis C treatment for a cost similar to what the state was paying before [the deal]," Tummalapalli said. It also led to reductions in mortality from hepatitis C. "It was extremely effective," she said.

She added that gene therapies on the horizon are likely to be the most expensive therapies yet. "These are revolutionary, one-time curative therapies that can approach $1 million or $2 million," she said. But they could one day prove transformative for kidney diseases like polycystic kidney disease or tubular interstitial diseases, so it is essential to figure out payment. She noted that CMMI has created a voluntary demonstration cell and gene therapy access model that will negotiate on behalf of state Medicaid programs for sickle cell gene therapies. Tummalapalli explained that 34 states and 2 manufacturers are already participating and suggested that there is also a need for new approaches to stimulate innovation in kidney failure care.

"We want to incentivize innovation," Tummalapalli said. "It's not that we don't want to pay for things, but we do want to allow for reasonable pricing that reflects the effectiveness of the therapy and allows more patients to gain access to it to maximize utilization. We cannot afford to wait as a kidney community." ■

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The Kidney-Heart-Brain Connection: Interactions Linked With Brain Symptoms in People With Kidney Diseases

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among kidney, heart, and brain health and suggesting potential future screening or treatment strategies. Other recent work has identified the need for additional study on how to prevent cognitive impairment in people undergoing dialysis, strategies to maintain brain health at all stages of kidney disease, and how to prevent cognitive impairment in children with kidney diseases (1).

Kidney-heart-brain axis

Some investigators at the National Institutes of Health are focusing on what they recently named the kidney-heart-brain, or cardiorenal-cerebral, axis, according to Olga V. Fedorova, PhD, a senior associate scientist at the National Institute on Aging's Intramural Research Program.

"Cognitive decline in CKD is not driven by one mechanism," explained Khitan, who was part of a multi-institutional team that collaborated with Fedorova on a recent study (2). "It reflects a kidney-heart-brain interaction involving uremic toxins, inflammation, oxidative stress, vascular stiffness, hypertension, cardiac remodeling, impaired cerebral perfusion, and possibly altered amyloid beta 42/tau proteins handling," he said.

Fedorova said that failing kidneys produce toxic compounds that directly damage the brain and brain cells. They may also release profibrotic factors and other compounds that increase blood vessel stiffness, making the heart work harder. This can lead to changes in blood pressure and an increase in pulse wave velocity and blood pressure pulsatility that may damage small blood vessels in the brain or other organs. When pulsatility is high, every single heartbeat sends a tiny "shockwave" deep into the brain that will cause microbleeds, scars (lesions), and disruption of the brain's ability to wash away toxic proteins like amyloid beta, she explained. Healthy kidneys also clear amyloid beta 42 proteins from the blood, but failing kidneys may be ineffective, allowing the protein to re-enter the brain and contribute to the formation of neurodegenerative plaques, Fedorova said. Additionally, kidney disease-associated heart failure can lead to reduced blood flow to the brain and result in neurodegeneration.

In their study, Fedorova, Khitan, and colleagues compared markers of cardiovascular disease, cognitive health, fibrosis, and neurodegeneration in approximately 65 men and women with stage 4–5 CKD (2). The results showed that cognitive impairment in men with kidney disease appeared to be driven by heart problems, whereas memory domain dysfunction in women appeared to be driven by blood levels of amyloid beta 42 and the sodium potassium ATPase inhibitor marinobufagenin, which can contribute to fibrosis. The team is now planning to conduct a longitudinal study to assess the long-term consequences of these biomarker elevations on brain health.

"Cognitive risk in CKD should be viewed as part of a multiorgan syndrome, not an isolated neurologic problem," Khitan said. "This study reframes CKD-related cognitive decline as a systems-level disorder driven by kidney-heart-brain interactions, with distinct sex-specific mechanisms."

Alzheimer biomarkers

In another study, Francesca Gasparini, MD, a geriatrician and PhD student at the Karolinska Institute in Stockholm, Sweden, and coauthors looked at an emerging set of Alzheimer disease biomarkers in 2279 community-dwelling older adults without dementia at the start of the Swedish National Study on Aging and Care in Kungsholmen (3). They found that over an average of 8 years of follow-up, 362 participants developed dementia. They also showed that worsening estimated glomerular filtration rates were associated with increasing levels of Alzheimer disease-linked biomarkers. However, she and her colleagues concluded that decreased kidney function alone did not appear to cause dementia but may have accelerated symptoms in patients with these conditions. "It accelerated the clinical expression of the disease in participants who already [had] the neuropathology," Gasparini explained.

She suggested that additional studies are needed to confirm the results because interpreting Alzheimer biomarkers in people with reduced kidney function is complicated, and the study was observational. Gasparini expressed that it is also important to identify the potential mechanism and conduct longitudinal studies on the long-term relationship between these biomarkers and brain health. She noted that her study assessed kidney function using only creatinine but that adding cystatin C to kidney function assessments may further improve accuracy.

Gasparini was hopeful that further study would lead to the development of tailored thresholds for Alzheimer disease biomarkers in people with reduced kidney function. She noted that some countries are already using these biomarkers in clinical practice to help rule out Alzheimer disease, so there is some urgency to assess the impact of reduced kidney function on results. "In the next couple of years, [the biomarker screening] will be entering clinical practice more broadly," she said.

Important gaps

Given the high rate of cognitive impairment and its impact on both patient quality of life and patient care, Clara Bohm, BScH, MD, MPH, an associate professor at the University of Manitoba and nephrologist at Kidney Health Manitoba in Winnipeg, Canada, and her colleagues conducted a research needs assessment that surveyed 152 patients, caregivers, and clinicians (1). They found strong agreement across all groups that research on preventing and treating cognitive impairment is the most urgent need.

Bohm noted that there is not currently a validated tool for measuring cognitive impairment, specifically in people with kidney diseases, and there are questions about when to measure cognitive impairment and potential harms associated with a diagnosis. "It has a lot of impact on people's quality of life to know they have cognitive impairment," she explained. She noted that although it may enable clinicians to treat the impairment or help patients set up systems to manage it, it can also cause anxiety, stress, and worry about what it means for the future. It may also have implications for insurance coverage.

Bohm said that there is also a dearth of information on how best to intervene when cognitive decline is detected in people with kidney diseases, but she expects this to change within the next 2 to 5 years, given the ongoing mechanistic work. She noted that longitudinal studies are currently underway to identify risk factors for cognitive decline. The next step, she said, is to conduct rigorous, interventional trials to determine whether interventions, such as adjustments to dialysis regimens, may help. "From a research perspective, there needs to be a focus on really trying to find some treatments that are making a difference and testing them in a rigorous manner," Bohm suggested.

Fedorova and her colleagues used the Mini-Mental State Examination in their study, and she suggested that it might be a useful tool to use annually to assess patients' cognitive function and detect early changes. She advised working with a neurologist for testing and treatment of those experiencing cognitive decline. In addition to the Mini-Mental State Examination, other tests (e.g., the Montreal Cognitive Assessment) can be used by a neurologist to assess the early stages of mild cognitive impairment in people with CKD. She noted that existing cardiovascular medications, including antihypertensive therapies; angiotensin-converting enzyme inhibitors, which have been shown to improve cognitive function; or lifestyle changes, may help. She explained that these steps are already part of the standard of care for CKD. "Drugs that have been used for decades can be helpful if they are used at the right time," she said.

Khitan agreed with the need for early and regular screening and suggested that nephrologists take a comprehensive approach. When cognitive impairment is detected, he advised simplifying medication regimens and avoiding sedating or neurotoxic medications. He also suggested working with caregivers, providing repeat patient education and written materials, aggressively treating cardiovascular risk factors, correcting anemia and metabolic derangements, and factoring in cognition when discussing dialysis modality.

Gasparini emphasized a whole-person approach with screening and care for comorbid conditions. She also recommended medication review; optimizing patients' overall health, including addressing anemia and fluid balance; and minimizing polypharmacy.

Newer cardiovascular-kidney-metabolic medications may also help. Khitan noted that sodium-glucose cotransporter-2 inhibitors may reduce CKD progression and heart failure risk, whereas glucagon-like peptide-1s may improve cardiometabolic risk factors, weight, glycemia, and vascular inflammation. "Conceptually, by reducing cardiovascular strain, inflammation, oxidative stress, and kidney disease progression, these medications may indirectly reduce cognitive risk," he said. However, he noted that a prospective study is needed to verify that hypothesis.

Gasparini also recommended caution in prescribing these medications for older adults, noting, "There are still a lot of things we don't know about the physiology of the clearance of these drugs in the body."

Recognizing cognitive impairment is key, as is helping patients manage it day to day through strategies for memory loss or for anxiety related to cognitive impairment, said Bohm. She also suggested working with a multidisciplinary team, for example, with a geriatrician, who may be able to identify whether medications or polypharmacy may be contributing. Occupational therapists or physiotherapists could help with assessment and management of day-to-day activities or exercises, and mental health specialists may also be beneficial. "Multidisciplinary teams can address all of these issues that affect quality of life, and I think they are the way of the future," she surmised.

Bohm, who is also the medical lead of the Kidney Health Manitoba Exercise Program, added that physical activity has been shown to boost cognition and quality of life in people with CKD. She suggested identifying patients' motivators, such as wanting to carry groceries or play with grandchildren, and working with them to design an exercise or activity program. Some patients may like to cycle during dialysis sessions; others may enjoy walking or a group program at the gym.

"The nephrology community is starting to recognize that physical activity benefits many different aspects of kidney disease and is useful in many aspects of disease management," Bohm explained. "However, it requires an individual who is experienced in prescribing, implementing, and supervising exercise, probably not a nephrologist or a nephrology nurse but an exercise specialist." ■

Disclaimer: The opinions expressed by Dr. Fedorova in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the US government.

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Beyond Creatinine: Are Cell-Cycle Arrest Biomarkers Ready for Obstetric AKI?

By Suman Behera

https://doi.org/10.62716/kn.003532026

Pregnancy-associated acute kidney injury (AKI) continues to pose significant diagnostic uncertainty. Physiologic declines in serum creatinine (SCr) across gestation blunt usual triggers, and oliguria around labor can be iatrogenic or physiologic. As a result, Kidney Disease: Improving Global Outcomes (KDIGO)-based algorithms built on SCr and urine output struggle in obstetrics. Against this backdrop, Clark and colleagues report on the NephroCheck AKI risk score (1). NephroCheck (bioMérieux/Astute Medical Inc.) is a rapid diagnostic test derived from the product of two urinary biomarkers that act as signals for G1 cell-cyle arrest, namely tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) (2, 3). The test is being investigated as a candidate for an early-warning tool in pregnant patients. The research letter in *Nephrology Dialysis Transplantation* highlights the biologic rationale and the gap: Although [TIMP-2] × [IGFBP7] risk stratifies nonpregnant adults who are critically ill, its association with pregnancy-associated AKI has been largely untested (1).

NephroCheck reads stress rather than function, and elevation of serum markers precedes SCr (2). The test received US Food and Drug Administration marketing authorization in 2014 for patients in an intensive care unit (ICU) who are at risk of moderate to severe AKI, and multiple reviews have since described its clinical performance and operational advantages. Industry materials likewise emphasize its intended-use boundaries (adult ICU populations with hemodynamic or respiratory compromise), underscoring that obstetric use would be off-label and hypothesis-generating (4, 5).

