

KidneyNews

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New Technology May Help Fuel Shift Toward Home Dialysis

By Bridget M. Kuehn



As a veteran of both in-center and home dialysis, patient Richard Crawford knows that dialysis is a “tough proposition” in terms of time and its impacts on the body. But he was impressed by a new experimental home dialysis device called Tablo that he tried as part of a clinical trial.

“It seemed to sync with my body much better than both in-center devices and systems I used at home,” Crawford said. He explained he found it intuitive to use, that it reduced the likelihood of user error, and gave him better biochemical clearance. In fact, he said he had enough energy after using the device to jump on the treadmill within a couple hours of finishing.

Results of the trial, which the device’s manufacturer Outset Medical (San Jose, CA) is using to apply for US Food and Drug Administration (FDA) clearance to market the device for home dialysis, were presented at Kidney Week 2019 in Washington, DC. The trial enrolled 30 patients from 8 US dialysis units and met its endpoints for safety and efficacy, and 28 patients completed the treatments. Patients received home dialysis 4 times per week for 32 treatments after first completing

32 in-center treatments and 8–16 transition treatments, according to the abstract. The device has already received FDA clearance for use in-center.

“Above and beyond anything, this device has shown that it works at home,” said Principle Investigator Troy Plumb, MD, associate professor of medicine at the University of Nebraska Medical Center. With FDA clearance for home use, “it’s going to give patients another option,” he said.

The Tablo device is one of a growing number of high-tech, user-centric home dialysis devices in development. A clinical trial for another experimental home dialysis device from CVS Health called the HemoCare Hemodialysis System launched in July 2019. The company hopes to win FDA approval for the trial and be able to market the device by 2021. A British company called Quanta also launched a US study of its SC+ home hemodialysis system in August 2019 as a step toward seeking FDA clearance.

Fresenius’ NxStage System One device, which allows patients to administer home hemodialysis without help,

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Transformation in Kidney Care Takes Center Stage at Kidney Week

By Bridget M. Kuehn

Inventor Dean Kamen said he is hoping to one day put himself out of business in both the dialysis and insulin pump industries. He created the first insulin pump and the first home peritoneal dialysis machine. The home hemodialysis machine he helped develop is currently being tested in an in-center clinical trial as part of CVS Health’s foray into home dialysis.

“We shouldn’t be making insulin pumps for kids, we should be transplanting beta cells in the pancreas,” Kamen said during a Kidney Week 2019 state-of-the-

art plenary talk. “We should not be doing dialysis. We should give people a replacement kidney.”

The inventor, who has more than 440 patents to his name including one for the Segway, acknowledged that new technologies and the disruption they bring can be frightening. But he challenged nephrologists to embrace the changes that transformative technologies are bringing to the field. Kamen was joined in the plenary by Bruce Culleton, MD, vice president and chief medical

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Home Dialysis

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received FDA clearance in 2017 and has greatly expanded access to home dialysis, according to Thomas Golper, MD, Medical Director of Home Dialysis at Vanderbilt University Medical Center. NxStage currently accounts for much of the market for home dialysis in the US.

“NxStage is easier to use than the equipment we were using before, and the more frequent [dialysis sessions with the device] have reduced the complication rate,” said Golper, who also serves on the advisory board for NxStage. He explained the device also doesn’t require changes to patients’ homes to use and patients can be trained to use it in a shorter time frame.

These developments, along with Advancing American Kidney Health (AAKH), created by an executive order by President Donald Trump in July 2019, are expected to help increase the number of patients on home dialysis. The AAKH will create payment incentives to increase patient access to home dialysis and kidney transplant.

The same machine that [the patient] becomes comfortable with in the hospital can follow the patient through their journey, whether that might be in a conventional clinic setting, or in the future all the way to home.

—Outset Medical CEO Leslie Trigg

User-friendly technology

The latest generation of portable dialysis devices emphasize high-tech, user-friendly features. Tablo needs only a plug and tap water. NxStage can be combined with another device the company makes to use tap water as well.

Leslie Trigg, CEO of Outset Medical, said the Tablo device was designed to be patient-friendly in any setting, from an intensive care unit to a dialysis clinic, and if their application is approved by the FDA, eventually in the home setting. “The same machine that [the patient] becomes comfortable with in the hospital can follow the patient through their journey, whether that might be in a conventional clinic setting, or in the future all the way to home,” Trigg said.

Bruce Culleton, chief medical officer for CVS Kidney Care, said the company wanted to develop a device that would be easy to use for a broad population of patients, would ease the burden on patients and their caregivers, and help alleviate patients’ and caregivers’ fears about safety. Only half of patients trained to do home dialysis are still on the therapy one year later, Culleton noted.

“We do not believe that home hemodialysis will be sustainable if dropout rates are as high as they are today,” Culleton said. “That’s just not a way we think home hemodialysis is going to grow.”

As a patient, Tablo clinical trial participant Crawford said the flurry of new devices in development is encouraging. Often, he said, current dialysis options whether home or center-based are not “conducive to traveling,” which limits his professional prospects. He said he hopes the new technologies becoming available make travel easier.

“Technological advancements should help reduce the cost of these systems and give the patient more options,” he said.

Training and policy needs

In addition to the need for easier-to-use technology, systems-level and policy changes are needed to make home dialysis more widely available.

“While better technology can make it easier to facilitate the use of certain renal replacement therapies at home, healthcare system-level improvements can have a larger impact by ensuring implementation of comprehensive, effective approaches to the care of patients with end stage

kidney disease,” said Leonid V. Pravoverov, MD, chief of nephrology at Kaiser Permanente’s East Bay service area.

Pravoverov was the lead author of a study published recently that showed Kaiser Permanente of Northern California was able to increase enrollment of new dialysis patients in home peritoneal dialysis (PD) from 15.2% in 2008 to 33.8% in 2018 with 80% continuing on home PD beyond one year. The results, which far outstripped the US-wide increase from 6.1% in 2008 to 9.7% in 2016, were enabled by a multi-disciplinary, systemwide initiative to expand PD. That program included identify-

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Troubleshooting in Disaster Zones

Planning, Partnerships, and New Devices to Help Kidney Patients

By Bridget M. Kuehn

The one-two punch of Hurricanes Irma and Maria in the United States and the Caribbean in 2017 was a wake-up call to the nephrology community and first responders. The twin disasters left more than 56,000 dialysis patients in the lurch, and kidney transplant patients in destroyed communities desperately seeking immunosuppressive medications.

To better prepare for future disasters, ASN created the Emergency Partnership Initiative (EPI), which held its first meeting in September 2019. The partnership aims to bring together dialysis and transplant clinicians; patients; federal, state, and local emergency responders; public health leaders; and companies that make up the supply chain to anticipate and prepare for kidney patients’ needs in future disasters, said Nicole Lurie, MD, chair of the EPI and former Health and Human Services (HHS) Assistant Secretary for Preparedness and Response.

“It comes very much out of the experience of ASN members who have been called upon or found themselves in disaster situations where the system broke down for patients,” Lurie explained. The EPI, she said, is working to anticipate such problems and be proactive in working with partners to support patients, clinicians, and first responders before and when disasters strike.

One of the challenges during hurricanes and other disasters is that dialysis patients may be displaced from their homes and usual care providers. Other providers may be unable to handle the surge of patients or may be incapacitated by the disaster.

“You have to be able to anticipate that and have a plan for how you’re going to deal with it so that people don’t get into even more emergency situations,” Lurie said. “Then, when the crisis is over, to the extent that it’s possible, you need to get patients back into their regular routine.”

That process starts with knowing who the dialysis patients are and how to reach them in an emergency, knowing how much surge capacity dialysis providers have, and preparing to provide additional dialysis as needed. To help expand capacity, HHS recently awarded a contract to Outset Medical (San Jose, CA). HHS will purchase Tablo Hemodialysis Systems devices and supplies to deploy in communities experiencing a disaster. The portable devices have received US Food and Drug Administration clearance for center-based use. Outset Medical has already delivered 25 of the 50 machines ordered by HHS and expects to deliver the other half by the end of the year.

Outset Medical CEO Leslie Trigg said that during recent disasters there was limited access to dialysis in the affected communities and many patients on dialysis were temporarily relocated to other cities across the US for weeks or months. The situation takes a psychological toll on patients and their families and is also costly for the government, she noted. To curb these costs and allow patients to stay close to home, the HHS put out a request for proposal for devices that could more easily be used in communities affected by disasters and Tablo was selected. Tablo doesn’t require as much infrastructure as other systems, Trigg said. The device only requires a plug and tap water and can handle tap water with a wide range of characteristics, she said.

“I think they chose Tablo for its flexibility,” Trigg said. “It offers a lot more options about where patients can be treated in the affected areas.”

Lurie said she’s glad both the HHS and EPI are considering patients’ experiences in their disaster planning.

“I’m very excited that we have some forward thinking and proactive thinking about dialysis and disasters [through the EPI and HHS’s purchase of Tablo devices],” Lurie said. ■



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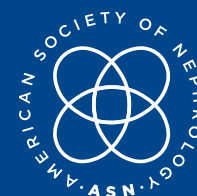
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Home Dialysis

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ing and educating patients with advanced chronic kidney disease about their options, providing continuing education and support for clinicians on how to provide PD, and a streamlined system process, noted the senior author of the work, Alan S. Go, MD, a research scientist in the Kaiser Permanente division of research.

“We firmly believe that there are additional opportunities to grow the population of kidney disease patients receiving home-based therapies, including peritoneal dialysis,” Go said. But he noted improvements in current regulations are needed, such as support for new models of care, including assisted-at-home dialysis, dialysis in skilled nursing facilities, and simplified rules for respite care.

A major hurdle to expanding home dialysis in the

US is training physicians how to do it, said Golper, who runs a course called Home Dialysis University. But many physicians have not been trained, and Golper said he’d like to see parts of his course taught in every training program across the country.

“A big part of the problem is that doctors don’t know how to do home dialysis,” he said.

More telehealth is also needed to support patients doing home dialysis, agreed both Crawford and Golper. Crawford explained that it would be helpful to have easy audio and video conference access to a support team who could help home dialysis patients when issues arise.

Starting in January 2019, Medicare began covering telehealth visits for home dialysis patients, Golper noted.

“That in and of itself should have caused an explosion of home dialysis,” Golper said. But physicians, he noted, are still learning to use the technology. Additionally, there can be technical hurdles. For example, he and

his colleagues will only start offering telehealth in January because changes had to be made to their electronic medical records system to enable it.

“There’s no question, no question that technology is going to play a role [in expanding access to home dialysis, whether it’s simpler to use equipment, or communication, or telehealth,” Golper said. “All those things will be positive, but none of it can happen until the physicians know how to do the therapy.”

Culleton said that “systems changes are more important than technology,” for example, implementing some of the changes outlined in the AAKH. It’s also important, he said, to address the overall costs of care to enable providers to improve the way they care for patients receiving dialysis at home.

“There are a lot of things that need to happen to change behavior at the provider and physician level,” he said. ■

Transformation in Kidney Care

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officer of CVS Kidney Care, and ASN Executive Vice President Tod Ibrahim.

“We’re not going to slow down the pace of the advancing technology,” Kamen said. “You can be on the bus or you can be under the bus of this accelerated pace of technology. I plan to be on it.”

Stalled progress

Inequity and poor outcomes currently plague the more than 850 million patients with kidney disease around the world. Many patients globally die without access to any care, Ibrahim noted. Additionally, 13 die each day on the US transplant waitlist while 77 usable kidneys are discarded and most dialysis patients die within 5 years, he said. Patients who are not white are more likely to progress to kidney failure and less likely to have access to home dialysis, he said.

Culleton cited a letter he received from a 72-year-old patient who had been on dialysis since 2018. She deals with low blood pressure, vomiting, and vertigo and is often unable to go to church, family engagements, or even on a hike with her dogs.

“It’s very isolating and depressing,” Culleton said. “It shouldn’t come to anyone’s surprise that about 20% of all patients who are on dialysis that die, do it intentionally and withdraw from dialysis.”

Despite these pressing needs, progress in the field has stalled technologically, Ibrahim noted. He cited underfunding from governments and investors in nephrology as one contributor. He noted that dialysis was created the same year as the mainframe computer.

“Seventy-six years later, we carry a more powerful computer in our pocket, yet mostly rely on the same technology to treat kidney failure in in-center dialysis,” Ibrahim said.

