ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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All of Us Research Program Aims to Catapult Personalized Medicine Forward

May Help Define Both Good Kidney Health and Disease Contributors

By Bridget M. Kuehn

As a cancer patient for 23 years—who was eventually cured with the help of precision medicine—Eric Dishman brings a very patient-centric view to his work leading the National Institutes of Health's (NIH) ambitious *All of Us* Research Program.

In late May, the more than $200 million project began enrolling the first of what will eventually be 1 million study participants, making it one of the largest research programs ever attempted. Participants will represent a broad range of health statuses, ages, and walks of life. Investigators plan to follow participants for decades and collect reams of biological, lifestyle, and healthcare data. This trove of data will provide a rich resource for researchers trying to better understand risk factors for disease, find ways to more precisely target treatments, reduce health disparities, and advance personalized care.

"The more we understand about individual differences, the better able we will be to effectively prevent and treat illness," said NIH Director Francis S. Collins, MD, PhD, in a statement about the program.

Fully engaged and empowered patients will be essential to the massive program's success.

"We still have to teach people to put the patient's voice first," Dishman told attendees at the May 2017 Kidney Health Initiative (KHI) meeting in Silver Spring, MD. KHI is a public-private partnership between the American Society of Nephrology, US Food and Drug Administration, and over 75 companies and organizations focused on enhancing patient safety and fostering innovation in kidney disease.

Dishman said his kidney transplant care was the first time he received truly comprehensive care. But if *All of Us* is successful in its goals, it may help accelerate the shift toward personalized medicine.

Beta testing

Already more than 300 participants age 18 and older have enrolled in the *All of Us* Research Program, according to Akinlolu Ojo, MD, MPH, PhD, MBA, a nephrologist at the University of Arizona and one of the project's principle investiga-

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Catheters Continue to Be Linked to Most Bloodstream Infections in Dialysis Patients

By Tracy Hampton

Newly reported data representing nearly all US outpatient dialysis facilities reveal that most bloodstream infections in dialysis patients continue to occur in those with central venous catheters used for vascular access. The findings, which are published in a recent *Clinical Journal of the American Society of Nephrology* study, come from the first year of data used by the Centers for Medicare & Medicaid Services to assess facility performance based on bloodstream infections.

Increasing attention is being paid to reducing vascular access–related infections in dialysis patients. "Hemodialysis patients are at high risk for infections, which increase mortality, hospitalization, and healthcare costs. Therefore, surveillance of infectious adverse events among hemodialysis patients is very important," said the Centers for Disease Control and Prevention's (CDC's) Duc Bui Nguyen, MD, lead author of the study. "Tracking infections helps guide intervention and prevention efforts to reduce severe events."

In the late 1990s, the CDC initiated a system to help facilities track in-

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Inside

All of Us Research Program

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tors. Eventually, the program will also enroll children.

"People are excited about the opportunity to understand more about themselves," Ojo said. He noted they were also interested in learning more about disease processes that might affect them and their families.

Participants may enroll through dozens of organizations that provide health care, including regional medical centers, community health centers, and US Department of Veterans Affairs Medical Centers (https://allofus.nih.gov/about/program-components/health-care-provider-organizations). Or they can volunteer directly online at joinallofus.org or by calling the program. Those direct volunteers who are asked to provide biological samples and physical measurements may be directed to a local health clinic at a Walgreens or Quest Diagnostic.

Participants will fill out surveys about their medical history and lifestyle; may have measurements like height, weight, and blood pressure taken at their enrollment site; and may also submit blood or urine samples. Eventually, participants may be asked to have their whole genome sequenced.

The program has established very rigorous systems to protect patient privacy and data security, something deemed essential by focus groups of potential participants convened to help plan the study. Patient samples will be stored and managed by a state-of-the-art biobank at the Mayo Clinic in Rochester, MN. The program has also created online systems to manage and secure the project's "big data."

The study aims to enroll a racially, ethnically, and geographically diverse cohort. This may make the program a particularly rich source of data for those researching kidney disease because racial and ethnic minorities in the US have a 3- to 4-fold risk of developing kidney disease, Ojo noted.

"It is important to have a diverse population to understand the complex processes and the pathways that lead to disease," Ojo said.

The first data from the project should be available within a year. At that time, researchers from many different backgrounds—from traditional federally funded academic investigators to biotech company researchers and even citizen scientists—may be able to use data from the study, Ojo noted. A national institutional review board will review study proposals as needed.

"It's going to occur very rapidly," Ojo said.