Thus, how can NephroCheck be used in this scenario? Because it reads *stress* rather than function, and elevations can precede an SCr rise by hours to days, it potentially enables kidney-protective measures before overt injury (2).

What do the data in pregnant individuals show so far? The evidence is mixed. Small single-center cohorts in obstetric patients who are critically ill have reported strong discrimination, with cutoffs in the 0.3- to 0.4-(ng/mL)^2/1000 range, with sensitivities and specificities in the mid-90s for subsequent AKI—encouraging but preliminary (5–7). Conversely, another prospective study from an obstetric ICU found no predictive value for [TIMP-2] × [IGFBP7] (area under the receiver operating characteristic curve, <0.5) despite high AKI incidence, highlighting heterogeneity in case mix, timing, and assay platforms (6, 8). The research letter (1) usefully frames these discrepancies: Pregnancy physiology, labor interventions (e.g., oxytocin), and variable catheterization and fluid protocols complicate urine-output criteria and may shift biomarker baselines in ways not seen in general ICU populations (1, 6).

Two pragmatic implications follow:

1. If used, NephroCheck should complement (not replace) structured clinical assessment in obstetric pathways—more as a "rule in risk" signal to prompt nephrotoxin stewardship, hemodynamic optimization, and closer surveillance, rather than as a stand-alone diagnostic. That aligns with broader AKI-biomarker guidance and real-world implementation lessons from nonpregnant settings.
2. Obstetric-specific validation is essential. Multicenter studies should standardize sampling time points (e.g., at admission to an obstetric high-dependency unit or an ICU, during a preeclampsia evaluation, and immediately postpartum), adjudicate pregnancy-associated AKI with pregnancy-adapted creatinine thresholds, and report outcomes meaningful to parent–infant dyads (1, 5, 6).

Until those data arrive, how should nephrologists counsel obstetric teams (Figure)? Be clear about scope: NephroCheck is the only commercial [TIMP-2] × [IGFBP7] assay, to date, validated in specific adult ICU contexts; obstetric use remains investigational (1, 5, 6). Needed are local protocols to pilot it; its results to be embedded in AKI bundles and quality-improvement loops; and parental, fetal, and resource outcomes to be prospectively captured. Meanwhile, primary principles to be remembered include timely blood pressure control, volume assessment, prevention of contrast and drug nephrotoxicity, and early nephrology–obstetrics co-management, which still have a major role in combating pregnancy-associated AKI. Biomarkers like a [TIMP-2] × [IGFBP7] assay may sharpen our timing, but they do not substitute for fundamentals (1, 2, 7). ■

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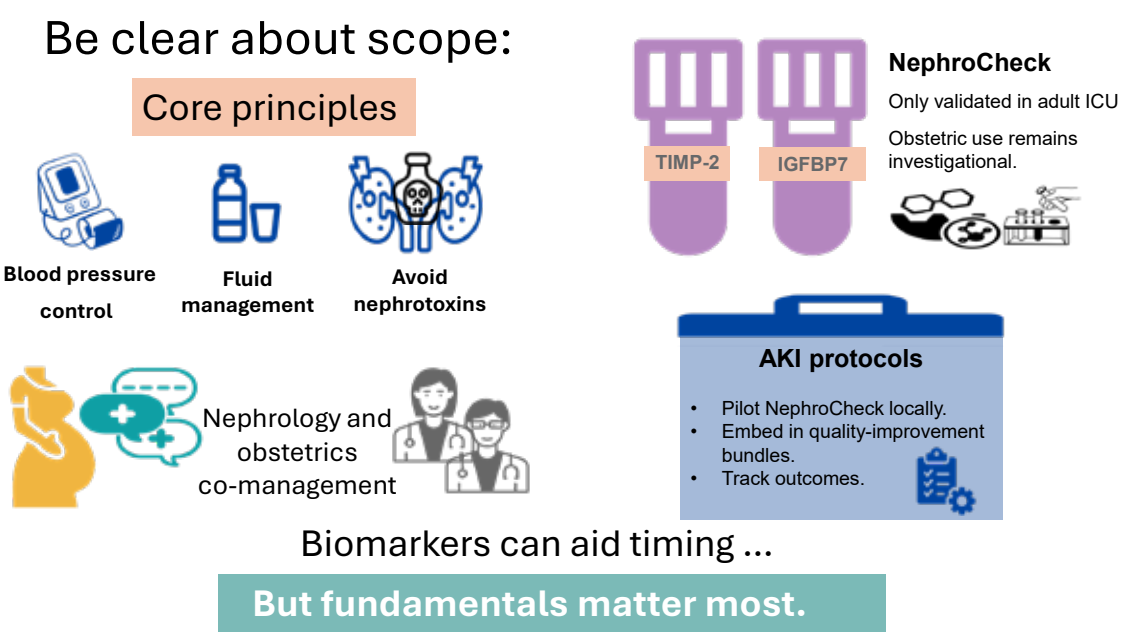
The author reports no conflicts of interest.

Figure. Guiding obstetric teams in pregnancy-associated AKI



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Who Submits Matters: Rethinking Sex Disparities in High-Impact Publishing

By Sameen Aamer, Sourabh Sharma, and Sabine Karam

https://doi.org/10.62716/kn.003642026

In academic medicine, and certainly in nephrology, we all understand the unspoken hierarchy of journals. Among these, *Nature*, *Science*, and the *Proceedings of the National Academy of Sciences* remain powerful gatekeepers of visibility, funding, and career advancement. For decades, discussions about bias in publishing have focused on what happens after submission: Who gets accepted? Who gets rejected? Do reviewers treat everyone fairly?

A recent study by Ni et al. (1) offers a helpful shift to an earlier perspective: Who decides to submit in the first place? Rather than focusing only on acceptance rates or reviewer bias, the authors evaluated submission behavior directly. Their findings are striking but intuitive (Table). Women are less likely than men (37% versus 49%) to submit to these journals and, when they do, tend to submit fewer manuscripts. Yet once a manuscript is submitted, acceptance and desk-rejection rates are statistically indistinguishable between sexes. The gatekeeping, in other words, is largely happening before the gate is even reached.

For many of us, this likely resonates. The internal debate of whether a paper is novel enough or worth the risk of rejection is familiar. Women are more likely to answer those questions conservatively, to cite concern that their work is not sufficiently groundbreaking, and to report having been advised against submitting to elite journals. Meanwhile, men are somewhat more inclined to take the chance. This is not about differences in ability or quality. The authors found no meaningful sex difference in how researchers rated the quality of their own work. The gap is about how high the bar is set before deciding to submit, and that bar appears, on average, to be higher for women. That asymmetry compounds quietly over a career. Fewer submissions to flagship journals likely mean fewer high-visibility publications and grant opportunities, leading to fewer invitations to speak and lead. The pipeline narrows at a point we rarely audit.

The reasons behind these patterns are likely multifactorial. Some may relate to risk tolerance or perfectionism, but the finding about external advice deserves particular attention. Women were significantly more likely to report being told not to submit to top journals. That raises questions about mentorship: What messages are we sending to trainees and junior faculty, and are we even aware we are sending them? Encouragement to aim high is not equally distributed, and the study by Ni et al. (1) suggests that the consequences are real and measurable.

The study has limitations worth acknowledging. The response rate was under 2%, raising reasonable questions about whether respondents represent the broader research population or skew toward those already attuned to equity concerns. All data were self-reported, and submission decisions recalled years after the fact may be vulnerable to memory bias. Academic rank was captured at the time of the survey rather than at the time of manuscript submission, which may misrepresent the career stage at which key choices were actually made.

If this disparity is driven partly by who chooses to submit, fixing peer review alone will not solve the problem. Interventions need to happen upstream, in mentorship conversations, in how we talk about ambition with early-career colleagues, and in the cultures that shape whether someone feels entitled to aim for the best possible venue.

Equity in publishing is not just about fair review, it is about fair participation. Until we address what happens *before* submission, the promise of a meritocratic publishing system will remain a promise. ■

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The authors report no conflicts of interest.

Reference

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Table. Key findings and implications of sex differences in submission behavior

Domain	Findings	Interpretation	Implications
Submission rates	Women submit less frequently than men (37% versus 49%).	Lower propensity to target high-impact journals	Reduced visibility in elite publications
Manuscript volume	Women submit fewer manuscripts overall.	More conservative submission strategy	Cumulative disadvantage over career trajectory
Acceptance outcomes	No significant sex difference in acceptance or desk rejection	Peer-review process appears equitable after submission.	Bias likely occurs before submission.
Self-perceived quality	No meaningful sex difference in self-assessed research quality	Disparity is not due to perceived inferiority of work.	Suggests behavioral rather than capability gap
Decision threshold	Women set a higher bar before submission.	Greater risk aversion or perfectionism	Fewer attempts at high-impact dissemination
External influence	Women were more often advised against submitting to top journals.	Potential mentorship bias	Unequal encouragement may affect career progression.
Structural impact	Fewer submissions, fewer high-impact publications, and fewer opportunities	Compounding career disadvantage	Pipeline attrition at early stage
Study limitations	Low response rate (<2%), self-reported data, and recall bias	Potential sampling and reporting bias	Findings should be interpreted cautiously.
Overall conclusion	Disparity arises primarily at the submission stage.	“Pre-gatekeeping” phenomenon	Interventions should target mentorship and academic culture.

Gene Therapy for Cystinosis—Early Insights

By Amy A. Yau and Mohamed Emlemdi

https://doi.org/10.62716/kn.003692026

Cystinosis is a multisystem lysosomal storage disorder caused by pathogenic variants in *CTNS* (17p13), which encodes cystinosin, a lysosomal transmembrane cystine transporter. Loss of cystinosis results in lysosomal cystine accumulation and crystal formation, which lead to progressive organ dysfunction. The most severe form of cystinosis can lead to kidney failure at a young age. Cysteamine, the current approved therapy for cystinosis, helps break down lysosomal cystine to allow it to exit the lysosome. Despite therapy, even when started early, patients still develop kidney failure at an average age of 13.4 years (1). Of note, this therapy differs from therapy that is targeted at raising the urine cystine saturation in individuals who develop kidney failure from recurrent cystine kidney stones.

Because of the natural history and limited therapeutics, gene editing therapy for cystinosis is an emerging field of study. In mice, stem cells with functional *Ctns*, when colocated with diseased tissue, allow for lysosomal exchange using nanotubules between diseased host tissue and engrafted hematopoietic stem and progenitor cell (HSPC)-derived macrophages and microglia. Therapy helps preserve kidney, thyroid, and eye function in the animals, but it is unclear whether these animal model findings will translate to humans. This brings us to a recent publication by Barshop et al. (2) of six patients who underwent autologous HSPC gene therapy for cystinosis (Figure).

The six individuals were all diagnosed at 6 years of age or younger. All had some degree of chronic kidney disease, and four had already undergone kidney transplant. Autologous CD34+ HSPCs were collected and underwent lentiviral transduction of a functional *CTNS* gene. After conditioning with busulfan, genetically modified HSPCs were administered intravenously. The results were encouraging. There was stable gene expression and a 25% to 86% reduction in white cell cystine levels, which is an accepted biomarker of disease control. Biopsied intestinal tissue and confocal microscopy confirmed reduced cystine crystal deposition. However, the two individuals with chronic kidney disease had continued kidney decline in the 5.5-year follow-up period. The authors note the lack of serious adverse effects from the therapy; however, there were side effects from the conditioning regimen.