Home dialysis still lags, with only about 12% of dialysis patients receiving it, Culleton said. Most dialysis patients, he noted, begin with a catheter in their neck and at least one-third of patients with kidney disease receive no care prior to kidney failure, he said. The Centers for Medicare & Medicaid Services (CMS) pays more than \$110 billion annually caring for patients with chronic kidney disease and kidney failure, Culleton said.

From dialysis- to patient-centered

But the speakers were optimistic that a combination of emerging technologies and the Advancing Ameri-

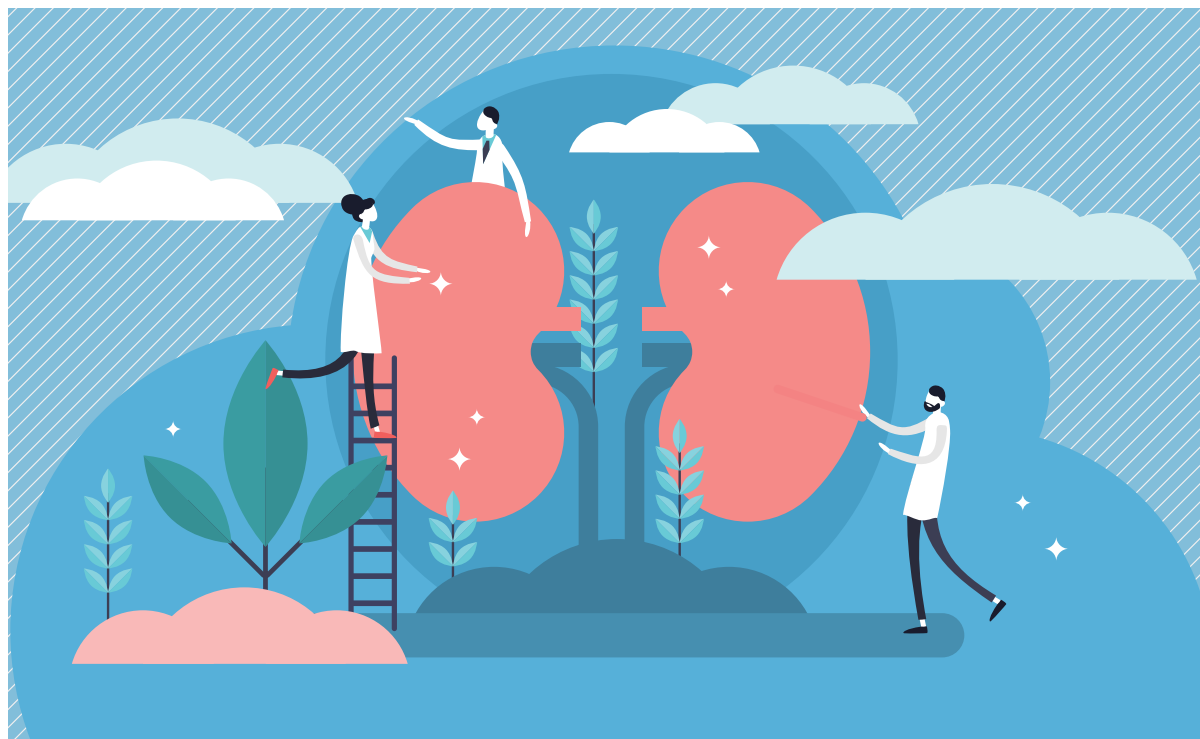
can Kidney Health initiative, announced by President Trump in July 2019, would help jumpstart progress in the field. Ibrahim noted that the ASN worked closely with the US Department of Health and Human Services to craft the program.

“This historic plan—the nation’s first kidney health strategy—aims to reduce the number of Americans with kidney failure by 25% over the next decade,” Ibrahim said. “The US government also intends to double the number of kidneys available for transplant and provide more options for people with kidney failure such as greater emphasis on alternatives to in-center dialysis.”

lead to innovation. “The invention part is easy,” he said. “Getting the world to accept change is hard.” He noted it took 20 years to get CMS to cover the insulin pump despite endocrinologists’ enthusiasm.

“We need as a community to embrace these changes and fully move forward,” argued Culleton. “Nephrologists need to lead the way.”

Culleton acknowledged that being a nephrologist isn’t easy given the complexity of care and the regulatory demands in the field. But he said the field is in a position to reorganize kidney care around patients’ needs and that technology will play an important role, for example



Kamin said progress is being made to speed the production of new technology for kidney care. For example, he noted the creation of the Advanced Regenerative Manufacturing Institute, which is working to scale up bioengineering technology. The institute has 150 members and has received \$80 million in funding from the US Department of Defense and \$214 million in matching funds from technology companies. They have already been able to demonstrate a system for generating induced pluripotent stem cells, which through an automated process can generate a 7-centimeter segment of bone and ligament in 40 days. They hope to be able to eventually create processes for making more sophisticated organs.

Kamen warned, however, that technology itself won’t

through better dialysis machines, telehealth, or machine learning to help identify patients with kidney disease.

“This is a once in a generation opportunity to change the kidney care paradigm in this country,” Culleton said.

Ibrahim urged the field of nephrology to make the most of this opportunity by demanding government and public support, and by revamping nephrology training, reimbursement, and career paths in the field.

“Together we must demand attention,” Ibrahim said. “We must advocate for kidney health. By thriving as a meaningful specialty, nephrology will extend the lives and quality of life for millions who otherwise will continue to die prematurely and unnecessarily, unjustly, inequitably.” ■

Policy Update

Kidney Care Policy: An Update on AAKH, Payment Models, and Predictions for Action Ahead

By David White

On Sunday, November 10, at Kidney Week, the final policy session of the week, “Hot off the Press,” drew an unprecedented packed crowd to hear the latest details on kidney care policy, with a strong focus on the Advancing American Kidney Health (AAKH) Executive Order. A wide range of policy efforts are underway to support the following objectives of the AAKH:

- Reducing the risk of kidney failure.
- Improving access to and quality of person-centered treatment options.
- Increasing access to kidney transplants.

Kevin F. Erickson, MD, MS, and Crystal A. Gadegbeku, MD, FASN, moderated the session with presenters Tom Duvall, Acting Division Director at the Centers for Medicare and Medicaid Innovation (CMMI); Nick Uehlecke, advisor in the office of the Secretary of Health and Human Services (HHS); Suzanne Watnick, MD, FASN, CMO of Northwest Kidney Centers; and Rachel Meyer, ASN Director of Policy and Government Affairs.

The session provided a glimpse into the thinking inside the office of HHS Secretary Alex M. Azar II on the development of kidney policy, particularly in the area of innovation, contained within the Executive Order. Speaking personally and not on behalf of Secretary Azar, Uehlecke described how kidney healthcare policy took on an urgent status with the arrival of the new HHS Secretary. Azar was personally invested in improving kidney healthcare after watching his father develop kidney failure, endure dialysis, and, ultimately, receive a kidney transplant. Uehlecke provided the backdrop for how the most sweeping changes in kidney healthcare in 50 years came into existence.

The session also provided a deeper dive into aspects of the voluntary and mandatory kidney care models, while mixing in some old-fashioned predictions for the road ahead on the regulatory and legislative fronts.

In his talk, “Deep Dive on New Kidney Care Delivery Models,” Duvall provided a firsthand look at the provisions in the Kidney Care Choices (KCC) Model—the voluntary model with its four payment pathways. Duvall and his team at CMMI created the KCC Model, which is based on the Comprehensive ESRD Care (CEC) Model that began in 2015 and expires at the end of 2020. The four payment pathways are the Kidney Care First (KCF) Option for nephrologists/nephrology practices only and the three Comprehensive Kidney Care Contracting (CKCC) Options that must include nephrologists/nephrology practices and transplant providers; however, they may also include dialysis facilities, and other kidney care providers on an optional basis (Table 1).

The KCC Model is expected to run from 2020 through December 31, 2023, with the option for one or two additional performance years at CMS’s discretion. Those healthcare providers that apply and are selected to participate will begin their participation in 2020, although financial accountability will not begin until 2021. During 2020, referred to as the Implementation Period, participants will focus on building necessary care relationships and infrastructure. Applications are due through January 22, 2020.

The following are the five payment mechanisms in the KCC model:

1. **Adjusted Monthly Capitated Payment (AMCP):** capitated payment paid to model participants to manage ESRD, based on the monthly capitated payment.
2. **CKD Quarterly Capitated Payment (CKD QCP):** capitated payment paid to model participants to manage CKD 4/5 patients.
3. **Kidney Transplant Bonus (KTB):** incremental reimbursement for successful kidney transplant up to \$15,000 over three years of allograft survival.
4. **Shared Savings/Losses:** based on total cost of care compared to benchmark (available to CKCC option participants only).

5. **Performance Based Adjustment (PBA):** upward or downward adjustment to the CKD QCP and AMCP based on participant’s year-over-year continuous improvement and performance relative to peers (available to KCF practices only).

The AAKH Executive Order also included some very ambitious goals:

- Reducing the number of Americans developing kidney failure by 25% by 2030.
- Aiming for 80% of new kidney failure patients in 2025 to be receiving home dialysis or transplant.
- Doubling the number of kidneys available for transplant by 2030.

The inclusion of the 80% incident ESRD number in the proposed rule for the mandatory ESRD Treatment Choices (ETC) Model created consternation for many in the kidney community. ASN’s comment letter, like the overwhelming majority of comment letters provided to CMMI, urged the Innovation Center to drastically reduce that number. Watnick embraced the goal in principle in a sometimes tongue-in-cheek presentation that played on the 1980s titled “Incident Home Dialysis & Transplant: Aim for 80!” She described past policies that led to the impetus to aim for such an ambitious combined rate of home dialysis and kidney transplantation, such as passage of the Medicare Improvement for Patients and Providers Act (MIPPA) of 2008, creation of the ESRD Prospective Payment System (PPS) bundle in 2011 and the ESRD Quality Incentive Program (QIP) in 2012, and the biggest contributor to value-based care: passage of the Affordable Care Act (ACA) in 2010. The ACA directly created CMMI with authority to test new models with reimbursement based on the volume of shared risk (and shared savings) and create Accountable Care Organizations (ACOs).

When asking, “Why now?” Watnick outlined the kid-

Table 1. Overview of the Kidney Care Choices (KCC) Models

Payment Options	Overview	Participants
Kidney Care First (KCF) Option	Based on the Primary Care First (PCF) Model – nephrology practices will be eligible to receive bonus payments for effective management of aligned beneficiaries	Nephrologists/nephrology practices only
CKCC Graduated Option	Based on existing CEC Model One-Sided Risk Track – allowing certain participants to begin under a lower-reward one-sided model and incrementally phase in risk and additional potential reward	Must include nephrologists and nephrology practices as well as transplant providers; may also include dialysis facilities and other kidney care providers on an optional basis
CKCC Professional Option	Based on the Professional Population-Based Payment Option of the Direct Contracting Model – with 50% of shared savings or shared losses in the total cost of care for Part A and B services for aligned beneficiaries	
CKCC Global Option	Based on the Global Population-Based Payment Option of the Direct Contracting Model – with risk for 100% of the total cost of care for all Part A and B services for aligned beneficiaries	

ney disease statistics known to all nephrologists including prevalence, mortality rates, expense of care, but, ultimately concluded that this time the nation has an HHS Secretary for whom kidney failure and kidney health are personal. That personal approach has led to an HHS-wide set of policies to increase kidney transplantation and access to alternatives to in-center hemodialysis, especially peritoneal dialysis (PD).

Infrastructure and the need for patient and provider education are among the barriers to increased use of PD. Watnick reviewed how the models and the overall Executive Order could address these challenges. For example, the models waive numerous restrictions on providing kidney disease education, from who must provide it to who may use it, adding stage 5 and the first six months of dialysis all in service of increased home dialysis.

The government is also undertaking multiple steps to increase organ supply by issuing new regulations to create transparent metrics for Organ Procurement Organizations (OPOs), streamlining organ allocation procedures, and expanding living donor support to remove barriers to living donation. Watnick consistently encouraged Kidney Week participants to embrace the direction HHS has identified for improvement but to not get obsessed with the 80% goal—it is very likely to be reduced.

ASN's Meyer closed the session with a snapshot of current kidney care policy:

1. Kidney health policy is enjoying unprecedented attention in Washington, DC.
2. The administration is outstripping Congress on kidney health policy.
3. The presidential Executive Order is only the starting point for change.