The project is starting with a so-called beta testing phase in which the initial 10,000 participants will help to test and provide feedback on how the program and its systems are working. Such beta testing is a common practice for technology companies as they begin to roll out new products. It also reflects Dishman's background in information technology. He previously served as vice president of the Health and Life Sciences Group at Intel Corporation.

"Our beta testers will help us find problems with our systems and processes, so we can fix them and improve the experience for everyone going forward," Dishman explained in a statement. "And most importantly, they will help us evaluate and improve our messaging, our engagement approaches, and our relationship building with diverse communities across the country."

Kidney health clues

Ojo said he expects the *All of Us* cohort may include about 50,000 people with kidney diseases, based on the incidence of kidney diseases in the US. The program may help speed the development of kidney disease treatments targeted to specific populations, Ojo said.

"The *All of Us* program will help us to quickly find the causes of kidney disease in different populations and help us develop new treatments for it and other common diseases," Ojo said.

Precision medicine initiatives, which target specific subgroups of patients to come up with personalized treatments, are particularly critical for kidney disease patients who may have very different genetic backgrounds and disease presentations, according to Dave White, a self-described kidney warrior and health care consultant who participated in the KHI meeting. White, who is African American, recently celebrated the 2nd anniversary of his kidney transplant. He is currently stable but carefully monitors his cholesterol and takes medication to manage high blood pressure. By way of example, he explained that another patient undergoing dialysis might have Asian or Hispanic ancestry and have diabetes but no high blood pressure.

"One size does not fit all," White said. "Precision medicine tailors the right treatment to the right person at the right time."

The data collected by the program, which aims to follow participants through their lifespan, might also help scientists better understand what causes kidney diseases and how to prevent them. Some patients will likely develop kidney diseases over the course of the study, which will provide genetic and physiological data that may help scientists "understand the background in which kidney disease develops," Ojo said.

Engaged and informed

Significant challenges lie ahead for such a large, long-term, and ambitious project, Ojo acknowledged. Another large NIH-funded project, the National Children's Study, which planned to follow 100,000 children from gestation to age 21, was cancelled in 2014. But he and his colleagues have studied what went wrong with the project to try to avoid replicating its difficulties.

"We have learned important lessons from the National Children's Study," he said.

A strong emphasis on community, participant, and investigator engagement across the country is one strategy the program hopes to use to promote its long-term success. Focus groups of potential participants and other stakeholders began before enrollment. Participant representatives have been invited to serve on the program's Steering Committee, and several of the local sites have established participant advisory boards to help advise and guide the program.

"One of the core values [of the *All of Us* Research Program] is that participants and their representatives will have a prominent role not just as advisors to the research team, but they will also play a role in governance, determining which research will be done, monitoring studies, and disseminating research results," Ojo said.

White agreed that patient engagement is critical to the success of any research project.

"Research is kind of pointless unless it results in outcomes important to the patient, and the only way to make sure that happens is to make sure that the patient voice is heard," White said. "One of the most important considerations for patients is not letting kidney disease affect what you want to do with your life."

The NIH is partnering with manufacturers of electronic medical records systems on a pilot program to allow individuals to access their electronic health records and share the information with researchers through mobile apps and websites.

"We plan to use information technology to the utmost, while making sure those without access can still participate," Ojo said.

White encouraged patients who want to see advances in personalized medicine to get involved in research, like *All of Us*, or participate in advocacy programs.

"We all have a part to play in this," White said. "Those of us who can kind of have a duty to get the best care possible and the best way to do that is to participate in advocacy and research."

All of Us Research Program Announces National Tour to Engage Communities

By Ryan Murray

The *All of Us* Research Program, an element of the National Institutes of Health's (NIH) Precision Medicine Initiative (PMI), will allow researchers, health care providers, and patients to work together and develop individualized care. In a truly historic effort, the *All of Us* Research Program aims to collect data from more than 1 million people to accelerate health research and medical innovation through precision medicine. This project is a network of US industry and universities that seeks to generate new knowledge on the biological, environmental, and behavioral influences on diseases with the goal of developing more effective therapies to treat them by leveraging the statistical power of a cohort of this significant size.

Currently in beta testing, the *All of Us* Research Program will look to identify and enroll a diverse group of interested and eligible participants later this year. Interested individuals over the age of 18 and living in the US are encouraged to apply when enrollment opens by visiting www.joinallofus.org.