Because of the small number of patients followed, no clinical outcomes can be concluded, but Barshop et al. (2) demonstrate feasibility of gene therapy and underscore its promise. Indeed, lentiviral vector and clustered regularly interspaced short palindromic repeat (CRISPR) gene therapies are already US Food and Drug Administration approved for sickle cell disease (3). There is emerging research for viral vector gene therapy for other lysosomal storage disorders such as metachromatic leukodystrophy and Fabry disease (4, 5). Larger, longer-term studies are necessary, but these early insights propel the field of gene therapy forward. ■

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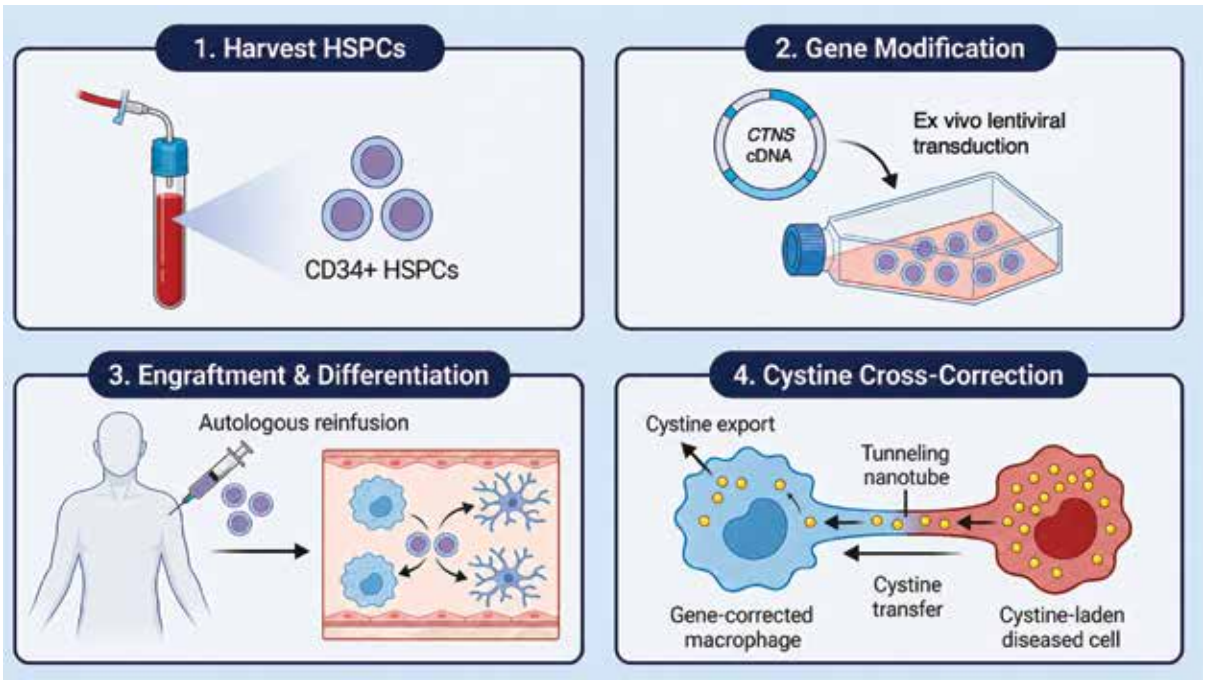
The authors report no conflicts of interest.

Figure. Mechanism of autologous HSPC gene therapy for cystinosis



1) HSPCs are harvested and 2) undergo gene modification with lentiviral transduction of functional *CTNS* DNA. 3) HSPCs are then infused back into the patient and undergo engraftment and differentiation. 4) Gene-corrected cells then help with cystine transfer from native, nonedited cells using nanotube tunneling.

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Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy and the Kidney: A New Era for Complement Targeting

By Rimda Wanchoo and Kenar D. Jhaveri

https://doi.org/10.62716/kn.003342026

Hematopoietic stem cell transplantation (HSCT)-associated thrombotic microangiopathy (TA-TMA) remains one of the most serious complications after transplant, carrying substantial morbidity and mortality. At its core is endothelial injury, which sets off a cascade of microvascular thrombosis, hemolytic anemia, thrombocytopenia, and progressive end-organ damage. Kidney involvement often presents early, most commonly as worsening hypertension, proteinuria, and acute kidney injury, and may precede the classic hematologic abnormalities. For that reason, clinicians should maintain a high index of suspicion for TA-TMA even before the full laboratory picture is apparent.

Over the past decade, advances in complement biology have begun to redefine the treatment landscape for TA-TMA. Yet in practice, the field has continued to rely largely on terminal complement blockade with complement component 5 (C5) inhibition—an approach adapted, in many respects, from the atypical hemolytic uremic syndrome playbook.

A growing body of evidence points to lectin pathway activation as a meaningful driver of TA-TMA, with elevated mannan-binding lectin–associated serine protease-2 (MASP-2) levels observed in patients who are affected (1). On that biologic foundation, lectin pathway inhibition was first tested clinically in a single-arm, open-label pivotal trial of narsoplimab (NCT02222545) (1). In that 28-patient trial, the response rate was 61%, organ function improved in 74% of patients, and 100-day survival after diagnosis was 68% overall and 94% among responders. Given these promising results, a global expanded access program (EAP) was established facilitating a compassionate use program. This included children (aged <16 years) and adults (aged ≥16 years), who were treated with narsoplimab between October 2017 and October 2023. They were analyzed for survival outcomes (2). The cohort was enriched for severe disease: Most patients who were high risk had organ dysfunction at the time of TA-TMA diagnosis, and kidney involvement was the most common organ manifestation in both children and adults.

Key outcomes from EAP were strikingly stratified by timing. Among pediatric allogeneic recipients with high-risk TA-TMA, 1-year overall survival (OS) was 75.0% when narsoplimab was used as first-line therapy (n = 12) compared with 56.2% when given as second-line or later (n = 25); notably, 20 of the patients with second-line treatment were refractory to eculizumab (2). In adults with high-risk TA-TMA after allogeneic HSCT, 1-year OS was 58.0% with first-line narsoplimab (n = 49) versus 40.5% when used second-line or later (n = 16) (2). Importantly, for safety-conscious transplant programs, the investigators reported no concerning safety signals in this EAP population (2). The late-2025 US Food and Drug Administration (FDA) approval of narsoplimab-wuug (Yartemlea), a MASP-2 inhibitor, marks a notable shift toward lectin pathway targeting in HSCT-TA-TMA (1–3).

These results matter because they arrive against a backdrop of heterogeneous outcomes with C5 blockade in TA-TMA. Eculizumab experience spans retrospective adult series, pediatric cohorts, and—more recently—a prospective multi-institutional study in high-risk TA-TMA. In a 2024 prospective multi-institutional study published in *Blood*, survival was reported at 71% at 6 months after a high-risk TA-TMA diagnosis and at 62% at 1 year (4). Retrospective adult data have shown response rates and survival that vary widely by cohort severity, timing, and dosing and monitoring strategies (4–8). A 2024 pediatric analysis similarly highlighted that response evolves over time (27.6% at 1 month and 55.2% by 3 months) and that survival is substantially better among responders than nonresponders (7) (Table).

Two abstracts presented at the recent American Society of Hematology meetings shed some light into two more potential treatment options for TA-TMA. Beyond MASP-2 inhibition, upstream complement blockade is emerging. Iptacopan, an oral small molecule factor B inhibitor, has been reported in a small adult case series with improvement in hematologic markers and reduction in proteinuria, supporting a role for alternative pathway inhibition, although infectious complications remain a concern (9). A prospective phase 2 study of iptacopan in high-risk TA-TMA is now listed on ClinicalTrials.gov (NCT07347990). Pegcetacoplan (a C3 inhibitor) has been described in pediatric off-label cases and is under prospective investigation, reflecting interest in broader complement control for refractory disease (10).

How should nephrologists interpret these studies? Cross-study comparisons are inherently limited by differences in inclusion criteria, risk stratification, and severity of organ dysfunction at presentation. Still, the broader message is hard to miss: Earlier kidney-centered recognition, especially through surveillance for hypertension and proteinuria, creates a better chance to intervene before TA-TMA becomes entrenched. Furthermore, across complement-targeted approaches, earlier treatment appears to be associated with better outcomes. Notably, a substantial share of patients receiving narsoplimab in later-line settings have already been exposed to eculizumab, highlighting the role of lectin pathway inhibition when terminal pathway blockade falls short (1, 2).

Practically, the post-HSCT kidney should be treated as a sentinel organ: New hypertension plus proteinuria (even before an overt creatinine rise) warrants a TA-TMA diagnostic workup and risk assessment. The availability of an FDA-approved lectin pathway inhibitor may help drive more standardized, multidisciplinary care pathways that bring nephrology in earlier—ideally before multiorgan failure sets in (2, 3).

Finally, the field's next step should be precision: validated biomarkers that distinguish competing endotheliopathies (i.e., graft-versus-host disease–associated, infection-mediated, and drug-mediated) and comparative effectiveness work that clarifies which patients benefit most from MASP-2 inhibition versus C5 blockade

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Table. Selected outcomes reported with narsoplimab versus eculizumab in TA-TMA

Therapy/study	Population	Number	Key outcomes reported	Notes
Narsoplimab (MASP-2)/ Schoettler et al. (2) (EAP)	Pediatrics and adults; enriched severe TA-TMA; Oct. 2017–Oct. 2023	136	1-Year OS; pediatrics: allogeneic high-risk first-line 75.0% versus ≥second-line 56.2%; adults: allogeneic high-risk first-line 58.0% versus ≥second-line 40.5%	Many patients with ≥second-line treatment previously received eculizumab; no concerning safety signals were reported.
Eculizumab (C5)/Jodele et al. (4) (prospective multi-institutional)	High-risk TA-TMA (prospective)	See study.	Survival: 6 months, 71%; 1 year, 62%	Prospective design; dosing and monitoring protocol; outcomes dependent on early recognition and risk phenotype
Eculizumab (C5)/Dhakal et al. (5)	Adults; retrospective	See study.	Reported high response rate and 1-year survival in refractory TA-TMA	Retrospective; varied cohort selection and definitions
Eculizumab (C5)/Carabante et al. (7) (pediatrics)	Pediatric high-risk TA-TMA	See study.	Overall response: 27.6% at 1 month; 55.2% by 3 months; superior survival among responders	Illustrates time-dependent response; highlights importance of early therapy
Eculizumab (C5)/Alhomoud et al. (8) (adults)	Adult high-risk TA-TMA; comparative cohort	47 (16 Eculizumab)	Complete response: 56% with eculizumab; 1-year OS for entire cohort: 61%	Comparative analysis versus conventional therapy; baseline severity adjustment

Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy and the Kidney

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(or sequential strategies). The Schoettler et al. EAP experience (2) provides a large, practice-proximate dataset, suggesting that lectin pathway inhibition can deliver meaningful survival, including in patients previously treated with eculizumab. The challenge now is to place this option into an evidence-based, kidney-centered diagnostic and treatment algorithm. ■

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How Often Is Often Enough? CMV Monitoring After Solid Organ Transplantation

By Emily C. Lydon, Madeline R. Heldman, and Ajit P. Limaye

https://doi.org/10.62716/kn.003382026

Nearly 50 years since it was coined the "troll" of transplantation (1), cytomegalovirus (CMV) continues to cause invasive disease and is associated with graft dysfunction and mortality, particularly among recipients who are high-risk donor-positive/recipient-negative (D+/R–) (2, 3). Over decades of research, two prevention strategies have emerged (4). The first, preemptive therapy (PET), relies on viral load monitoring to trigger antiviral treatment in the immediate post-transplant period. The second, antiviral prophylaxis, uses scheduled antiviral treatment in the immediate post-transplant period, often followed by surveillance after prophylaxis (SAP) as an approach to detect and prevent late-onset CMV disease once prophylaxis is discontinued. Yet, one practical question remains unsettled for both approaches: How often should clinicians monitor CMV viral loads to detect infection and initiate antiviral therapy before asymptomatic infection progresses to disease?