She followed with “Five Must-Hear Debuts in Kidney Health Policy”:

1. The appropriations stalemate continues.
2. Legacy transplant legislation lingers.
3. Bold HHS action on transplant care is underway.
4. The Kidney Awareness Campaign mandated by AAKH kicks off.
5. (Some) reimbursement changes are coming into focus.

In more detail, at press time, the appropriations process has stalled and another short-term continuing resolution is being crafted. For 2020, ASN is currently advocating for a \$2 billion increase for the National Institutes of Health (NIH), \$10 million for KidneyX, and \$10 million for the National Living Donor Assistance Center—a \$6.5 million increase over current funding.

ASN and other kidney advocacy groups are still pushing for a change in the three-year limit on Medicare immunosuppressive drug coverage. However, this year, HHS has directed the agency to review the costs of such a move

and has reported that it estimates a savings of at least \$300 million over 10 years. With the Living Donor Protection Act building more cosponsor support in Congress, Meyer was cautiously optimistic on the transplant legislation front.

As for bold HHS action on transplant care, the Trump administration is planning to address the procurement of organs by OPOs, the allocation of those organs, and ways to reduce barriers to living donation. At press time, ASN's policy team awaited two proposed rules: 1) OPO Metrics Overhaul and 2) Living Donor Reimbursement Expanded Access.

The nationwide kidney awareness campaign mandated by AAKH got off the ground on November 4, 2019, when HHS, ASN, and the National Kidney Foundation signed a memorandum of understanding to jointly conduct the awareness campaign. More details will follow.

Last, some reimbursement changes are coming into focus. Meyer outlined some of the success ASN and others have had in bringing new devices into the bundle but also pointed out how much more needs to be done, such as adding new money to the bundle to cover these items.

Meyer concluded with a set of macro and micro predictions that thematically stressed that most advancements in kidney policy are coming from the executive branch. Her last prediction was that “Nephrology will become cool again.” ■

Pipeline of Wearable Kidney Devices Grows

By Bridget M. Kuehn

Results from the first-in-humans trial of the automated wearable kidney (AWAK) found the device to be safe, according to work presented at Kidney Week 2019. And results from an animal study of a similar device, the Wearable Artificial KIDney (WEAKID) presented at the meeting set the stage for that device to progress to human trials as well.

The developments are the latest steps in progress toward the development of a wearable artificial kidney.

Developing an artificial kidney is now a priority of the US government under Advancing American Kidney Health, established by Executive Order in July 2019. The Kidney Health Initiative has provided the technical roadmap to achieve this goal, and KidneyX, a public-private partnership between the US Department of Health and Human Services (HHS) and ASN is holding a series of prize competitions to advance development of innovative solutions to improve the lives of those living with kidney diseases. To actualize this goal, a formal Request for Information (RFI) was released by KidneyX for an artificial kidney prize.

Nanotechnology and the use of sorbent technology that can regenerate dialysate have made it possible to create a wearable or implantable artificial kidney, according to a recent review in the *American Journal of Kidney Diseases*. Now, those early devices are being tested in animals and small human trials to pave the way for the larger human studies that would be needed to gain US Food and Drug Administration clearance for the devices. If these efforts are successful, they could reduce the burden of care on patients receiving in-center or home dialysis.

“With all of the current modalities, patients are hooked up for hours a day,” said Megha Salani, MD, assistant professor in the Department of Nephrology at Vanderbilt

University Medical College and lead author of the review. “It really affects their ability to work and do things they enjoy. With wearables they would be able to keep on a more normal schedule.”

In the AWAK trial, 15 peritoneal dialysis patients in Singapore underwent 9 AWAK therapies over the course of 3 to 4 days. None of the patients experienced serious adverse events during therapy or at 1-week or 1-month follow-up visits after the trial, although 71% reported abdominal discomfort, 36% reported bloating, and 36% had fibrin in the drain. All the patients who completed at least one AWAK therapy achieved weekly peritoneal Kt/Vurea ≥ 1.7 with median weekly peritoneal Kt/Vurea = 3.04.

“The 15-patient first-in-human trial has shown that the device is safe to use for up to 9 therapies each running up to 7 hours each,” said lead author Marjorie Wai Yin Foo, MD, head and senior consultant in the Department of Nephrology at Singapore General Hospital in China, who presented the results from the AWAK trial.

Vanderbilt's Salani called the results “very promising,” although she cautioned that it is difficult to draw conclusions from the short duration of the follow-up.

“At the very least we can feel satisfied the labs are better and certainly not inferior,” she said.

Results of a small study in uremic pigs of 8 hours of daytime, 3 animals, or nighttime, 8 animals, use of WEAKID, another wearable kidney that uses sorbent technology to regenerate dialysate, were also presented at the meeting.

Senior author Giulia Ligabue, PhD, of the Laboratorio di Nefrologia Policlinico at the University of Modena, Italy, said the results compare well to conventional peritoneal dialysis. “WEAKID treatment was well tolerated and no serious adverse events occurred,” Ligabue said. “Treatment

improves the mass transfer area coefficient (MTAC) and plasma clearance. In the pig model, the system enhances clearance of creatinine [2-fold] and of phosphate [1.6-fold], significantly increases the MTAC [1.9-fold], and it doesn't show acute systemic toxicity.” The group hopes to next test the device in clinical trials.

“This innovative treatment may offer improved blood purification, prolonged technique survival and optimal patient tolerability compared to conventional peritoneal dialysis,” Ligabue said. “WEAKID will represent a huge leap forward for dialysis patients and it is expected to significantly improve health and quality of life.”

Salani said having multiple devices in development may drive competition and lead to improved quality in artificial kidney devices. It may also help increase funders' interest in this area.

“It's a great thing for the field of nephrology,” she said. She cautioned that there may still be hurdles ahead, such as unanticipated complications associated with the use of the devices.

Foo said the next step for her team will be conducting a multi-center, international trial to demonstrate the safety and efficacy of the AWAK over a longer time frame.

“If future studies prove to be successful, this technology will revolutionize the way peritoneal dialysis has been done for the past decades,” Foo said. “Patients on peritoneal dialysis will have greater freedom in terms of traveling, flexibility of therapy, and ease of doing the procedure.” ■

“Effect of Automated Wearable Artificial Kidney (AWAK) Device on Toxin Clearance and Safety in Peritoneal Dialysis Patients” Oral Abstract 101

“Evaluation of a Wearable Artificial Kidney for Peritoneal Dialysis in a Uremic Pig Model” Poster 522

KidneyX Plans Artificial Kidney Prize; Redesign Dialysis Phase II Open for Submissions

KidneyX was established in April 2018 as a public-private partnership between the American Society of Nephrology (ASN) and the Department of Health and Human Services (HHS) with a mission to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases.

KidneyX aims to achieve this mission through a series of competitive prize competitions. The first competition hosted by KidneyX is a phased competition centered on improving dialysis. Redesign Dialysis Phase I asked innovators to accelerate the development and commercialization of next-generation dialysis products, specifically to design possible solutions or solution components that can replicate normal kidney functions and improve patient quality of life. Fifteen winners were selected from among 167 submissions, and a total prize amount of \$1,125,000 was distributed.

Announced and open for submission as of November 18, 2019, Redesign Dialysis Phase II challenges participants to

build and test prototype solutions, or components of solutions, that can replicate normal kidney functions or improve dialysis access. The total prize pool amounts to \$1,500,000 and up to 3 recipients may be selected. Entries must be submitted by January 31, 2020.

To further advance innovation in the field, a Request for Information (RFI) has been issued outlining an Artificial Kidney Prize. This prize is being put forth in order to fulfill the goals set by KidneyX and Section 6 of the Executive Order on Advancing American Kidney Health. The Artificial Kidney Prize intends to build off Redesign Dialysis and to advance the development of an artificial kidney that can replace physiological kidney function to sustain life and improve patient quality of life. The RFI asks for constituents' feedback on the following questions, and welcomes additional comments:

1. How would you prioritize the modular challenges described in section I.C, Scope of the Prize Competition? Are there additional challenges that should be considered?

2. For patients and care partners: What criteria should the Artificial Kidney Prize use for judging a solution's ability to improve the quality of life for patients?
3. What criteria would you propose for award of the moonshot prize, to both ensure that all promising approaches are considered on their merits and that the field advances beyond the current state toward human testing of an artificial kidney?
4. What forms of technical or operational support would enable you to participate, or accelerate your development timeline, in either track of the Artificial Kidney Prize?
5. If you entered the Artificial Kidney Prize, would you be more interested in participating in the moonshot track or modular track? What would you consider in deciding which track to enter?

Feedback on the RFI must be received on or before December 13, 2019, to be considered. Responses may be emailed to KidneyX@hhs.gov. ■



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The Time is Now A Perspective on the Opening Plenary at Kidney Week 2019

By Mukta Baweja

As representatives of the US Department of Health and Human Services (HHS), Centers for Medicare & Medicaid Services (CMS), and Center for Medicare and Medicaid Innovation (CMMI) joined the audience of thousands in the nephrology community from around the world, ASN President Mark E. Rosenberg, MD, FASN, kick-started Kidney Week 2019 with the opening plenary, galvanizing the political energy and opportunity of Washington, DC.

The field of nephrology has been subjected to decades of stagnation, largely resulting from lack of sufficient funding and innovation.

Until now.

After a prolonged drought in innovation and regulatory adjustment in the kidney field, an alignment of opportunity is currently being seized by members of ASN, HHS and CMS with programs including KidneyX, the Kidney Health Initiative (KHI) and the recently introduced executive order on Advancing American Kidney Health (AAKH).

Acknowledging the struggle and lack of attention that kidney diseases have endured, HHS Secretary Alex M. Azar II remarked, “We were told that just identifying all of the problems in American kidney care, and all the opportunities we have to improve it, was more attention than federal leaders had paid to this issue in a long time.”

For far too long, nephrologists and patients have been subjected to the same suboptimal treatments. Dialysis has been the accepted treatment for kidney failure despite the prognosis of those requiring dialysis being worse than that for many cancers. Many of our patients die on the transplant waiting list with a shortage of organs and significant barriers to living donor transplantation. Over 37 million patients in the United States and over 850 million in the world

When I first started speaking with legislators and staff years ago, they were not familiar with the burden of kidney disease that millions of their constituents have struggled with. At this year’s Kidney Community Advocacy Day, however, they were able to complete my sentences before we even finished telling them about the need for expanding transplant immunosuppression coverage and protecting living donors with the Living Donor Protection Act.

live with kidney disease, with exponentially rising costs on the order of \$35 billion per year in the US—from Medicare alone—with unacceptable outcomes including an over 50% mortality rate for kidney failure patients after 5 years. This unsustainable trajectory has finally led to a breaking of the dam, and as Dr. Rosenberg remarked, we have begun a “War on Kidney Diseases,” committing the US to a “system that pays for kidney health, rather than kidney sickness.”

The 2019 ASN opening plenary began with a focus on KidneyX, a public-private partnership to accelerate innovation. As of now, with the help of KidneyX, Redesigning Dialysis has become a reality as prototypes are being developed, with a future goal of an artificial kidney. In addition to KidneyX, the AAKH has outlined a comprehensive kidney health strategy to rise to the challenges in the kidney sphere including preventive care, dialysis innovation and increasing home dialysis utilization, and tackling the barriers to kidney transplantation, including addressing the organ shortage and facilitating living donation.

Additionally, members of CMS and CMMI have developed payment models geared toward incentivizing optimal dialysis modalities and improved quality metrics with a focus on increased utilization of home dialysis and ultimately transplantation. The FDA and Kidney Health Initiative (KHI) have begun collaborative efforts to focus on novel treatments to prevent progression of kidney disease, in yet another immensely powerful tool in the process of changing nephrology.

Over the past year, the heavy groundwork for catalyzing change in kidney care was laid by several crucial figures at HHS, who received the ASN President’s Medal in recognition of their commitment to helping transform nephrology for the benefit of people with kidney diseases: HHS Secretary Alex M. Azar II, HHS Deputy Secretary Eric D. Hargan, CMS Administrator Seema Verma, former

Deputy Administrator for CMMI Adam Boehler, Assistant Secretary for Health Admiral Brett P. Giroir, Senior Advisor to the HHS Secretary James Parker, Open Innovation Manager Sandeep Patel, Associate Director of Innovation and Technology Murray Sheldon, HHS Chief Technology Officer Ed Simcox, former HHS Advisor Abe Sutton, and Advisor Nicholas Uehlecke.