In a recent issue of the *American Journal of Transplantation*, Dahl and colleagues address this question using data from more than 3400 solid organ transplant recipients, most of whom were kidney transplant recipients (KTRs), across three separate centers in Denmark and Switzerland (5). The investigators analyzed CMV polymerase chain reaction (PCR) monitoring intervals as a time-dependent exposure—an important strength that reflects real-world practice, in which surveillance intervals often vary because of missed tests or deviations from the standard monitoring plan. Their analysis revealed a clear signal: A monitoring interval longer than 7 days was associated with higher risk of CMV disease in patients undergoing PET or SAP. The benefit of more frequent monitoring was more pronounced among recipients who were D+/R– than those who were R+, with 11 versus 71 patients, respectively, needing to undergo more frequent testing to prevent one case of CMV disease. Most CMV disease occurred within the first 3 months of PET or SAP; beyond that window, monitoring frequency had little apparent effect.

Several limitations warrant consideration. First, as an observational analysis, monitoring frequency was not randomized, and unmeasured confounding could have influenced results. Clinicians may have preferentially monitored patients with higher risk more frequently, although, if anything, this bias would attenuate rather than overestimate the observed associations. Second, the proportion of patients who developed CMV disease was lower than expected; only 6% of recipients who were D+/R– and 1% who were R+ developed CMV disease during PET or SAP, whereas major recent clinical trials report 1-year CMV disease rates of approximately 10% to 20% among KTRs who were D+/R– (6, 7). Although incomplete ascertainment of CMV disease could contribute to these lower rates, there is little reason to expect that under-reporting would systematically differ by monitoring interval. Third, the analytic framework censored patients at the time of the first CMV infection. Although necessary for the time-dependent modeling approach, this design limits insight into how CMV viral load monitoring should be approached after an initial CMV episode. Fourth, patients were not followed beyond 6 months after PET or SAP, and rebound cases of CMV occurring after cessation of surveillance were not captured. As such, the study does not inform the optimal duration of PET or SAP, although the observed concentration of CMV disease within the first 3 months suggests that this may be the highest yield period for surveillance.

The findings intersect with the longstanding debate over CMV prevention strategies (4). CMV disease risk depended on monitoring frequency, not the specific prevention strategy. This raises an important question: If the success of PET and prophylaxis/SAP ultimately depends on intensive viral load surveillance, does combining prophylaxis with surveillance simply delay CMV rather than prevent it, while exposing patients to the costs, toxicities, potential drug interactions, and logistical burden of two sequential strategies? Although the study evaluated CMV disease risk with PET versus prophylaxis/SAP, the available data were not further stratified by the donor and recipient CMV serostatus. Because recipients with CMV D+/R– have the highest risk of CMV disease, additional stratification by both CMV serostatus and prevention strategy could provide more granular insight into the relative effectiveness of these approaches in specific populations. Although this observational study cannot definitively resolve the PET versus prophylaxis/SAP debate, it does provide important real-world evidence supporting PET effectiveness.

The CAPSIL randomized clinical trial (NCT01552369) found that PET reduced the risk of CMV disease compared with prophylaxis in liver recipients who were D+/R– (8). Other real-world studies have identified weekly CMV monitoring, use of sensitive quantitative PCR assays for CMV viral load, and prompt initiation of antiviral therapy at the first detection of CMV DNA at any level as key determinants of PET efficacy (9). An ongoing phase 3 randomized trial (KPoP [NCT06798909]), which directly compares PET with prophylaxis, is designed to definitively answer this question in KTRs with high-risk CMV D+/R–.

Ultimately, the practical takeaway for KTRs is straightforward. The first 3 months of PET or SAP represent the time of greatest CMV disease risk, and weekly viral load monitoring detects most infections early enough to intervene before disease develops (Figure). Accordingly, these findings reinforce current guideline recommendations rather than redefine them (10). In a disease as dynamic as CMV, successful prevention depends on ensuring that surveillance keeps pace with the virus itself. ■

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The authors report no conflicts of interest.

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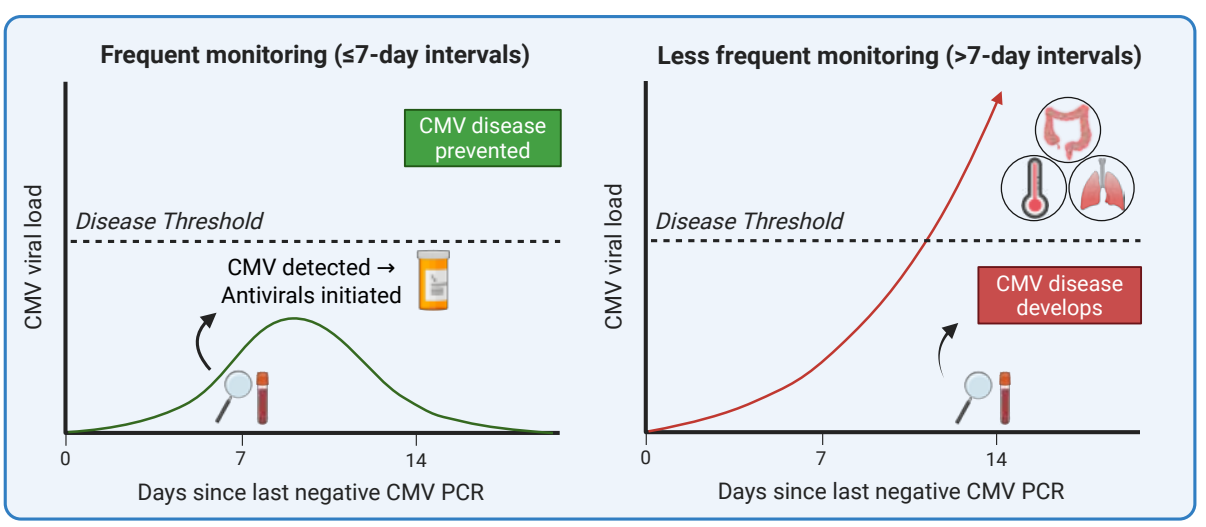
Figure. CMV viral load monitoring frequency and early detection and prevention



With frequent monitoring (≤7-day intervals; left panel), rising CMV viremia is detected before reaching the threshold associated with CMV disease, allowing initiation of antiviral therapy and prevention of disease. In contrast, with less-frequent monitoring (>7-day intervals; right panel), viral load may exceed the disease threshold before the next scheduled test, resulting in delayed detection and clinical CMV disease. The dashed lines represent a conceptual viral load threshold associated with disease onset. This figure illustrates how shorter monitoring intervals during high-risk periods may enable earlier intervention and reduce the risk of CMV disease. Created in BioRender.

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New Drugs, High Stakes: SGLT2 Inhibitors and GLP-1 Receptor Agonists in Kidney Transplant Recipients

By Vineeta Kumar and Gaurav Agarwal

https://doi.org/10.62716/kn.003412026

A recent systematic review and meta-analysis of 32 studies and 7834 kidney transplant (KT) recipients (1) offers the strongest evidence to date that sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve survival and protect the allograft. Although KT remains the gold standard for kidney failure (2), recipients still face a high burden of cardiovascular disease, diabetes, and allograft dysfunction (3). These complications that SGLT2 inhibitors and GLP-1RAs may help address in KT recipients are now guideline-supported in nontransplant populations (4, 5).

What the data show

Survival and cardiovascular protection

In the largest propensity-matched SGLT2 inhibitor cohort (N = 1970), to our knowledge, users had 68% lower all-cause mortality and roughly half the rates of major cardiovascular and kidney events compared with matched controls (6). Similarly, in the largest propensity-matched cohort (N = 3297), to our knowledge, GLP-1RA use was associated with a 61% reduction in mortality, along with comparable cardiovascular and kidney benefits (7).

Metabolic gains without allograft harm

Both classes reduced weight and hemoglobin A_{1c} (HbA_{1c}) significantly (1). Critically, neither caused a significant deterioration in the estimated glomerular filtration rate—the key safety concern that had kept many clinicians hesitant, particularly because early trials largely excluded KT recipients (8). A related concern is lack of proteinuria benefit because both drug classes are established antiproteinuric agents in nontransplant populations. The most plausible explanation is that included populations had relatively low baseline proteinuria, limiting statistical power. A KT recipient phenotype with distinct patterns of allograft injury and typically lower proteinuria thresholds may require specifically designed studies to capture signals that were readily apparent in the CREDENCE (NCT02065791) or the DAPA-CKD (NCT03036150) trial.

A novel finding: Magnesium and uric acid

The review and meta-analysis is the first, to date, systematic analysis of SGLT2 inhibitor effects on these electrolytes in KT recipients (1) (Figure, C). Serum magnesium rose by 0.11 mg/dL, and uric acid fell by 0.62 mg/dL—both common post-transplant problems. Hypomagnesemia is driven largely by calcineurin inhibitor-induced renal wasting (9), whereas hyperuricemia is a well-recognized consequence of cyclosporine (10). Prior meta-analyses have documented these SGLT2 inhibitor effects in nontransplant populations (11, 12), but this study presents systematic evidence in KT recipients.

What to watch for

Almost certainly inflated effect sizes

Mortality reductions of 60% to 68% exceed anything seen in landmark nontransplant trials, such as EMPA-REG OUTCOME (NCT01131676) (13), DECLARE-TIMI58 (NCT01730534) (4), or LEADER (NCT01179048) (5). The most plausible explanation is healthy-user bias: These drugs were likely prescribed to recipients who were clinically stable. Although propensity matching reduces this bias, it cannot eliminate it (1). The field still needs randomized controlled trials.

Broadly reassuring safety—with one unresolved gap

No excess genitourinary infections or pancreatitis were detected in the largest cohorts (6, 7). However, no study, to our knowledge, was adequately powered to evaluate biopsy-proven acute rejection—a critical unanswered question, particularly in light of emerging preclinical evidence that both drug classes may have immunomodulatory properties (14, 15).

High heterogeneity limiting pooled precision

I^2 values of 85% to 96% across metabolic outcomes (Figure, E) indicate near-maximal, between-study variability. Pooled point estimates should be read as directional signals, not precise effect sizes (1).

The bottom line

The evidence base for the use of SGLT2 inhibitors and GLP-1RAs has strengthened substantially. Transplant physicians, who have been deferring these prescriptions, now have a more defensible foundation for offering them to eligible recipients with diabetes. The appropriate stance is cautious adoption, not continued abstention. The randomized trials that this population deserves remain one of the field's most urgent priorities. ■

Vineeta Kumar, MD, FAST, FASN, is a tenured professor of medicine and the inaugural Robert and Cutessa Bourge Endowed Professor in Transplant Nephrology, and Gaurav Agarwal, MD, FASN, is a professor of medicine, both with

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Figure. Key findings on SGLT2 inhibitors and GLP-1RAs in KT recipients

The findings from Lee et al. (1) include (A) adjusted hazard ratios for matched control outcomes (see Sheu et al. [6] and Lin et al. [7]); (B) pooled metabolic effects; (C) a novel finding of systematic evidence of SGLT2 inhibitor effects on magnesium and uric acid in KT recipients; (D) a safety scorecard; (E) I^2 heterogeneity statistics; and (F) outstanding evidence gaps. aHR, adjusted hazard ratio; AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MACE, major adverse cardiovascular event; MAKE, major adverse kidney event; MD, mean difference; Mg^{2+}, magnesium ion; PK, pharmacokinetics; RCT, randomized clinical trial; SGLT2i, SGLT2 inhibitor; SMD, standard MD; UPCR, urine protein-to-creatinine ratio.

New Drugs, High Stakes

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The authors report no conflicts of interest.

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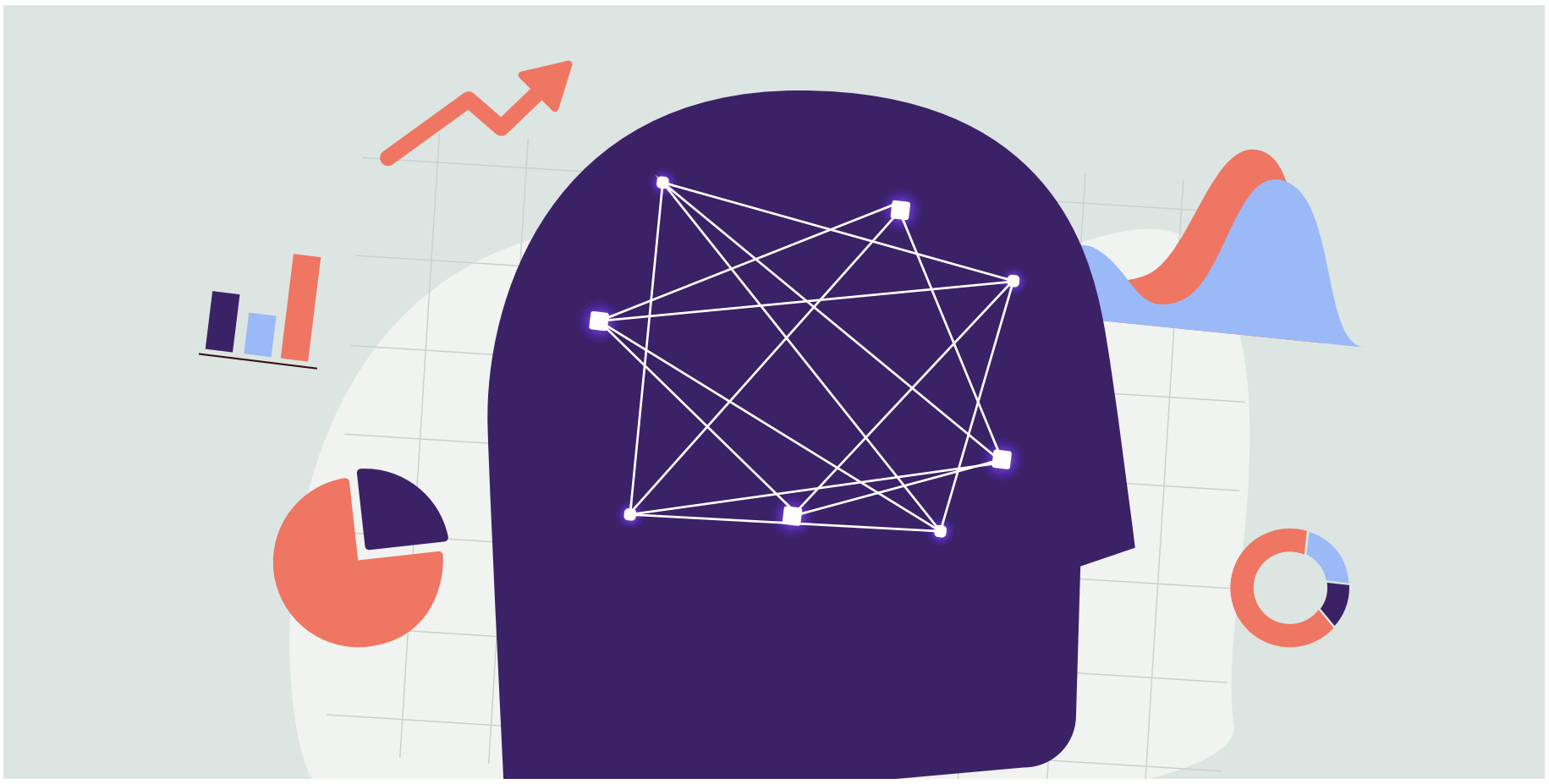

Why Benchmarks Miss the Real Test of Large Language Models as Medical Assistants

By Karin Bergling and Hanjie Zhang

https://doi.org/10.62716/kn.003402026

Large language models (LLMs) have rapidly become everyday assistants for a wide range of tasks, including guidance about when and where to seek health care (1, 2). LLMs score impressively on medical licensing exams (3–5), write with fluency and confidence, and offer a seductive vision: immediate, accurate medical guidance for anyone with internet access. Bean and colleagues offer a timely correction to that narrative (6). Their study shows that what an LLM can do on its own is not the same as what people can do with it.

In this randomized trial (6), 1298 members of the public were presented with common medical scenarios and were asked to identify relevant conditions and to decide what level of care was needed, from self-care to calling an ambulance, either with assistance from one of three LLMs or using whatever information sources they would normally consult at home. The strength of the study lies in moving beyond benchmarks and simulated users to test LLMs in the hands of the general population under conditions that more closely resemble how medical advice is sought.

The central findings are striking. Although the LLMs correctly identified relevant conditions in nearly 95% of cases when prompted directly on the scenarios, the findings did not translate into better decisions when members of the public used them to guide their own assessments. Participants, assisted by LLMs, were no better than control individuals at deciding what care was needed and were less likely to identify relevant conditions, with controls demonstrating 1.76 times higher odds of identifying a relevant condition. Users often failed to provide enough clinical details, and even when the LLMs suggested the right condition, users often failed to recognize it or carry it through to their final assessment. The gap, in other words, was not in knowledge alone but in the human–artificial intelligence partnership itself.

This may seem like a new problem in the age of LLMs, but it reflects an old truth in medicine: Good care depends on more than expertise alone. Even the best clinical advice requires a successful exchange, one in which relevant information is elicited, uncertainty is communicated, and guidance is understood and implemented (7, 8). Passing an exam is one thing; helping a concerned person make a safe decision at home is another.

The specific LLMs studied by Bean and colleagues already belong to an earlier generation (6). Newer systems are arriving quickly, with even stronger benchmark results and increasingly polished presentations (9, 10). Rather than weakening the study's central message, this makes it more urgent. Bean and colleagues highlight the test that actually matters: not whether LLMs can answer medical questions but whether people can use them safely when deciding what care to seek (6). This underscores a broader design imperative for the next generation of medical artificial intelligence tools. Ultimately, the promise of LLMs in health care will depend less on correct answers in isolation than on safe, comprehensible, and actionable conversations with the people whom they are meant to serve. ■

Karin Bergling, MD, PhD, and Hanjie Zhang, PhD, are with the Renal Research Institute, New York, NY, a wholly owned subsidary of Fresenius Medical Care.

The authors report no conflicts of interest.

Disclosures: Drs. Bergling and Zhang are inventors of patents in the kidney space, none related to the current work.

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Finally, an RCT in Hyponatremia Management: A "HIT" or a Miss?

By Samiddhi Weerasiri and Matthew A. Sparks

https://doi.org/10.62716/kn.003432026

New studies examining historical practices of hyponatremia management explore the relationships among the hyponatremia rate of correction, comorbidities, and incidence of osmotic demyelination syndrome (ODS). However, these studies have also received criticism, and they provide insufficient evidence to draw conclusions that uniformly modify practice. As a result of this tension, more recent studies of hyponatremia management have transitioned to evaluating hard outcomes.

In a recent randomized clinical trial (RCT) (NCT03557957), Refardt and colleagues (1) assigned 2173 patients with chronic hyponatremia who were hospitalized to either targeted correction or routine hyponatremia care. The composite primary outcome was 30-day mortality and rehospitalization. The intervention aimed to raise sodium levels between 2 and 12 mmol/L in 24 hours. It involved direct assessment of the primary cause of hyponatremia by the trial team, who provided stepwise instructions for use of urea, crystalloid fluids, vaptans, and other interventions for escalation of management. The control group had management decisions directed by the attending physician.

The median baseline sodium of all participants was 127 mmol/L. The median number of treatments was two in the targeted correction group and one in the control group. By the end of the 30-day trial, patients receiving the intervention had a maximum mean sodium change of 10.0 mmol/L compared with 8.7 mmol/L for those receiving the control. Furthermore, 60% of the intervention group achieved a normal sodium level during the study compared with 46% of the control group. The primary outcome occurred in 21% of the intervention group and 22% of the control group (p = 0.45).

Taken together, although the targeted intervention more effectively managed hyponatremia, it did not reduce the primary outcome. Post hoc analyses echoed the conclusions of prior studies (2): that reaching a normal plasma sodium level at discharge, independent of treatment strategy, reduced the odds of the primary outcome (odds ratio, 0.74 [95% confidence interval, 0.60–0.91]). This observation potentially underscores two principles. One suggests that even mild chronic hyponatremia is not benign and should be treated to decrease risk of falls, cognitive impairment, and other sequelae (3). The second, alternatively, implies that those with treatment-resistant hyponatremia may have more advanced primary disease (i.e., heart or liver disease) that independently increases odds of mortality or rehospitalization in this group. Although feasible, the latter consideration requires additional investigation because the Charlson Comorbidity Index was not analyzed to detect a difference between those with corrected sodium at discharge and those without.

One limitation of this study is the sparse representation of patients with severe hyponatremia (sodium <120 mmol/L), accounting for 6.2% of the cohort. Patients with severe hyponatremia have the greatest risk for mortality (4), ODS (5), and hospital readmission (6). A difference in the primary outcome may have been detected in this study if more such patients had been included. Critically, even if patients with severe hyponatremia were better represented, the study's design would not discriminate the driver—either the hyponatremia itself or its accompanying comorbidities—of the primary outcome in these patients.

Safety analyses revealed that overcorrection (an increase in sodium >12 mmol/L in 24 hours or >18 mmol/L in 48 hours) occurred in 2.3% of patients in the intervention group and 1.4% in the control group (p = 0.14). No cases of ODS were observed.

In summary, this study represents a new, large RCT examining hyponatremia management strategies and their effect on 30-day mortality and rehospitalization. The investigators found no difference between targeted intervention and standard of care with respect to the primary outcome. ■

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The authors report no conflicts of interest.