On November 6, 2019, I had the opportunity to talk with legislators on Capitol Hill along with 15 organizations representing 30 states during Kidney Community Advocacy Day (KCAD). When I first started speaking with legislators and staff years ago, they were not familiar with the burden of kidney disease that millions of their constituents have struggled with. At this year’s KCAD, however, they were able to complete my sentences before we even finished telling them about the need for expanding transplant immunosuppression coverage and protecting living donors with the Living Donor Protection Act.

Advocacy is working for our patients and the community, and transformation of kidney care is here—the time is now, and change cannot arrive fast enough.

“At this moment, a remarkable alignment exists among patients, researchers, clinicians, healthcare organizations, and policy makers. [...] Today, now, is the moment for nephrology and for people with kidney diseases.” – Dr. Mark Rosenberg. ■

Mukta Baweja is an Assistant Professor of Medicine and Nephrology at the Icahn School of Medicine at Mount Sinai in New York City. She serves on the Public Policy and Advocacy Committee of the American Society of Nephrology. She is an advocate for patients and at risk-populations and an agent in optimizing public healthcare delivery.

Disrupting Nephrology: From Technology to Developing Organs-on-Chips

By Mukta Baweja

Seamlessly carrying on the energy of change and transformation in the kidney sphere captured during plenary sessions at Kidney Week 2019, two sessions brought the potential for such transformation to life: Disruptors on the Move and Organs-on-Chips: Human Kidney Microphysiological Systems.

The panel of innovators and experts in healthcare innovation for the Disruptors on the Move session included current PCORI Interim Executive Director and *CJASN* Editor-in-Chief Josephine P. Briggs, MD, former Depart-

ment of Health and Human Services CTO and current Kaiser Permanente VP of Medicaid Transformation Bryan Sivak, CVS Kidney Care CMO Bruce Culleton, MD, Cricket Health CMO Carmen Peralta, MD, FASN, and Outset Medical CEO Leslie Trigg.

Patient centeredness, which took center stage in the discussion on disruption, is important to the disruption of care for at least 3 reasons, Briggs stated:

1) Patients bring a sense of urgency and impatience to the discussion.

2) The questions change when patient centeredness is being evaluated on a continual basis.
3) A patient-centered approach will also bring innovation and better implementation into the process.

These sentiments were echoed by the other panelists. “Everything comes to your phone—a taxi, food, even your friend. So why can’t the care (sic) come to you?” asked

Continued on page 10 ➤

Disrupting Nephrology

Continued from page 8

Cricket Health's Peralta. "It's not just all about reaching [patients] geographically but also psychologically."

Meaningful disruption requires three things, according to Outset Medical's Trigg: 1) an entrepreneurial ecosystem such as that provided by Kidney X, 2) an early adopter environment, and 3) capital flow.

Investors are less excited to provide capital flow if 1) and 2) are not present, she said.

In other fields, particularly with cardiac devices, a crucial ingredient to successful innovation was alleviating practitioners' sense of fear regarding adoption of a new technology—although it may have flaws and imperfections—in order for users to learn through trial and error what could work, Trigg said.

The need to quell fear among practitioners in adopting new technology also came to mind during the session Organs-on-Chips: Human Kidney Microphysiological Systems.

Jonathan Himmelfarb, MD, FASN, spoke about "A Human Kidney-on-a-Chip for Precision Medicine" and

Neil Lin, PhD, spoke on 3D Vascularized Kidney Tissues-on-Chip for Drug Toxicity and Disease Modeling.

The idea of a credit-card-sized chip that could mimic a human organ for use in precision medicine was born out of a partnership of the National Institutes of Health with DARPA and the Food and Drug Administration in 2012. The goal has been for utilization of such a chip for pre-clinical safety and drug testing with the benefit of genetic diversity and for conceivable use in clinical trials.

There is also the amazingly brilliant concept of a kidney organoid, "a multicellular unit in vitro containing nephron-like epithelial structures with podocyte and tubular segments," and the capabilities are being developed to create human stem cells and organoids from urine samples. The potential for revolutionizing patient care is extraordinary with this technology.

"The tools that are becoming available are now allowing us to combine those technologies [CRISPR] with microfluidics to allow us to create a field that is personalized," Himmelfarb said.

Leadership from nephrologists needed

But what ties this basic science revolution with the innovators and industry disruptors in care is that there is a

need for leadership from nephrologists and a translation from bench to product that is currently not optimal. Trigg noted that there are currently 7000 medical startups, but less than 20 of these are kidney-based startups.

Our colleagues have developed technologies that years ago were unfathomable—that even may have been considered scientific fiction, as Himmelfarb noted—but perhaps we are not tapping into the full potential of utilizing this knowledge without a willingness to take on the risks of disrupting care and embracing the leadership roles waiting to be seized.

There will be roadblocks and obstacles along the way—we need to address our current barriers in the healthcare system and disparities in care that are community based and find a way to minimize them.

No one said disruption would be easy. But we know this: the technology and science are getting bolder and more exciting, and it is up to us to start somewhere. ■

Mukta Baweja is an assistant professor of medicine and nephrology at the Icahn School of Medicine at Mount Sinai in New York City. She serves on the Public Policy and Advocacy Committee of the American Society of Nephrology. She is an advocate for patients and at-risk populations and an agent in optimizing public healthcare delivery.

Making the Dialysis Experience Person-Centered: The Celeste Castillo Lee Memorial Lecture at ASN Kidney Week 2019

By Zach Cahill

ASN Kidney Week is unique among medical society gatherings for elevating the patient voice during the annual meeting. Accelerating innovation and discovery in the kidney disease space makes including the perspectives of people with kidney disease in scientific meetings and other forums essential. During the ASN Kidney Week Annual Meeting, more than 10 people with kidney disease gave talks on a variety of topics.

The foremost of the patient presentations was the Celeste Castillo Lee Memorial Lectureship, a rare example of a lecture endowed in the name of a patient and presented during a medical society meeting. Established in 2017, the lecture continues the legacy of Celeste Castillo Lee, who championed people with kidney disease for 30 years. She served in many leadership roles throughout the community, including on the Kidney Health Initiative (KHI) Board of Directors and as the founding chair of the KHI Patient and Family Partnership Council, bringing her experience with peritoneal dialysis, hemodialysis, and transplantation to drug and device development. Her life inspired and motivated a generation of people with kidney disease and kidney health professionals.

Derek Forfang, a 10-year veteran of advocacy on behalf of people with kidney diseases, delivered this year's lecture, which focused on the topic, "How can patients be treated as individuals?" For 20 years, Mr. Forfang has had kidney failure. He experienced in-center hemodialysis before receiving a kidney transplant. His experience in and with people on dialysis provided firsthand knowledge into the culture of dialysis clinics and how the current system is not designed to be people centered.

A need for patient-centered measures?

The emphasis on current healthcare measurement in clinics demonstrates how the system is not people centered such that measurement approaches often do not align with patient and family preferences and values. He said people with kidney disease are not involved in meaningful ways in developing the measures, resulting in the feeling that they are

subjects of measures rather than decision-makers or drivers of care. For example, the Centers for Medicare & Medicaid Services (CMS) End-stage Renal Disease Quality Incentive Program, used to evaluate and pay kidney health professionals, is primarily driven by measures that are clinical in nature, rather than metrics that are important to patients. This system results in people feeling disengaged and that they are just being moved in and out of treatment.

Mr. Forfang posited that even the Advancing American Kidney Health initiative could benefit from additional focus on patient preferences where transplantation and home dialysis utilization are concerned.

A person-centered experience helps people with kidney disease navigate their dual lives, respects them as individuals, and acknowledges how their identity evolves over time. Mr. Forfang applied this philosophy to clinical measures and emphasized that it is possible to align such measures so they are meaningful to people with kidney disease.

True patient-centered measurement is driven by a patient's expressed preferences, needs, and values and informs progress toward better health, better care, and lower costs. CMS is already evolving to provide better measures. The agency's Meaningful Measures Initiative proposed measures that empower patients and emphasize the person as a partner in care. The National Quality Forum is investing in patient-centered planning and coordination. Mr. Forfang served on a CMS Technical Expert Panel that evaluated patient-reported outcomes (PROs) for kidney failure. The group was expected to recommend quality of life or recovery time after dialysis as PROs, but because of meaningful input from the patients on the panel their actual PRO recommendation was life goal-directed care. That recommendation pivots CMS's priorities toward the values and priorities of people with kidney disease.

Mr. Forfang attributed these institutional evolutions to a growing knowledge of a person's experience with kidney disease. Kidney disease, he explained, is a journey, and priorities and values change over time. The identified needs and priorities of people with kidney disease should drive care.

Payers are realizing that care plans should be built around what matters most to people as individuals.

Care plans are a tool dialysis providers may use to provide more individualized care. Typically care plans are discussed once a year, are problem-centered, and are focused on umbrella clinical outcomes. They often do not feel meaningful and are not individualized.

Aligning dialysis care with patient goals

In contrast to a problem-centered plan, Mr. Forfang proposed a person-centered dialysis care plan that aligns dialysis care and the goals of people with kidney disease. Patients and care teams jointly develop an individualized plan that includes patient-identified needs and priorities. A person-centered care plan is a feasible approach that can work in the current care and regulatory context.

Kidney care professionals may start forming a person-centered care plan by asking open-ended questions about what a patient's life is like outside the clinic and what their life goals are. This approach requires advance preparation. The patient should be provided educational materials and invited to attend a meeting off the dialysis floor. Second, the care team should hold a care planning meeting that addresses the following:

- Identifies patient needs, priorities, and barriers.
- Discusses options to align dialysis care with needs, priorities, and barriers.
- Works with the patient to make decisions and develop an individualized care plan.

Last, a person-centered care plan will include timely follow-up and regular check-ins. Mr. Forfang helped develop My Dialysis Plan with the University of North Carolina Kidney Center to expand on the ideas of the person-centered care plan and provide kidney health professionals and people with kidney disease the tools they need for more individualized care. ■

Zach Cahill is Marketing and Communications Specialist with the Kidney Health Initiative.

Late-breaking Trials Address Itch Relief in Dialysis, Cost-Saving Immunosuppression, and Disappointing Results for Supplements in Diabetes

Itch Relief in Dialysis

Difelikefalin may offer dialysis patients some relief from the persistent itching associated with chronic dialysis, according to results from the KALM-1 trial presented during Kidney Week 2019.

The results were presented at the High Impact Clinical Trials session. Other trials presented during the session showed that azathioprine (AZA) may provide equivalent immunosuppression at a fraction of the price of mycophenolate mofetil (MMF), while vitamin D and omega-3 fatty acids failed to offer kidney protection for patients with diabetes.

Itching has proven to be a difficult-to-treat side effect of dialysis despite its substantial impact on patients' quality of life and mortality, said Steven Fishbane, MD, chief of nephrology at Northwell Health in Manhasset, New York. In fact, he noted he's seen negative trial result after negative trial result throughout his career. Currently, antihistamines

are commonly used along with moisturizers or ultraviolet light therapy, Fishbane said. He said light therapy can work well but it adds to a patient's treatment burden.

"When you have [itching] chronically, it is a very tough sentence that affects quality of life," Fishbane said. "[It affects] sleep quality and is actually associated with infections, decreased erythropoietin response, and even mortality."

But Fishbane was buoyed by the promising results he presented from the KALM-1 trial. The phase 3 trial randomized 377 patients to receive intravenous difelikefalin or placebo after dialysis 3 times per week for 12 weeks. The trial met both its primary and secondary endpoints, with 51% of patients in the difelikefalin arm achieving a 3-point or greater reduction in itching intensity based on the Worst Itching Intensity Numerical Rating Scale (WI-NRSA) compared with 28% of the placebo group at 12 weeks, and 39% of the treatment group achieving a 4-point or greater reduction in WI-NRSA compared to 18% of the placebo group. He noted that patients were about 3 times more likely to experience a clinically mean-

ingful reduction in itching in the difelikefalin group. Serious adverse events were similar between the 2 groups, but patients on difelikefalin were more likely to have diarrhea (9.5% vs. 3.7%), dizziness (6.9% vs. 1.1%), or vomiting (5.3% vs. 3.2%), but these symptoms resolved after a short time.