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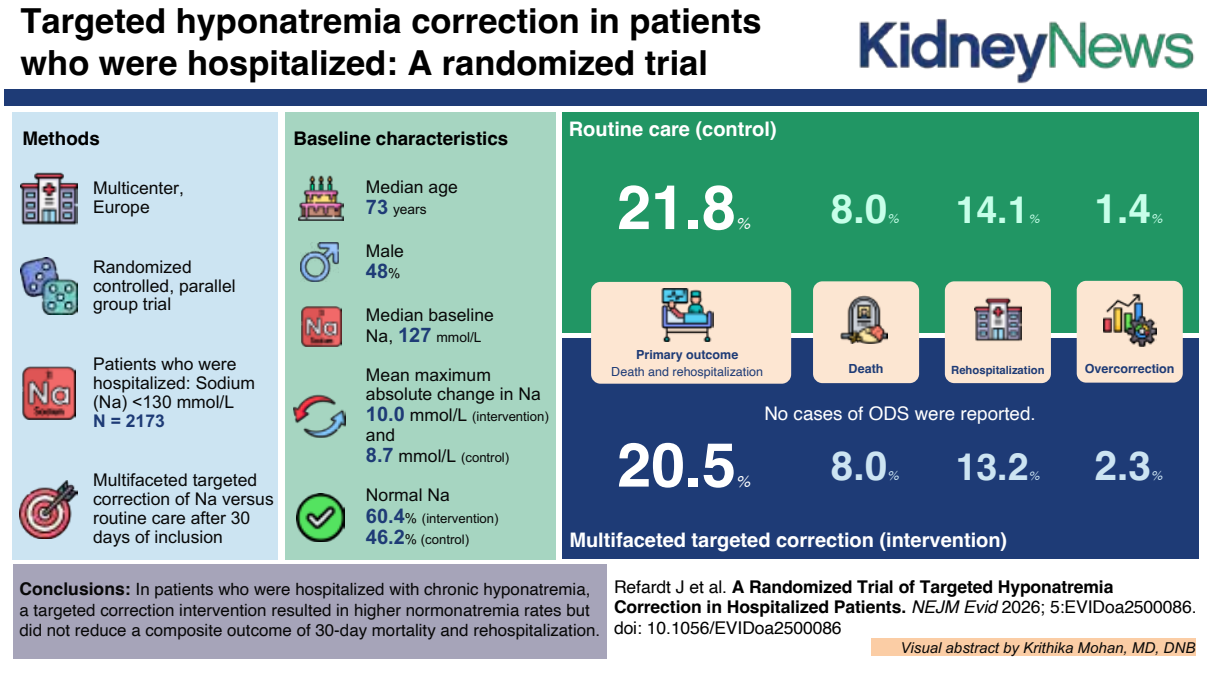

Strengthening Kidney Health Through Federal Leadership and Innovation

By Ryan Murray, Rachel Meyer, Lauren Ahearn, and Suzanne Watnick

https://doi.org/10.62716/kn.003782026

Through strategic legislative engagement, ASN is driving a transformative agenda that recently catalyzed two pivotal events: 1) a landmark House Ways and Means Health Subcommittee hearing on kidney care and 2) a bipartisan call for an "Officer of Kidney Health and Transplantation" within the Department of Health and Human Services (HHS).

On March 18th, the House of Representatives Committee on Ways and Means, Health Subcommittee, convened a hearing, titled "Improving Kidney Health Through Better Prevention and Innovative Treatment." This session served as a powerful platform for expert witnesses, including ASN Health Policy Scholar Suzanne Watnick, MD, FASN, to advocate for a paradigm shift in kidney care. The hearing underscored a stark reality: The current status quo is insufficient. To truly improve the patient care journey, there must be sustained federal investment in biomedical research and a commitment to foster innovation.

Witnesses and congressional leaders identified several key themes essential for progress. Chief among these is the necessity for improved screening, early diagnosis, and preventative measures to halt disease progression before it reaches the end stages. Furthermore, there is an urgent need to expand access to home-based therapies and transplantation, which often offer better outcomes and quality of life than traditional in-center hemodialysis. Watnick's testimony highlighted that achieving these goals requires more individualized care approaches and the integration of actionable symptom management into the patient experience.

"We must modernize Medicare coverage to better prevent and treat kidney disease, as well as improve patient outcomes," said Chair of the House Ways and Means Health Subcommittee Vern Buchanan (R-FL). "That means we must improve kidney health by supporting payment policies that increase innovation in treatments and care delivery."

However, clinical innovation alone cannot solve the systemic issues facing kidney health; this requires a dedicated administrative champion. Building on the momentum of the hearing, a bipartisan group of legislators took a significant step toward this goal. On April 1st, Chairman Buchanan and House Ways and Means Health Subcommittee Ranking Member Lloyd Doggett (D-TX) issued a formal letter to HHS. This letter urged the establishment of a dedicated Officer of Kidney Health and Transplantation (1).

The bipartisan push for this new leadership role is the culmination of years of advocacy by ASN and reflects a growing recognition that kidney diseases require coordinated federal oversight. Currently, efforts are often fragmented across various agencies. A centralized officer within HHS would provide the accountability and coordination necessary to streamline federal programs, manage the research priorities identified by initiatives like the ASN-led "Transforming Kidney Health Research" (TKHR) report (2), and ensure that kidney health remains a permanent legislative priority.

The current status quo is insufficient. To truly improve the patient care journey, there must be sustained federal investment in biomedical research and a commitment to foster innovation.

ASN partners with kidney community on congressional briefing

On April 23rd, ASN partnered with leading kidney health organizations to convene a Congressional Briefing on Capitol Hill, titled "Kidney Diseases: The Hidden Crisis in American Health Care," underscoring the urgent need for stronger federal action to address a growing and often overlooked public health challenge. Hosted by the American Kidney Fund, ASN, the American Society of Pediatric Nephrology, the National Kidney Foundation, and the Renal Physicians Association, the briefing aimed to educate lawmakers and staff on the scope, cost, and consequences of kidney diseases in the United States.

Moderator LaVarne A. Burton, MA, president and chief executive officer of the American Kidney Fund, opened the briefing by welcoming attendees and thanking members of the bipartisan Congressional Kidney Caucus. She highlighted growing government attention to kidney health, including a recent US House Committee on Ways and Means hearing and a report from the HHS Office of Inspector General elevating kidney diseases as a national concern. Burton also recognized Representatives Buchanan and Doggett for their leadership in supporting the creation of an Officer of Kidney Health and Transplantation within HHS, a key policy priority of ASN's.

Providing a clinical overview, Rebecca Schmidt, DO, FACP, FASN, of West Virginia University School of Medicine, Morgantown, and past president of the Renal Physicians Association, outlined the biology and prevalence of kidney diseases, which affect approximately one in seven US adults and are frequently undiagnosed. Schmidt also emphasized the central role of diabetes and hypertension; the importance of early screening and prevention; and the unique challenges of kidney failure, including the lack of a cure, decades of limited innovation, and the significant toll on quality of life. Beyond the human toll, the briefing emphasized that the financial burden of kidney diseases is substantial, with Medicare spending on kidney failure having reached $55.3 billion in 2023.

Policy solutions and sustained federal investment were central focuses of the briefing. Miriam Godwin, a living donor and vice president of Health Policy and Clinical Outcomes at the National Kidney Foundation, outlined legislative priorities, such as the Living Donor Protection Act and the Expanding Support for Living Donors Act, to reduce barriers to transplantation. ASN President Samir M. Parikh, MD, FASN, highlighted persistent research and innovation gaps, pointing to the TKHR report and the ASN and HHS public–private partnership—the Kidney Innovation Accelerator (KidneyX)—as key efforts to facilitate progress after decades of stagnation in kidney care. Finally, Patricia Seo-Mayer, MD, FASN, of Inova Children's Nephrology, Fairfax, VA, and the American Society of Pediatric Nephrology, provided a pediatric perspective, emphasizing the lifelong impact of kidney diseases and the need for earlier intervention across the lifespan.

The briefing delivered a clear, unified message: Without stronger awareness, sustained federal investment, and targeted policy action, kidney diseases will continue to pose a significant and growing threat to public health.

KidneyX challenge to award $4 million for solutions aimed at better supporting living kidney donors

In collaboration with HHS, ASN recently co-launched a $4 million prize competition to accelerate innovative solutions focused on reducing barriers, improving outcomes, and increasing awareness to better support living kidney donors (3). Reflecting a commitment at the highest levels of government to these heroic Americans, HHS Secretary Robert F. Kennedy, Jr., said, "Living kidney donation delivers some of the best outcomes for patients with kidney failure, yet avoidable barriers still stand in the way. Through the $4 million KidneyX EMPOWER Prize Challenge, we are calling on innovators to remove those barriers and expand access to patient-centered, equitable donation—so more Americans can live longer, healthier lives."

The KidneyX EMPOWER Prize encourages a wide range of participants, including patients, living donors, caregivers, health care professionals, researchers, technology and digital health companies, engineers, and entrepreneurs, to submit their solutions (scalable interventions or tools already in practice) or promising concepts for consideration.

The competition calls for solutions that reduce financial, logistic, and systemic barriers to living donation; support the health and long-term well-being of living donors; improve the donor and recipient journey, from evaluation through recovery; increase awareness, education, and trust in living donation; and expand access to transplantation, particularly in underserved communities. By advancing innovations in these areas, KidneyX aims to ensure that living donors are supported before, during, and after donation as they help more Americans receive life-saving transplants.

"Innovation in kidney care must begin with the experiences of people with kidney diseases and living donors," said Parikh. "By fostering innovations that empower living donors and streamline the process, we are not only better supporting Americans who save the lives of others but also reducing the long-term burden on the Medicare program, safeguarding both our nation's kidney health and its fiscal future."

HHS commits to advancing data standards and interoperability in kidney care

Alongside the KidneyX EMPOWER Prize announcement, HHS also unveiled an exciting, new commitment to work closely with the nephrology community to explore opportunities to improve data standardization and enhance interoperability across the kidney care ecosystem—another long-standing ASN policy goal.

Led by the HHS Office of the National Coordinator for Health Information Technology (IT), this effort will focus on identifying gaps and advancing solutions that enable more seamless, secure, and patient-centered data exchange, supporting better clinical decision-making, care coordination, research, and innovation in kidney diseases and transplantation. By strengthening the underlying data infrastructure, HHS and its partners, including ASN, aim to accelerate progress toward more equitable, efficient, and high-quality kidney care.

"Data and technology play a critical role in supporting patients, donors, and clinicians across the transplant ecosystem," said National Coordinator for Health IT Thomas Keane, MD, MBA. "By fostering innovation through this challenge and advancing more seamless,

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Strengthening Kidney Health

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interoperable data exchange, we can help ensure that individuals have the information and tools they need to make informed decisions and receive high-quality, coordinated care."

"Lack of interoperability between the places—clinics, dialysis units, transplant centers, the inpatient setting—where we provide care for our patients has long challenged the nephrology community, impeding our ability to provide timely, efficient care for our patients," said ASN Councilor Daniel E. Weiner, MD, MS, FASN. "Not only would developing uniform data standards in nephrology address this challenge, it would also unlock exciting scientific opportunities derived from linking databases and standardizing information we're collecting in our research efforts nationwide. I am grateful to National Coordinator for Health IT Thomas Keane and his entire team for their recognition of this as an important yet solvable challenge and for their willingness to work together with ASN and the entire community to tackle it collaboratively."

ASN outlines vision for the future of the KCC Model

As part of the society's longstanding efforts to engage with the federal government on improving value-based kidney care, ASN recently submitted a comprehensive set of recommendations to the Center for Medicare and Medicaid Innovation (CMMI) regarding the Kidney Care Choices (KCC) Model (4). Although the model has already catalyzed meaningful progress in advancing kidney care transformation, ASN emphasizes that targeted refinements to its financial and operational structures are needed to further improve patient outcomes, expand access to high-quality care, and support long-term stability.