"We've got the first drug available to be able to treat uremic pruritis," Fishbane said. "The drug was effective. The drug was well tolerated in this really difficult population of patients with hemodialysis."

"This is a wonderful development," said Pascale Lane, MD, a pediatric nephrologist at the University of Oklahoma Medicine in Oklahoma City. She noted that in addition to demonstrating improved quality of life, the drug is convenient. "It can be given at the end of treatment when we've already got vascular access ready and it hangs around until they get dialyzed again," she said. ■

"Efficacy and Safety of Difelikefalin in Patients Undergoing Hemodialysis with Pruritus: Results from a Phase 3 Randomized, Controlled Study (KALM-1)" Oral Abstract 134

Cost-Effective Immunosuppression

Azathioprine (AZA) could provide comparable protection against transplant rejection to mycophenolate mofetil (MMF) for kidney transplant patients taking a lower dose of a new more powerful formulation of cyclosporine while substantially reducing costs, according to another trial presented during the High Impact Clinical Trials session.

Paolo Cravedi, MD, PhD, assistant professor of nephrology at the Icahn School of Medicine at Mount Sinai Hospital in New York City, explained that in the mid-1990s two trials suggested that MMF provided a significant reduction in acute rejection compared to AZA when used with older formulations of cyclosporine. As a result, MMF, which costs 10 times more per dose, virtually replaced AZA.

"This choice had a major economic impact because switching patients from AZA to MMF over this time period cost over \$1 billion," Cravedi said.

But results from the ATHENA randomized trial presented by Cravedi add to a growing body of evidence that suggests that AZA offers comparable rejection protection

to MMF in kidney transplant recipients on low-dose, newer formulations of cyclosporine.

In the trial, 233 patients were randomized to receive MMF or AZA with a low-dose more stable microemulsion formulation of cyclosporin. At 3 years, 31.9% of the MMF patients had developed chronic allograft nephropathy vs. 32.4% of the AZA group and 18.5% vs. 21.1% had biopsy-proven acute cellular rejection. At 1-year posttransplant, 9.2% of the MMF group vs. 7% of the AZA group had subclinical acute cellular rejection and 5% vs. 6.1% had graft failure. The two groups had similar 3-year eGFR, and 16.1% of the MMF group vs. 18.4% of the AZA group successfully tapered their cyclosporine with only one episode of acute cellular rejection in each group.

"When we compared MMF versus AZA with the background of the new cyclosporine formulation, we couldn't find any benefit of MMF," Cravedi said. "They are virtually identical in terms of patient survival and graft survival." Cravedi said switching to AZA could save about \$3500 per year per patient in costs.

Lane, who moderated a press briefing on the high impact trials, said the results of ATHENA were "very promising, especially from a cost saving perspective." However, she cautioned that most kidney transplant patients in the United States are not taking cyclosporine. Instead, tacrolimus is the calcineurin inhibitor of choice at most US transplant centers. Lane said these results would likely also hold true for patients taking tacrolimus, but it would be necessary to do a clinical trial to confirm this. As US policies aim to shift away from dialysis and to more kidney transplants, such potential savings may be even more important.

"Transplants are already more cost efficient [than dialysis]," Lane said. "Saving roughly 90% of the costs of one of the immunosuppressive agents could only make it even more cost-effective." ■

"Mycophenolate Mofetil vs. Azathioprine in Kidney Transplant Recipients on Steroid-Free, Low-Dose Cyclosporine Immunosuppression: The ATHENA Trial" Oral Abstract 135

Vitamin D Disappoints in Diabetes

Results from a sub-analysis of the VITamin D and Omega-3 Trial (VITAL) did not find any benefit from either supplement in preventing or slowing kidney disease in patients with type 2 diabetes. Negative results from the primary analysis of the VITAL trial were published earlier this year showing no benefit of the supplements in cancer or cardiovascular diseases prevention.

The diabetic kidney disease portion of the trial randomized 1312 adults with type 2 diabetes to vitamin D or omega-3 supplementation or placebos and followed them for incidence or progression of kidney disease for 5 years. The purpose was to ask "whether we can use widely available and inexpensive and relatively safe supplements to prevent chronic kidney disease or progression early in the course of type 2 diabetes," said Ian DeBoer, MD, MS, professor in the Division of Nephrology and associate director of the Kidney

Research Institute at the University of Washington in Seattle.

The trial did not find a significant difference in change in eGFR in either of the supplement groups, dashing hopes that such an inexpensive intervention might help prevent or stall kidney disease. The University of Oklahoma's Lane was not surprised by the findings. She noted that results from preclinical studies that had suggested potential benefits to such supplements have not been confirmed so far in clinical trials.

"We're beginning to see big scale trials of these [supplements] and almost all of them are coming up negative," she said. ■

"Effects of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function and Damage in Type 2 Diabetes" Oral Abstract 138

Other trials presented during the session included:

- The PARAGON-HF trial also showed that sacubitril/valsartan reduced the risk of renal events and slowed the progression of kidney disease in patients with heart failure and preserved ejection fraction. (Oral Abstract 132)
- Phase 2 results from the NOBILITY trial showed that obinutuzumab was superior to placebo at treating lupus nephritis. (Oral Abstract 136)
- The Preventing Early Renal Loss in Diabetes (PERL) Study did not find a significant benefit of allopurinol on patients with type 1 diabetes kidney outcomes. (Oral Abstract 137)

Early Transitions to Home Dialysis Are Rare After Emergency Dialysis

Survival Varies Among Early Adopters

Very few patients who begin urgent in-center hemodialysis transition to home dialysis early, and the survival of those who do varies by modality, according to research presented at Kidney Week 2019.

Many patients who begin urgent, unplanned hemodialysis in a center may prefer to switch to home dialysis. To learn more about the patients who do make this switch and how it affects their survival, Sonny Nguyen, MD, a resident physician at Harbor University of California–Los Angeles (UCLA) Medical Center, and his colleagues analyzed data from the US Renal Data System on 190,642 patients who started urgent, in-center hemodialysis with a venous catheter, no maturing arteriovenous access, and no prior dialysis referral between 2005 and 2013.

They found that just 3923, or 2%, of these patients transitioned to peritoneal dialysis and 853, or 0.4%, transitioned to home hemodialysis during the first 90 days after initiating dialysis. They also found striking differences in the characteristics between the two groups. Patients who were younger, white, had private insurance, lived in rural areas, or initiated dialysis in a unit with a home peritoneal dialysis program were more likely to make an early transition to home peritoneal dialysis. Those who were older, frailer, from an urban area, or started dialysis at a center with a home hemodialysis program were more likely to make an early transition to home hemodialysis.

“Few patients who have an unplanned start on in-center hemodialysis make an early transition to home dialysis modalities,” Nguyen said. “Our study suggests that initiating such patients in centers that also have home dialysis programs might facilitate these transi-

tions.”

Additionally, patients who made an early transition to home peritoneal dialysis were less likely to die than those who stayed on in-center dialysis. Those who made the early switch to home hemodialysis had a higher risk of death than those who never transitioned to home dialysis. Nguyen suggested the difference in survival in the two groups was likely related to the different characteristics of the two groups.

“Those who transitioned to [peritoneal dialysis] were generally younger and healthier than those who remained on in-center hemodialysis,” Nguyen said. “Conversely, those who switched to home hemodialysis tended to be older and frailer. While we adjusted for these differences in observed characteristics using propensity score matched analyses, it is certainly possible that there is residual confounding by unobserved characteristics.”

For example, one potential confounder is that patients transitioning to home hemodialysis may have used central venous catheters longer than in-center patients, increasing the risk of bloodstream infections. Additionally, some frail, older patients may have been receiving home hemodialysis in nursing homes or with help from a home caregiver.

John Sim, MD, assistant clinical professor at the David Geffen UCLA Medical Center and Kaiser Permanente Los Angeles Medical Center, agreed that the mortality differences in the two groups likely represent “self-selection bias.”

Christopher Chan, MD, director of the Division of Nephrology at the University of Toronto, said the age and frailty of the patients in the home hemodialysis group alone may have explained the survival difference. However, he cautioned that it’s difficult to draw conclusions without specific data on the dose prescribed.

“We need to understand why there is a higher mortality among patients who transitioned to one particular modality,” Chan said. “If it is indeed the dialysis prescription per se, then we need to intervene because that’s not the usual trends in the home dialysis literature.” Chan noted that use of home dialysis in Australia, New Zealand, and the United Kingdom is at least two times higher than in the US and these trends have not been observed in studies in those countries. He noted there may be differences in expertise, the type of patients receiving home dialysis, and the doses in such countries.

Sim said the lower mortality in the peritoneal dialysis group raises interesting questions, for example, whether the home hemodialysis patients were more likely to develop complications related to catheter use and whether the lower infection risk associated with peritoneal dialysis was related to the catheter.

“Usually, peritoneal dialysis patients initiate therapy in an incremental treatment type manner, meaning their transition to peritoneal starts with less dialysis and the dose increases as they continue on peritoneal dialysis,” Sim said. “This approach may lead to less of a shock on the end stage renal disease patients resulting in a smoother transition to dialysis.”

Future studies may help resolve these questions.

“We plan to examine whether there is an increased risk of mortality in patients who transitioned to home hemodialysis when we restrict the cohort to non-institutionalized patients,” Nguyen said. “We also plan to test our theory that patients who transition to home hemodialysis use a catheter longer and are more likely to have infectious complications.” ■

“Early Transitions from In-Center Hemodialysis to Home Dialysis” Oral Abstract 090

Clinical Research in Nephrology: Trials, Trends, and Tools

By Meaghan Allain

Research in nephrology has been on the rise over the past 5 years and data show that the future is bright for both innovators and people living with kidney diseases. This glimmer of hope was displayed throughout Kidney Week, during which both people living with kidney diseases and kidney health professionals came together to learn and discuss the current and future state of clinical research.

During a session titled Clinical Research in Nephrology: Trials, Trends and Tools, Uptal Patel, Senior Director at Gilead Sciences and nephrologist by training, reviewed a dataset of clinical trials by subspecialty between 1966 and 2002 that displayed nephrology with the lowest proportion of all subspecialties. However, recent data show an increase in quality and quantity of trials in nephrology, including an increase in trials for devices, behavioral interventions, and rare kidney diseases.

As Jamie Dwyer, Director of Vanderbilt University’s Nephrology Clinical Trials Center, stated to the audience of kidney health professionals, there needs to be a shift in the culture of nephrology to focus on research readiness. More research being conducted in the field will assist with shifting to upstream and personalized care for patients living with

kidney diseases.

The following are the four areas to consider when implementing a research-ready culture:

- **Knowledge** – Everyone needs to know the value of research and how to message its importance. Knowing the protocol is key.
- **Processes** – Make processes sensible and clear. Intuitive processes will always succeed.
- **Communication** – Ensure that communication is clear. Follow-up communication with everyone on the care team helps ensure the subject continues participation on the drug/study.
- **Engagement** – Approach and engage with your patients about new studies they can participate in.

Mary Baliker, a healthcare consultant and transplant recipient, noted that it is crucial to consider the patient perspective in any clinical study. It is important to those who are participating in the study that the treatment is significant to them, the study duration and design are feasible, and the outcomes are relevant. By engaging patients early for feedback on study design and communicating data back to patients after studies are complete, this will increase the likelihood of positive experiences associated with participating in

clinical studies and continued participation, Baliker said.

Kidney patient and healthcare organizations are developing programs to support patients and families as well as clinicians, researchers, and the healthcare team as they consider and embrace a culture of research readiness. NephCure Kidney International (NKI) CEO Josh Tarnoff outlined the new NKI program called Kidney Health Gateway. Visit www.kidneyhealthgateway.com to sign up for alerts and information on clinical trials for nephrotic syndrome.

The Kidney Health Initiative, ASN’s public-private partnership with the US Food and Drug Administration, and its member organizations have also been collaborating to catalyze this change and uptake in clinical research. The perspectives outlined in this Kidney Week session reiterated the changes needed to bring promising therapies to people living with kidney diseases throughout the world. By engaging patients earlier in clinical trial design, embracing a research-ready culture, and implementing infrastructure for more efficient trials, the future of research in nephrology can shine even brighter. ■

Meaghan Allain is Senior Project Associate with the Kidney Health Initiative.

“

We can accomplish more together.

Even though I'm a pediatric nephrologist with a separate professional organization, I think it is important to volunteer my time to be sure that pediatric nephrology has a voice within ASN.

Michelle N. Rheault, MD
Minneapolis, MN



Medicare Coverage for Immunosuppressive Drugs Could Save Money

By Bridget M. Kuehn

Extending Medicare coverage for immunosuppressive drugs through the life of a kidney transplant could reduce the costs of a patient's care by \$3163 while improving their quality of life, according to research presented at Kidney Week 2019.

Using a Markov model and data on posttransplant outcomes from US patients with Medicare and private insurance coverage, Matthew Kadtz, MD, a clinical assistant professor in the Division of Nephrology at the University of British Columbia in Vancouver, and his colleagues analyzed the cost effectiveness of extending Medicare coverage for the life of a kidney transplant. Currently, Medicare only covers immunosuppressive drugs for 36 months after a kidney transplant, which can result in recipients losing access to coverage.

Even when the team reduced the expected transplant survival benefit associated with immunosuppressive drug coverage by 50% of what is seen in privately insured patients, extending coverage remained cost effective at a cost of about \$77,613 per quality adjusted life years, according to the research.

"Extension of the Medicare immunosuppression drug coverage will likely be, if not cost savings, a cost-effective strategy, and that's important for healthcare policy and decision-makers to understand," Kadtz said.

The study is the latest to show that extending Medicare coverage for posttransplant immunosuppressive drugs would likely be cost saving.

"It's a really important addition to a growing body of evidence that current Medicare policies for [immunosup-

pression coverage] don't make sense regardless of whether you look from a financial or patient perspective," said nephrologist Allyson Hart, MD, MS, assistant professor of medicine at the University of Minnesota in Minneapolis. A recent study by Hart and colleagues found very high rates of kidney allograft loss among patients who lose Medicare coverage for immunosuppressive drugs either before or after three years posttransplant.

Hart noted a few limitations of the analysis presented at Kidney Week. First, comparing outcomes to patients on private insurance might not be ideal because Medicare patients may differ in many ways from patients covered by private insurance. Another limitation is that many patients lose access to immunosuppressive medications even with Medicare coverage, possibly because they can't afford co-pays. This could reduce the benefits estimated by the model. Her study, for example, found "an astronomical rate" of allograft loss even among patients less than three years after transplant, who should have access to Medicare coverage.

"We need more information about which patients are losing Medicare coverage for immunosuppressive drugs early and late and why," she said. "Unless we get a better idea of the additional burdens of co-pays we won't see as much benefit as we expect."

Kadtz acknowledged that there are disadvantages to using data on privately insured patients' outcomes because of the socioeconomic and other differences between them and those covered by Medicare. But he noted that he and his colleagues adjusted for as many of those possible differences as they could. In Canada, where patients are guaranteed coverage through public insurance regardless of socioeco-

nomic status, transplant graft rates are equivalent among different socioeconomic groups, he noted.

The team also did a threshold analysis that found extending immunosuppression coverage was cost effective even if there was only a 5.5% reduction in the risk of transplant failure at a cost-effectiveness threshold of \$100,000 per quality adjusted life year, which is the typical threshold in the US. Kadtz suspects that the analysis may have even underestimated the potential cost savings of extending coverage. For example, he noted that some kidney transplant patients stay on disability in order to ensure continued coverage for immunosuppression, but if Medicare coverage were extended, they may be able to rejoin the workforce.

Over the past decade, there have been repeated failed attempts in Congress to pass legislation that would extend Medicare coverage for posttransplant immunosuppression, Kadtz noted. He explained that budgetary concerns have been a barrier.

"This really provides support to help get these legislators past the budgetary considerations," he said.

Hart agreed that it is essential to change public policy to ensure patients can access immunosuppressive medications and prevent graft loss. "My hope is with analyses like these we can show this is a case in medicine where patient outcomes and financial incentives are lining up," she said. "We have to have courage to spend money upfront [anticipating savings down the road]." ■

"Economic Evaluation of Lifelong Medicare Immunosuppressive Drug Coverage for Kidney Transplant Recipients" Oral Abstract 128.

Dialysis Industry Consolidation Continues *Monopolies a Growing Concern in Small Markets*

Small dialysis chains and independent dialysis facilities continue to disappear, increasing the risk of monopolies, particularly in small markets, according to an abstract presented at Kidney Week 2019.

The dialysis industry has become increasingly consolidated over the past 15 years, with 2 major dialysis chains now controlling 85% of the market, said the abstract's lead author, Caroline Sloan, MD, a general internist and chief resident at Duke University. About 300 small dialysis chains and independent facilities disappeared between 2006 and 2016 either through closure or acquisition by larger firms, according to the analysis. The number of such small or independent facilities decreased from 1353 to 1034, while the number of large dialysis facilities or facilities associated with large chains increased from 3216 to 5419 during that

same period.

"There's about a 1 to 2% rate of acquisition per year and about 1% closure rate per year for these smaller facilities," Sloan said.

Those facilities at greatest risk of acquisition were not-for-profit, smaller in size, or located in markets with fewer hospitals or where there were already few choices for dialysis care. Sloan explained that in markets already dominated by a single large dialysis provider, it may be hard for small facilities to stay open.

Kevin Erickson, MD, MS, assistant professor of medicine at Baylor University, said the findings provide an update on an ongoing trend in the field and suggest there may be a shift in where acquisitions are occurring with small markets becoming a new target.

"These are potentially markets where patients already have limited choice," Erickson said. "The potential effects of an acquisition on the set of choices available to patients and how the providers can change care delivery and pricing is potentially larger when you're already starting with fewer choices."

Additionally, in consolidated markets dialysis providers might offer fewer amenities or reduced quality of care, Erickson noted. There has also been recent evidence that patients who get care at larger, for-profit facilities are less likely to get transplants or may be more likely to be hospitalized, Sloan noted. Although her data didn't look at patient outcomes, Sloan expressed concern about the potential effects of this ongoing consolidation on patient outcomes.



Another potential concern is the effect of consolidation on the cost of care.

"There's a risk of price increases for private insurers," Erickson said. He noted that cost may be offset by potential savings through economies of scale or more bargaining leverage at large facilities, but more study is needed to fully understand the effects of consolidation in the industry. In the meantime, he said policymakers need to consider the potential costs and benefits of policies that may lead to more consolidation.

Sloan suggested policymakers should consider taking steps to maintain patient choice.

"We're urging policymakers to try to maintain competition, especially in the markets that are the most monopolistic," she said. ■

"Consolidation in the Dialysis Industry in the Era of Health Reform, 2006–2013" Oral Abstract 058

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NIH Director, Daughter Address Barriers to Women in Nephrology

By Bridget M. Kuehn

Margaret Collins, MD, a nephrologist who runs a hypertension specialty practice in Wilmington, North Carolina, knows well the challenges women in nephrology face from trying to get through a grueling nephrology fellowship during her childbearing years to trying to navigate demands for 90-hour weeks in practice with children at home.

At Kidney Week 2019, she and her father, Francis Collins, MD, the director of the National Institutes of Health (NIH), brought those challenges into focus at the Women in Nephrology's Nancy E. Gary Memorial Lecture. During an hour-long discussion, the pair delved into the barriers that prevent women from achieving their full potential in biomedicine and nephrology. They highlighted gender disparities in pay, lack of flexibility, and sexual harassment. Collins also highlighted some of the steps he and his colleagues are taking at NIH to increase gender equity.

"There has been an explosion of awareness that things are not the same for men and women in science and medicine," Margaret Collins said.

A broken pipeline

Francis Collins noted that many medical schools have an equal number of men and women and some specialties have achieved gender parity in residencies. Yet women make up only one-quarter of junior faculty at academic institutions.

"We lost a lot of talent along the way," he said. Without intervention to address this problem, Francis Collins noted that gender parity in academic faculty won't be reached until 2055.

The NIH has created a working group on Women in Biomedical Careers, which Francis Collins co-chairs, to better understand and address the problem. "At NIH, I want to do everything I can to make sure that we have the most vibrant, energetic, and remarkably productive workforce possible," he said. "Every bit of data we have says that happens when you have diversity."

So far, they've identified a host of issues, including women shouldering a greater share of family responsibilities, a lack of flexibility, and prohibitive child-care costs.

Another problem is that women are consistently paid less in many fields. "Women and men nephrology fellows are not paid the same," Francis Collins said.

Sexual harassment is another pervasive barrier for women in science and medicine. Francis Collins noted that the National Academies of Science, Engineering, and Medicine report on sexual

harassment in academia found that about half of women report experiencing sexual harassment from faculty or staff during their medical training. A recent survey of NIH staff and contractors found that

21% have experienced sexual harassment, he said.

Francis Collins acknowledged that sexual assaults do happen in these fields though they are less common than more

subtle forms of sexual harassment, such as cultures that make women feel they don't belong or suggest that they lack gravitas, he said.

NIH's Women in Biomedicine Work-



ing Group is working to address sexual harassment at the institute and at grantee institutions. It has created a hotline for reporting harassment by grantees that does not require victims to go through their institution's Title IX process. Francis Collins said they are also working to develop pathways for restorative justice so those harmed by harassment can get their careers back on track.

He said he declines invitations to participate in "manels," panels without any women, or in scientific meetings without

adequate diversity among speakers.

"As long as I'm NIH director, we're not sweeping this under rug," he said.

Flexibility needed

Margaret Collins described her firsthand experience with many of these issues. She noted a diagnosis of endometriosis forced her to accelerate her timeline for having children. She was 18 weeks pregnant when she took her first day of call in her nephrology fellowship at the University of North Carolina. By 7 months into her

pregnancy she found the physical strain too much and was shifted to clinic duty. She said she felt terrible leaving the 3 other fellows with more to do.

"It was awful," Margaret Collins said. "A lot of the shame was self-imposed."

After her fellowship, she became the only woman partner in a nephrology practice where 90-hour work weeks were expected. When that became too much, she tried to negotiate a reduced schedule for reduced pay, but that offer was declined so she left the practice. A 7-county

noncompete clause prevented her from joining another nearby nephrology practice. She eventually started her own specialty practice treating complicated hypertension and hypertension during pregnancy.

Margaret Collins said it would have helped her if there were more flexible options for fellowship or private practice, for example, having people to share a fellowship position with or having onsite childcare.

"The cookie cutter, one-size-fits-all approach was really the only option that was there and there wasn't creative thinking about how people might do the job of being a nephrology fellow or a private [practice] nephrologist," she said.

During the question and answer period, Francis Collins fielded questions about how women should ask for equitable pay and how women of color can balance the need to participate in panels and other events to increase diversity while not becoming overwhelmed. He suggested that women approach leadership as groups to address pay. He also suggested that women of color choose the opportunities that are most meaningful to them.

Francis Collins encouraged men to be mindful of how networks in the field may contribute to the lack of parity and challenged them to find ways they can help address this, for example, by following his lead on not participating in "manels." ■

Polycystic kidney disease (PKD) is characterized by the progressive enlargement of numerous fluid filled cysts in the kidney. The 2 main types of PKD are ARPKD,* and the most commonly seen ADPKD.^{†1,2}

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eGFR[‡] levels can remain steady over many years, but enlarging cysts continue to increase kidney volume, damaging renal tissue.^{2,3}

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*Autosomal recessive polycystic kidney disease.

†Autosomal dominant polycystic kidney disease.

‡Estimated glomerular filtration rate.

References: 1. Harris PC, Torres VE. Polycystic kidney disease. *Annu Rev Med.* 2009;60:321-337. 2. Braun WE. Autosomal dominant polycystic kidney disease: emerging concepts of pathogenesis and new treatments. *Cleve Clin J Med.* 2009;76(2):97-104. 3. Grantham JJ. Autosomal dominant polycystic kidney disease. *N Engl J Med.* 2008;359(14):1477-1485.



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Findings

SGLT2 Inhibitors Prevent Kidney Failure in Type 2 Diabetes: Meta-Analysis

Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower the risk of dialysis and other clinically important kidney outcomes in patients with type 2 diabetes, concludes a systematic review and meta-analysis in *The Lancet Diabetes & Endocrinology*.