Launched in 2022, the KCC Model is a voluntary value-based care model designed to reinforce the leadership role of nephrologists and incentivize coordinated, patient-centered care. The model emphasizes better preparation for dialysis, increased access to transplantation, expanded use of home dialysis, and earlier interventions to slow the progression of chronic kidney disease. In its letter of recommendations, ASN highlighted that early successes have emerged across several of these areas, including improvements in optimal dialysis starts, increased preemptive transplant waitlisting, and greater adoption of home dialysis modalities.

To ensure the model's scalability and long-term success, ASN underscores that several key refinements are necessary. Among its top-line recommendations, ASN encouraged CMMI to:

- **Improve financial predictability.** Refine benchmarking methods, limit retrospective adjustments, and maintain risk corridors to reduce volatility for participating practitioners.
- **Focus on early intervention.** Better align incentives with the natural progression of kidney disease by strengthening support for early-stage chronic kidney disease management to delay or prevent kidney failure.
- **Enhance operational efficiency.** Address administrative barriers and attribution delays that can limit participation, particularly for smaller and rural practices.
- **Commit to long-term evaluation.** Implement longer-term model cycles and post-model evaluation activities to accurately capture downstream impacts, such as delayed disease progression and sustained transplant success.
- **Expand integration.** Strengthen coordination with transplant centers and explore the inclusion of Medicare Advantage beneficiaries to enhance the model's reach.

As CMMI evaluates the future of value-based kidney care, ASN's message remains clear: The KCC Model shows real promise, but thoughtful adjustments and a commitment to measuring long-term savings are essential. By focusing on financial stability and early intervention, CMMI can ensure that the model effectively transforms care delivery and improves outcomes for all people across the kidney disease continuum. ■

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CREATIVE CORTEX

Renal Voyage

By Anil Saxena

https://doi.org/10.62716/kn.003142026

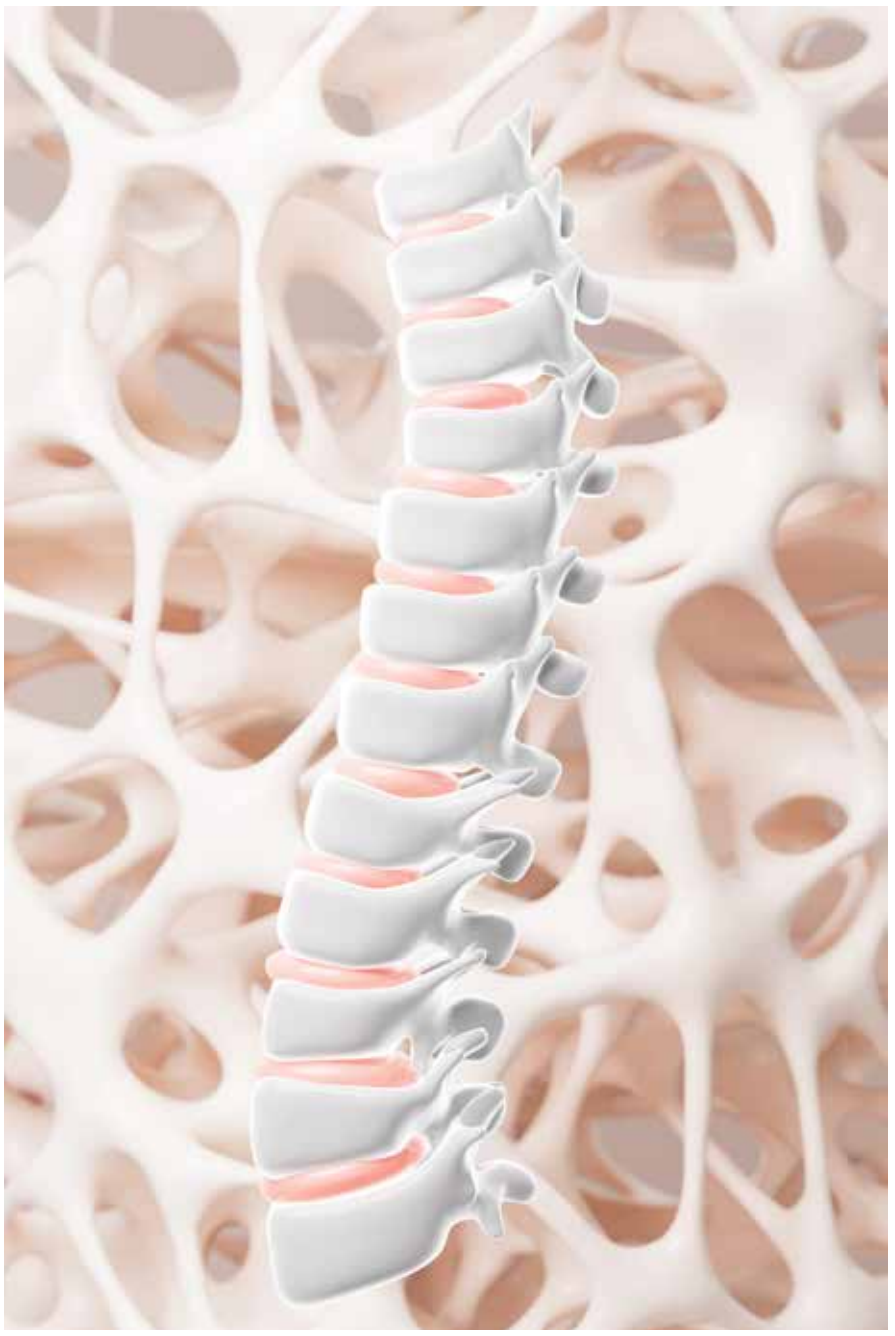
Artwork by AnilzArt. Anil Saxena, MD, FASN, is a digital artist based in Dubai, United Arab Emirates. His abstract artwork blends trained medical expertise with vibrant color palettes, creating visually captivating landscapes of human identity and transformation. Saxena's work has been exhibited internationally and featured on the covers of medical journals.

In the moon-kissed stillness, a solitary boat drifts upon the kidney's mirrored waters—silent guardians of equilibrium. Like this vessel navigating shadowed tides, the kidneys quietly filter life's turbid flow: purifying blood of excess and toxin, preserving essence, balancing the inner sea. In their humble labor lies profound wisdom—to discern, to cleanse, to sustain vitality amid the swirling chaos of existence, anchoring the soul's voyage through night. ■

Recovery, It Seems, Is Not Repair: Rethinking Bone Health After Kidney Transplantation

By Muneeb Iqbal

https://doi.org/10.62716/kn.003632026



Kidney transplantation is often framed as a turning point in the trajectory of chronic kidney disease–mineral and bone disorder. It is not uncommon to celebrate improving numbers, such as falling parathyroid hormone levels, rising hemoglobin, and stabilizing graft function. Bone mineral density (BMD), when checked months later, may also appear reassuring, yet the patient in front of us may still carry a persistently elevated fracture risk (1).

In this context, a recent study by Ziolkowski et al. challenges how we interpret this apparent recovery (2). This was a 24-month prospective cohort study of 60 kidney transplant recipients compared with 361 healthy controls to assess changes in bone density, structure, and biochemical markers. Using both dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), the authors demonstrated that skeletal changes after kidney transplant were not uniform or overtly beneficial. Although it was shown that BMD at the hip and spine improved beyond 6 months, crucially cortical bone underwent progressive thinning due to endocortical resorption. The longitudinal design—use of varying imaging modalities including pQCT, which distinguishes cortical and trabecular bone—was a notable strength. On the other hand, the single-center cohort and the exclusion of fracture outcomes may have limited the generalizability and interpretation of the findings.

The distinction between cortical and trabecular bone measures is important. DXA, the most widely used clinical tool, provides a two-dimensional estimate of areal BMD but critically cannot differentiate between trabecular and cortical bone. Consequently, apparent improvements in BMD may therefore mask ongoing structural decline. Prior studies have highlighted that cortical bone loss is a principal feature of chronic kidney disease-related bone disease, and its persistence after transplant goes toward explaining why fracture risk does not normalize despite improving biochemistry (3, 4).

The study also highlighted competing influences shaping post-transplant bone health (2). Somewhat intuitively and unsurprisingly, corticosteroid exposure was consistently associated with declines in both trabecular and cortical bone measures, reinforcing well-established evidence of glucocorticoid-induced bone toxicity (5, 6). In contrast, increases in body mass index and appendicular lean mass were associated with improvements in BMD, particularly at weight-bearing sites. These findings align with broader literature linking muscle mass to bone strength and suggest that recovery from sarcopenia may be a key determinant of skeletal recovery (7, 8).

Notably, improvements in mineral metabolism, particularly reductions in parathyroid hormone, were associated with increases in cortical volumetric BMD. However, these biochemical gains did not prevent progressive cortical thinning. This underscores the complexity of post-transplant bone disease and supports recent Kidney Disease: Improving Global Outcomes (KDIGO) guidance emphasizing caution in interpreting bone biomarkers in isolation (9, 10).

What does this mean in practice? First, improving BMD should not be equated with complete skeletal recovery. Second, attention to modifiable factors, particularly corticosteroid exposure and physical rehabilitation, may play a central role in shaping outcomes and could be just as important as pharmacologic interventions. Third, this study invites clinicians to think beyond DXA and consider the limitations of conventional tools when assessing bone health (11).

Recovery, it seems, is not repair. As nephrology continues to evolve toward more individualized care, recognizing the distinction between bone density and bone structure may be essential if we are to meaningfully reduce fracture risk in the growing population of transplant recipients. ■

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The author reports no conflicts of interest.

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B-Cell Modulators in IgA Nephropathy Wins NephMadness 2026

By Matthew A. Sparks

https://doi.org/10.62716/kn.003702026

NephMadness 2026 marked the 14th edition of the global educational tournament presented by the National Kidney Foundation and the *American Journal of Kidney Diseases*, continuing its tradition of celebrating World Kidney Day by spotlighting transformative topics in nephrology. Modeled after the National Collegiate Athletic Association's March Madness, NephMadness once again engaged clinicians, trainees, researchers, and kidney enthusiasts worldwide in a bracket-style competition, with winners selected by a distinguished Blue Ribbon Panel of trainees, nephrologists, patients, and kidney-health professionals.

NephMadness 2026 champion

The 2026 NephMadness champion is B-Cell Modulators in IgA Nephropathy. After advancing through a highly competitive bracket, B-Cell Modulators claimed the title by defeating Complement 3 Glomerulopathy (C3G) Treatment. This reflects the growing impact of B-cell–targeted therapies across multiple kidney diseases, including glomerular and autoimmune conditions. B-Cell modulators—B-cell activating factor and a proliferation-inducing ligand—are reshaping immunoglobulin A (IgA) nephropathy by directly attenuating pathogenic IgA1 class-switching and plasma cell survival, thereby reducing upstream production of galactose-deficient IgA1. This mechanism-based approach moves the field beyond nontargeted immunosuppression toward disease-modifying therapy aimed at the root immunobiology of IgA nephropathy.

2026 Tournament regions

NephMadness 2026 featured eight regions, each containing two teams that explored contrasting or complementary approaches within key areas of nephrology:

- **IgA Nephropathy**
  B-Cell Modulators versus *Complement Inhibition*
- **Artificial Intelligence**
  Computational Pathology versus *Natural Language Processing*
- **Animal House**
  Dogs versus *Cats* (comparative and translational animal models in kidney research)
- **Trolls of Transplantation**
  BK Virus (BKV) versus *Cytomegalovirus (CMV)* (persistent viral infections in kidney transplant)
- **C3G**
  Diagnosis versus *Treatment* (evolving paradigms in rare complement-mediated disease)
- **Cerebronephrology**
  In Chronic Kidney Disease (CKD) versus *In End-Stage Kidney Disease (ESKD)* (brain–kidney interactions across disease stages)
- **Point-of-Care Ultrasound (POCUS)**
  In Acute Kidney Injury (AKI) versus *In ESKD* (bedside ultrasound transforming nephrology practice)
- **Genetics**
  Polycystic Kidney Disease (PKD) Masqueraders versus *Fabry Disease Treatment*

As in prior years, NephMadness 2026 sparked worldwide engagement, with lively debates unfolding across social media under #NephMadness and institutions hosting NephMadness parties, educational sessions, and creative celebrations. The tournament continued to underscore NephMadness's unique role in blending rigorous scholarship with community, creativity, and fun. Do not miss out on year 15 of NephMadness in 2027! ■

Matthew A. Sparks, MD, FASN, is an associate professor of medicine and Fellowship Program Director in the Division of Nephrology, Duke University School of Medicine, Durham, NC. He is a cocreator of NephMadness and serves on the NephMadness 2026 Executive Team.

The author reports no conflicts of interest.

Findings

Preemptive Strategy Reduces Lupus Kidney Flares

https://doi.org/10.62716/kn.003562026

For individuals with lupus nephritis (LN) with asymptomatic serologic reactivation, a strategy of preemptively increasing immunosuppression reduces disease flares, according to a recent study in *Kidney International*.

The randomized trial included 49 patients in China with LN who developed asymptomatic serologic reactivation during clinical remission. All patients were in clinically stable condition, on maintenance immunosuppressive therapy, with low-dose glucocorticoid and mycophenolate or azathioprine.

Patients assigned to the intervention group received preemptive increases in prednisolone (from ≤5.0 mg/day to between 0.4 and 0.5 mg/kg/day) and mycophenolate (to 1.5 g/day) or azathioprine (to 100.0 mg/day). Prednisolone was then tapered to the original dosage within 12 weeks. The primary endpoint was survival, free of kidney flares, at 24 months.

Patients assigned to the preemptive strategy had no kidney flares compared with five flares among control individuals assigned to observant management. Two-year survival, free of kidney flares, was 100% in the preemptive group versus 80% in controls. The preemptive group also had increased survival, free of extra-kidney flares, of 91% versus 72% in the control group and free of overall flares of 91% versus 52% in the control group.

The preemptivee strategy was associated with improvements in anti–double-stranded DNA and complement component 3 levels, whereas immunologic measures were unchanged in the control group. The two groups had similarly low adverse event rates and stable kidney function.

Prevention of disease flares is a critical objective in the management of patients with LN receiving maintenance therapy, particularly those with chronic kidney disease. Management of patients with serologic reactivation, who may remain clinically stable for a prolonged period, is a key challenge.

This small randomized controlled trial supports the effectiveness of preemptively increasing immunosuppression in patients with LN with asymptomatic serologic reactivation. Compared with observant management, the preemptive strategy "effectively reduces the risks of renal and extra-renal relapses with an acceptable safety profile," the researchers write [Yap DYH, et al. A prospective multi-center randomized controlled trial preemptive increase in immunosuppression for asymptomatic serological reactivation in patients with lupus nephritis in clinical remission. *Kidney Int*, published online March 27, 2026. doi: 10.1016/j.kint.2026.02.037]. ■

Prevention of Recurrent Kidney Stones—What Works?

https://doi.org/10.62716/kn.0035620266

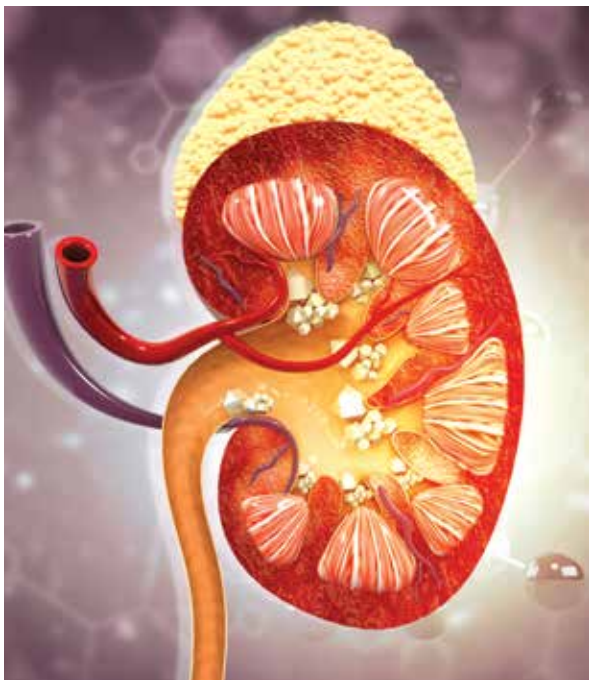
Increased fluid intake, dietary changes, and selected medications are effective in reducing the risk of recurrent kidney stones, concludes a systematic review in the *Annals of Internal Medicine*.

A review of PubMed, the Cochrane Library, and clinical trial registries was performed to identify studies evaluating dietary, pharmacologic, and surveillance imaging strategies to prevent recurrent nephrolithiasis. Data from 26 randomized controlled trials and 5 nonrandomized trials were analyzed. All but three studies were limited to adults; no surveillance imaging studies met criteria for study inclusion.

Evidence suggested that increased water intake and a diet with normal to high calcium, low protein, and low sodium had at least small benefits in lowering recurrence risk in adults with calcium oxalate or phosphate stones. Pharmacologic treatment with thiazides, alkali, and allopurinol was associated with reduction of recurrent stones in the same group of patients. For all interventions, strength of evidence was rated as low.

Studies of infection-related stones suggested reduced stone growth with acetohydroxamic therapy, with low strength of evidence. However, there was insufficient evidence for prevention of stone recurrence and moderate evidence for an increased risk of minor adverse events. Lemon juice was associated with an increased risk of minor adverse events. There was no increased risk of harms due to serious adverse events with thiazides or allopurinol, again with low strength of evidence.

The study provides an updated analysis of evidence on dietary and pharmacologic interventions to prevent recurrent kidney stones in adults. The researchers note the low strength of evidence for most of the benefits detected and the dearth of studies in pediatric patients. The authors discuss priorities for further research, including studies based on specific stone subtypes and associated risk factors [Asher GN, et al. Prevention of recurrent nephrolithiasis in adults and children: A systematic review. *Ann Intern Med* 2026; 179:696–707. doi: 10.7326/ANNALS-25-04452]. ■



Moderate Protein Restriction May Lower Long-Term Dialysis Risk

https://doi.org/10.62716/kn.003792026

For people with chronic kidney disease (CKD), moderate dietary protein intake (DPI) is associated with a lower rate of dialysis initiation at long-term follow-up compared with higher DPI, suggests a study in *JAMA Network Open*.

The retrospective cohort study included patients with stage 3 or 4 CKD receiving care from an Israeli health service between 2007 and 2022. The study included objective assessment of normalized DPI (nDPI), with 24-hour urinary nitrogen excretion normalized to adjusted body weight. Participants were classified into lower and higher nDPI groups at a threshold of 1.0 g/kg per day.

Among the 1441 included patients, the mean age was 67 years; about 65% of patients were men. Outcome analyses included 530 patients in propensity score-matched cohorts (n = 265 each) with either lower or higher nDPI. In both groups, most patients had protein intake above the recommended dietary allowance of 0.8 g/kg per day. The primary outcome was a composite of 50% or greater reduction in estimated glomerular filtration rate (eGFR), dialysis initiation, or death from any cause.

At a median follow-up of 67 months, patients with an nDPI of less than 1.0 g/kg per day were at lower risk of adverse kidney outcomes. The hazard ratio for the primary composite outcome was 0.77, mainly reflecting a reduced risk of dialysis initiation (hazard ratio, 0.65). Reduction in the composite outcome remained significant in multivariable Cox models.

Lower versus higher nDPI was unrelated to the slope in the eGFR or albuminuria. Nutritional markers were also similar between groups.

There is a lack of data on the optimal strategy for dietary protein restriction in people with CKD. This new analysis of routine clinical practice data finds that moderate protein restriction—defined as an nDPI of less than 1.0 g/kg per day—is associated with a reduced risk of long-term dialysis initiation.

The researchers highlight the role of 24-hour urinary nitrogen monitoring in routine CKD care. They conclude: "Given the pragmatic, clinical practice approach to monitoring intake, these findings may be especially relevant to clinical settings where long-term adherence and feasibility are key considerations" [Beberashvili I, et al. Protein intake and kidney outcomes in nondialysis chronic kidney disease over 15 years. *JAMA Netw Open* 2026; 9:e269575. doi: 10.1001/jamanetworkopen.2026.9575]. ■

"IMPACTS-BP" Improves Hypertension Control in Patients With Limited Income

https://doi.org/10.62716/kn.003802026

A team-based intervention provides greater reduction in systolic blood pressure (BP) in patients with hypertension seen at federally qualified health centers (FQHCs) compared with usual care, reports a randomized trial in *The New England Journal of Medicine*.

The cluster-randomized Implementation of Multifaceted Patient-Centered Treatment Strategies for Intensive Blood Pressure Control (IMPACTS-BP) trial enrolled patients receiving care for uncontrolled hypertension at 36 FQHC clinics in Louisiana and Mississippi. Clinics were assigned to the team-based implementation strategy or enhanced usual care (physician education on clinical guidelines). Modeled after the Systolic Blood Pressure Intervention Trial (SPRINT [NCT01206062]), the study intervention included an intensive BP-management protocol, BP audit and feedback, coaching on lifestyle change and medication adherence, and home BP monitoring.

Mean change in systolic BP from baseline to 18 months was compared between groups, along with a medication adherence summary score. The analysis included 1272 patients aged 40 years or older. The mean age was 59 years; 57% were women. Most patients (76%) were unemployed and had an annual family income of less than $25,000.

At follow-up, the mean reduction in systolic BP was 15.5 mm Hg in the intervention group and 9.1 mm Hg in the control group, for a between-group difference of 6.4 mm Hg. Patients at intervention clinics were more likely to achieve a systolic BP of less than 120 mm Hg (21.8% versus 15.1%) or 130 mm Hg (47.7% versus 36.4%). Most of the BP-lowering effect occurred in the first 6 months of intervention.

The implementation group also had better medication adherence during follow-up: a mean summary score of 2.8 versus 2.1 on a 0-to-4 scale. In both groups, the serious adverse event rate was about 21%.

The team-based strategy improved BP control and medication adherence in this population with low income facing substantial health disparities. "This proven, multifaceted approach is scalable to other primary care settings and could improve hypertension control in underserved populations," the researchers conclude. They also discuss several factors that contributed to the success of the study intervention [Mills KT, et al. Multifaceted strategies for hypertension control in low-income patients. *N Engl J Med* 2026; 394:1376–1387. doi: 10.1056/NEJMoa2504068]. ■

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