The review identified four randomized controlled trials of SGLT2 inhibitors that reported data on major kidney outcomes in patients with type 2 diabetes. The EMPA-REG OUTCOME trial evaluated empagliflozin in 7020 patients; the CANVAS Program and CREDENCE trial evaluated canagliflozin in 10,142 and 4401 patients, respectively; and the DECLARE-TIMI 58 trial evaluated dapagliflozin in 17,160 patients. The CREDENCE study was designed as an event-driven kidney outcome trial; the other three studies were cardiovascular outcome trials.

Meta-analysis included data on 38,723 patients, mean age 63.0 to 63.9 years and 65% male. Percentage of patients with chronic kidney disease (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m²) ranged from 7.4% in the DECLARE-TIMI 58 trial to 59.9% in CREDENCE. The primary outcome of dialysis, transplantation, or death due to kidney disease occurred in 252 patients. Incident kidney failure occurred in 335 patients and acute kidney injury (AKI) in 943.

Treatment with an SGLT2 inhibitor was associated with a one-third reduction in the risk of the primary outcome: relative risk (RR) 0.67, compared to placebo. Patients receiving SGLT2 inhibitors were also at lower risk of kidney failure, RR 0.65; and AKI, RR 0.75. All of these effects were consistent across studies.

Some data suggested that the benefit of SGLT2 inhibitors might be reduced at lower levels of eGFR. However, there was significant benefit in all eGFR subgroups; for patients with a baseline eGFR of 30 to 45 mL/min/1.73 m², the RR was 0.70.

The reduction in adverse kidney outcomes with SGLT2 inhibitors was similar for subgroups defined by baseline albuminuria and use of renin-angiotensin system inhibitors. Effects on long-term eGFR slope varied, with the greatest placebo-subtracted difference observed in the CREDENCE trial: 2.74 mL/min/1.73 m² per year.

Cardiovascular outcome trials have reported promising effects of SGLT2 inhibitors on kidney outcomes. However, there are limited data on their effects in patients at high risk of patient-level kidney outcomes.

This meta-analysis of more than 38,000 patients with type 2 diabetes finds significant reductions in dialysis, transplantation, or death due to kidney disease with SGLT2 inhibitor therapy [Neuen BL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019; DOI: 10.1016/S2213-8587(19)30256-6]. ■

Racial/Ethnic Minority Groups Have Higher Risk of Diabetes at Lower BMIs

Compared to white Americans, racial/ethnic minority groups have a higher prevalence of diabetes and prediabetes at a lower body mass index (BMI), reports a study in *Diabetes Care*.

The study included approximately 4.9 million adults aged 20 years or older in 2012–2013. Data were drawn from a consortium of three US integrated healthcare systems (Kaiser Permanente, HealthPartners Minnesota, and Denver Health). Race/

ethnicity was classified as white in 50% of individuals, Hispanic in 21.6%, Asian in 12.7%, black in 9.5%, Hawaiian/Pacific Islander in 1.4%, and American Indian/Alaska Native in 0.5%.

Cases of diabetes and prediabetes were ascertained by diagnosis, laboratory results, and use of antihyperglycemic medications. Racial/ethnic disparities in prevalence were assessed across BMI levels. The analysis included adjustment for socioeconomic and/

or environmental disparities.

Standardized for age, estimated prevalence was 15.9% for diabetes and 33.4% for prediabetes. Prevalence of diabetes increased along with BMI in all racial/ethnic groups, although prediabetes prevalence did not. Diabetes prevalence was 27.7% in Hawaiians/Pacific Islanders, 22.2% in Hispanics, 21.4% in blacks, 19.6% in American Indians/Alaska Natives, and 19.3% in Asians, compared to 12.2% in whites.



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For prediabetes, prevalence was 37.1% in Asians, 36.7% in Hawaiian/Pacific Islanders, 35.3% in Hispanics, 32.0% in blacks, 31.1% in American Indians/Alaska Natives, and 31.0% in whites.

Compared to whites, all racial/ethnic minority groups had a higher diabetes prevalence at a given BMI, with the differences being most marked at lower BMI levels. In the normal weight range, 5% of whites had diabetes, compared to about 10% of Asians and American Indians/Alaska Natives and 13% to 14% of Hispanics, blacks, and Hawaiian/

Pacific Islanders. On adjusted analysis, the association between BMI and diabetes was strongest in whites and lowest in blacks.

Obesity and race/ethnicity are major risk factors for diabetes, but racial/ethnic disparities in diabetes do not correspond to differences in obesity. This study in a very large insured population finds that Americans of racial/ethnic minority groups have a higher prevalence of diabetes and prediabetes at lower BMI levels.

The findings suggest that factors other than obesity contribute to the disproportio-

nately high burden of diabetes/prediabetes in racial/ethnic minorities, who are at increased risk even at relatively low BMI levels. The findings “highlight the importance of tailored screening, prevention, and intervention strategies to mitigate the risk of diabetes and prediabetes,” the researchers write [Zhu Y, et al. Racial/ethnic disparities in the prevalence of diabetes and prediabetes by BMI: Patient Outcomes Research To Advance Learning (PORTAL) multisite cohort of adults in the U.S. *Diabetes Care* 2019; DOI: 10.2337/dc19-0532]. ■

iBox Score Predicts Allograft Loss After Kidney Transplantation



A new integrative box risk prediction (iBox) score performs well in predicting long-term kidney allograft failure across countries and clinical settings, reports a study in the *British Medical Journal*.

The score was developed using data from a prospectively enrolled derivation cohort of 4000 consecutive adult kidney transplant recipients (from living or deceased donors) at three French hospitals between 2005 and 2014. Allograft loss, defined as definitive return to dialysis or preemptive transplantation, was assessed using follow-up data to 2018. Independent predictors on multivariable analysis—including demographic factors, measures of allograft function and histology, and the recipient's immunologic profile—were incorporated into the iBox score. The score was validated in cohorts of 2129 recipients from European centers and 1428 from North American centers, with additional validation using data from three randomized trials.

The combined cohorts comprised 1775 transplant recipients; at a median follow-up of 7.12 years, the allograft failure rate was 14.1%. The iBox score had accurate calibration and discrimination, with a C index of 0.81 in both the derivation and validation cohorts. Its discriminative capability was confirmed using 3-, 5-, and 7-year follow-up data. The iBox score also performed well in data from randomized trials evaluating therapeutic interventions.

The new risk prediction score was validated in clinical scenarios involving immunosuppressive regimens and response to rejection therapy. In a systematic review, the iBox score provided additional value over previously reported risk scores, as well as scores based on measures of allograft function.

The iBox score meets the need for an integrated tool for predicting the long-term risk of allograft failure after kidney transplantation. Combining demographic, functional, histologic, and immunologic variables, it can be readily implemented for risk prediction in clinical practice. An online interface for calculating allograft survival estimates for individual patients is available at www.paristransplantgroup.org [Loupy A, et al. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. *BMJ* 2019; 366:l4923]. ■

It's time for kidney talk

When you see unexplained signs of kidney disease, think **Alport syndrome**. It can filter through a family.

Incurable disease

- Alport syndrome (AS) is a **permanent, hereditary condition** responsible for a genetically defective glomerular basement membrane, causing chronic kidney inflammation, tissue fibrosis, and kidney failure¹⁻⁶
- Across the entire range of AS genotypes, **patients are at risk of progressing towards end-stage kidney disease (ESKD)**^{3,7,8}

Hidden signs

- Patients often go undiagnosed**, as the clinical presentation of AS is highly variable and family history may be unavailable^{3,9-11}
- Persistent, microscopic hematuria is the cardinal sign of AS** and should prompt immediate diagnostic investigation—particularly when combined with any family history of chronic kidney disease^{8,11,12}

Early action

- Expert guidelines published in the *Journal of the American Society of Nephrology* now **recommend genetic testing as the gold standard for diagnosing Alport syndrome**⁸
- Early AS detection via genetic diagnosis, and its ability to guide a patient's treatment decisions, demonstrates the **powerful impact of precision medicine in nephrology**¹²⁻¹⁴

Reata and Invitae have collaborated to offer no-charge genetic testing for rare chronic kidney disease diagnosis and greater clinical insights. For more information regarding the KIDNEYCODE program or to order a test, please visit www.invitae.com/chronic-kidney-disease or contact Invitae client services at clientservices@invitae.com or 800-436-3037.

Abnormal kidney function can have a strong family connection—Alport syndrome

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Fellows Corner

Vitamin K and Vascular Calcification

By Pascale Khairallah



Pascale Khairallah

Despite many advances in the care of patients with chronic kidney disease (CKD) and ESKD, cardiovascular (CV) disease remains the leading cause of death in the kidney disease patient population. One of the factors explaining this excess mortality risk is vascular calcification, which predisposes patients to myocardial ischemia, left ventricular hypertrophy, and stroke (1).

The pathophysiology of vascular calcification in patients with CKD and ESKD is distinct from that in the general population. In the general population, vascular calcifications form in the intima of vessels and are linked to traditionally modifiable risk factors, including smoking, age, obesity, diabetes, hypertension, and hypercholesterolemia. By contrast, in CKD and ESKD, vascular calcifications form in the intima and media of medium and large arteries. Whereas the pathogenesis of intimal vascular calcification in CKD and ESKD mirrors that of the general population, the pathogenesis of medial vascular calcification is not well understood.

Medial vascular calcification occurs early in the course of CKD (2) and strongly predicts cardiovascular (CV) events and mortality. Mineral–bone disorder is a major factor involved in the development of medial vascular calcification (3, 4). Other involved factors include vascular smooth muscle cell osteochondrogenic shift (4), decreased levels of calcification inhibitors (5, 6), and increased levels of oxidative stress, all of which contribute to the progression of vascular calcification. Medial vascular calcification is a highly regulated multipathway process (4), but there are not yet any proven preventative treatments. Vitamin K supplementation is one potential therapy that is currently being investigated in clinical trials.

The role of vitamin K in vascular calcification

Matrix Gla protein (MGP) plays an important role in vascular biology. It is present in soft tissue, where it functions as a calcification inhibitor. MGP requires vitamin K to undergo γ carboxylation, an important step for MGP activity. In states of vitamin K deficiency, MGP remains decarboxylated and inactive, therefore increasing soft tissue propensity for calcification (Figure 1). Calcified vessels have higher concentrations of the dephosphorylated un-

carboxylated form of MGP (dp-ucMGP), whereas normal vessels have higher concentrations of the carboxylated form of MGP (cMGP).

Vitamin K in CKD and ESKD

Patients with CKD and ESKD have vitamin K deficiency, which stems from multifactorial causes. The Western diet does not provide enough vitamin K to activate MGP in all tissues. The poor oral intake and the dietary restrictions of patients with advanced CKD and ESKD further contribute to vitamin K deficiency. Additionally, it is suggested that some phosphate binders can sequester vitamin K in the gut, therefore compounding the deficiency. Finally, the use of vitamin K antagonists such as warfarin inhibits vitamin K–dependent carboxylation of MGP. These agents have historically been associated with the progression of vascular calcification in patients with kidney disease.

With the discovery of the role of MGP in vascular calcification, vitamin K was proposed as a treatment to modify the development of vascular calcification and the risk of CV disease in CKD. Circulating MGP is used as a surrogate of vitamin K status: dp-ucMGP level inversely correlates with vitamin K level. Multiple observational studies have shown significant associations between higher levels of dp-ucMGP and lower levels of cMGP with vascular calcification in patients with CKD and ESKD (Table 1). These studies were cross-sectional; therefore, causal inferences could not be made. Subsequent studies evaluated the effect of vitamin K supplementation on vascular calcification. In patients with ESKD, supplementation with vitamin K resulted in a decrease of dp-ucMGP levels (Table 2). However, we cannot make any conclusions with certainty

based on these studies because they were limited to 6 to 8 weeks of follow-up and did not measure vascular calcification scores. Clinical trials evaluating the effect of long-term vitamin K supplementation on vascular calcification, cardiovascular events, and mortality are currently ongoing.

What can we do now?

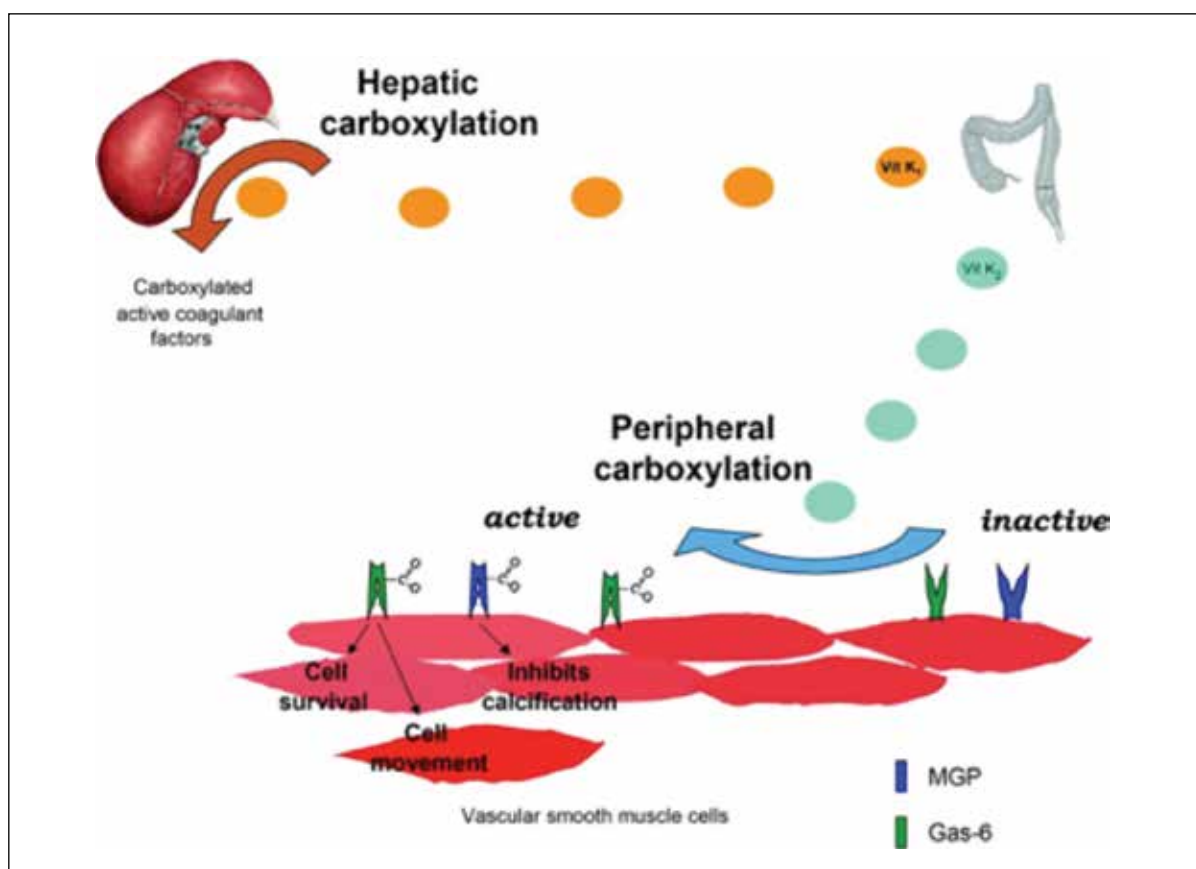
While we await the ongoing vitamin K supplementation clinical trials that will give us a more definite answer to the question whether vitamin K supplementation can improve CV outcomes in patients with kidney disease, should we be giving all our CKD and ESKD patients vitamin K supplements?

There is no known toxicity of vitamin K, nor is there an upper level of intake. Additionally, vitamin K supplementation does not seem to increase the risk of thrombosis or stroke. Therefore, it seems to be a treatment with relatively little harm but with potentially significant benefit—a treatment that we may be justified to use more liberally.

Furthermore, should we be actively switching our patients from vitamin K antagonists such as warfarin to the novel anticoagulants when possible? This is currently recommended in patients with calciphylaxis, but we should perhaps be more liberal in prescribing novel anticoagulant agents for our patients with CKD and ESKD. This effort may decrease CV events and improve outcomes in these patients.

In conclusion, vitamin K is one piece of the puzzle of vascular calcification—a process that is unlikely to be reversed by targeting one pathway only. Targeting several pathways, including vitamin K deficiency, mineral–bone disorders, and the bone–vascular axis could improve vascu-

Figure 1. Hepatic and peripheral carboxylation of vitamin K–dependent proteins



Vitamin K–dependent proteins undergo carboxylation to become biologically active, requiring vitamin K as a cofactor in the conversion. Abbreviation: MGP = matrix Gla protein. Adapted from Danziger J. Vitamin K–dependent proteins, warfarin, and vascular calcification. *Clin J Am Soc Nephrol* 2008; 3:1504–1510.

lar calcification development and progression. Further research into the mechanisms of vascular disease in CKD will ultimately lead to the development of therapeutic agents that can improve the risk of CV disease in kidney disease. ■

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Table 1. Association between vitamin K level and vascular calcification in CKD and ESKD

Study, year	Study design	Number of participants	Kidney disease stage	Vitamin K surrogate measured	Outcomes measured	Results
Cranenburg, et al., 2009 (7)	Cross-sectional	40	ESKD	ucMGP	Coronary artery calcification	ucMGP is inversely correlated with coronary artery calcification r = −0.41; p = 0.01
Schurgers, et al., 2010 (8)	Cross-sectional	107	CKD 2–5D	dp-ucMGP	Aortic calcification	dp-ucMGP is positively correlated with aortic calcification r ² = 0.143; p <0.0001
Schlieper, G et al., 2011 (9)	Cross-sectional	188	ESKD	dp-cMGP	Vascular calcification score	dp-cMGP levels are 12% lower in patients with higher calcification score p = 0.01
Fusaro, et al., 2012 (10)	Cross-sectional	387	ESKD	MK4	Aortic calcification	MK4 deficiency is associated with higher aortic calcification OR=2.82; p = 0.03
Delanaye, et al., 2014 (11)	Cross-sectional	137	ESKD	dp-ucMGP	Vascular calcification score	Higher dp-ucMGP levels are associated with higher vascular calcification score r ² = 0.03, p = 0.049
Meuwese, et al., 2015 (12)	Cross-sectional	97	ESKD	dp-ucMGP	Aortic augmentation pressure	There is no association between dp-ucMGP and aortic augmentation pressure p = 0.179
Thamratnookoon, et al., 2017 (13)	Cross-sectional	83	CKD 3–5	dp-ucMGP	Vascular calcification	dp-ucMGP is positively correlated with vascular calcification OR 1.002; p = 0.004

Abbreviations: CKD = chronic kidney disease; dp-cMGP = desphosphorylated-carboxylated MGP; dp-ucMGP = dephosphorylated-uncarboxylated MGP; MGP = matrix Gla protein; MK4 = menaquinone-4, a vitamin K2 homologue; OR = odds ratio; ucMGP = uncarboxylated MGP.

Table 2. Effect of vitamin K supplementation on dephosphorylated-uncarboxylated MGP level in ESKD

Study, year	Study design	Number of participants	Kidney disease stage	Intervention	Outcomes measured	Results
Schlieper, et al., 2011 (9)	Prospective	17	ESKD	Vitamin K2 at 135 µg/day for 6 weeks	dp-ucMGP level	Vitamin K2 supplementation resulted in a 27% reduction in dp-ucMGP levels p = 0.0027
Westenfeld, et al., 2012 (14)	Prospective	53	ESKD	Vitamin K2 at 45, 135, or 360 µg/day for 6 weeks	dp-ucMGP level	Vitamin K2 supplementation resulted in a dose-dependent decrease in the levels of dp-uc-MGP by 17.9%, 36.7%, and 61.1% in the 45-, 135-, and 360-µg groups, respectively, compared with baseline values p < 0.005
Caluwe, et al., 2014 (15)	Prospective	200	ESKD	Vitamin K2 at 60, 720, or 1080 µg thrice weekly for 8 weeks	dp-uc-MGP level	Vitamin K2 resulted in a dose-dependent decrease in the levels of dp-uc-MGP by 17%, 33%, and 46% in the 360-, 720-, and 1080-µg groups, respectively, compared with baseline values p < 0.001

Abbreviations: dp-ucMGP = dephosphorylated-uncarboxylated MGP; MGP = matrix Gla protein; MK4 = menaquinone-4, a vitamin K2 homologue; ucMGP = uncarboxylated MGP.



CKD Treatment News

AbbVie (North Chicago, IL) has dissolved its partnership with Reata Pharmaceuticals (Irving, TX) after nine years. The two companies were working together to develop, among other drug candidates, the therapeutic agent bardoxolone methyl for chronic kidney disease (CKD). The compound was moving along the approval pipeline until the FDA received findings that patients in the CKD treatment arm of a phase 3 study exhibited heart-related side effects, FierceBiotech.com reported.

Now the drug is being tested in more specific populations: patients with autosomal dominant polycystic kidney disease, a genetic disorder, as well as in patients with CKD caused by Alport syndrome, also an inherited disease. If results from current trials prove positive, then Reata will be in a much better position financially, reports Stockhouse.com.

“The deal is important to us because we get the rights to commercialized CKD indications on a worldwide basis,” said Reata CEO Warren Huff in a corporate statement. “Now we have all the rights, except those in southeast Asia, which are owned by our partner, Kyowa Kirin Co.”

AbbVie poured a total of more than \$800 million into the partnership. The deal asks Reata to pay back \$330 million in cash for the rights to the treatments, including bar-

doxolone, an orally available semi-synthetic triterpenoid, based on the natural product oleanolic acid. Pre-clinical studies indicated that the compound acts as an activator of the nuclear factor erythroid 2-related factor 2 (Nfr2) pathway. Nfr2 regulates expression of antioxidant proteins that protect against oxidative damage. Reata is also developing Nfr2 compounds to treat other diseases.

Another CKD drug candidate is moving to a phase 2 trial: DiaMedica Therapeutics’ (Minneapolis, MN) DM199, a synthetic form of human serine protease kallikrein, which plays an important role in kidney physiology, including blood flow, inflammation, fibrosis, and oxidative stress.

The phase 2 study will enroll about 60 patients with CKD. The two cohorts will include 1) patients with CKD caused by IgA nephropathy and 2) non-diabetic, hypertensive African Americans with CKD. African Americans are at greater risk for CKD than European Americans; those with the APOL1 gene are at even higher risk.

Primary endpoints of the study will include safety, tolerability, kidney function, and blood pressure. Kidney function will be evaluated by changes from the baseline level of estimated glomerular filtration rate and albuminuria, as measured by the ratio of urinary albumin to creatinine. ■

Clinical Trials Planned for FSGS, Diabetic Nephropathy Agents

Two companies recently announced clinical trials for promising drug candidates for kidney diseases.

Goldfinch Bio (Cambridge, MA) is entering into an agreement with Osaka, Japan-based Takeda to develop a drug to treat rare and metabolic kidney diseases. The agreement will grant Takeda worldwide rights to the cannabinoid receptor 1 (CB1) monoclonal antibody, which inhibits CB1. Goldfinch says terms are not being disclosed.

The company will assume development and commercialization responsibilities for the drug. Takeda reserves the right, however, to request that Goldfinch Bio negotiate with Takeda for sub-licensing of Japanese rights to the pharmaceutical.



A therapeutic agent will be developed from the preclinical CB1 monoclonal antibody, which has been renamed GFB-024. Goldfinch plans to file a new drug application and begin a phase 1 study in the second half of 2020.

Preclinical data support the inhibition of CB1 signaling as a novel treatment of two kidney-related conditions tracking with the obesity epidemic, diabetic nephropathy and obesity-related glomerulopathies (ORG). The compound potentially will provide metabolic benefits, help prevent fibrosis, and preserve kidney function, the company says.

Diabetic nephropathy develops in 30% to 40% of patients who have diabetes and is a leading cause of morbidity, mortality, and kidney failure in the United States and worldwide. ORG is a rare kidney disorder characterized by significant proteinuria and progressive renal dysfunction.

The Phase 2a clinical trial of ZyVersa Therapeutic’s drug candidate VAR200 should begin by year’s end. ZyVersa, based in Weston, FL, targets podocyte cholesterol accumulation that results from impaired efflux of cholesterol from the cells, causing structural damage that affects kidney filtration. The treatment would benefit patients with focal segmental glomerulosclerosis.

The article “Kidney is the New Liver” states: “Within the past 5 years, renal drug development has been de-risked due to FDA’s acceptance of short-term surrogate endpoints, such as proteinuria, and the ability to segment patients into homogeneous groups through AI and machine learning from large patient data bases, such as Neptune. This has resulted in a surge of interest and investment in this area, as was seen in the past with liver disease” (1). ■

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