In order to spread awareness of the program, NIH has announced a 37-week national tour called the *All of Us* Journey. This traveling exhibit officially kicked off in July 2017 with dates through 2018. Recognizing the value of engaging with trusted health care partners in local communities, the *All of Us* Journey is looking to coordinate with local community members to participate in events. These events will educate the community on the *All of Us* Research Program and provide individuals the opportunity to have their questions answered and enroll on-site.

In response to the announcement, the Chair of the ASN Policy and Advocacy Committee, Crystal Gadegbeku, MD, stated: "ASN appreciates that the National Institutes of Health has recognized the value of individualized care and the benefits it could provide to patients. I am truly excited about the promise that the *All of Us* Research Program offers for both the broader medical community and minority patients. By placing an emphasis on both a diversity of disease modalities and patient demographics, the cohort will serve as an invaluable tool for medical researchers and increase the likelihood of developing new therapies."

While the *All of Us* Research Program will collect information from individuals with a variety of diseases, the American Society of Nephrology recognizes the value of the opportunity for patients with kidney diseases to participate in this program and encourages health care providers to collaborate with the *All of Us* Journey.

More information, including how to apply to host the *All of Us* Journey and where and when the tour will be traveling, can be found by visiting https://www.asn-online.org/policy/webdocs/All_of_Us_Journey.pdf.

Nephrology of the Future: How Do We Get There?

Reflections on the Kidney Precision Medicine Project as Presented at the Fifth Annual Kidney Health Initiative Stakeholders Meeting

By Robert A. Star, MD, Jenna M. Norton, MPH, and Sandeep Dayal, PhD

The authors are affiliated with the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.

This article is based on content presented at the Fifth Annual KHI Stakeholders Meeting held May 24–25, 2017, in Silver Spring, MD, by Dr. Robert A. Star, Director of the Division of Kidney, Urologic and Hematologic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases. In his presentation, Dr. Star highlighted a new research initiative that will encourage bold, patient-centered cultural shifts in nephrology research and practice, ultimately leading to individualized approaches for the treatment of kidney disease.

Acute kidney injury (AKI) and chronic kidney disease (CKD) impose a significant global health burden; however, only a few drug therapies are available for CKD, and no effective drug therapies currently exist for AKI. Development of pharmacologic therapies for AKI and CKD has been hampered by non-predictive animal models, the inability to identify and prioritize human targets, and an underlying poor understanding of human AKI and CKD. A growing consensus suggests that CKD and AKI are not homogeneous diseases; rather, they are heterogeneous disorders that contain specific subgroups that are driven by different disease pathways. Thus, a better understanding of disease heterogeneity will likely inspire the development of more effective individualized treatment options.

One might envision a more individualized future for nephrology practice, where each person with kidney disease can find answers to important, patient-centered questions: What do I have? What will happen to me? What can I do about it? A nephrologist in this vision of the future might evaluate the person's disease profile using blood and urine tests, image the kidney in real-time to identify and biopsy areas of kidney damage, then analyze the biopsy tissue using a kidney tissue atlas (a tool designed to classify the location and health of kidney tissue components), and select the appropriate drug to start individualized treatment. The kidney biopsy is essential to this vision of the future, as it will provide the information needed to answer the patient-centered questions. The analysis of kidney biopsy tissue will identify the specific subtype of AKI or CKD and the precise molecular pathway(s) driving the patient's kidney disease. With this information, the nephrologist can select the appropriate therapy to enable individualized care for that patient.

How do we get to this future? We need to leverage novel technologies in multi-scale interrogation of single cells and biopsy tissue advanced primarily in oncology research. Such sophisticated technologies that have matured over the past few years can now be employed to analyze cellular and tissue heterogeneity (e.g., cell-, tissue-, and molecular pathway-specific markers; using two and three-dimensional imaging techniques) in exquisite detail, simultaneously using multiple markers at single-cell resolution to define specific kidney structures. Thus, researchers are now poised to initiate the construction of a complex kidney tissue atlas that can classify and locate different cell types, cell states (healthy, injured, dying, recovering, undergoing adaptive/maladaptive repair, etc.) and interstitial components (e.g., collagens, proteoglycans, signaling molecules, etc.). These breakthroughs will revolutionize renal pathology, and give tremendous insight into the patient-centered questions.

But technological advances alone are likely insufficient for precision medicine to be applied to AKI and CKD. These advances must be accompanied by changes in the culture of three distinct but connected groups involved in the clinical care process. First, pathologists must utilize histologic markers from the kidney tissue atlas to improve their diagnosis, prognosis, and therapy recommendations. Second, nephrologists will need to recognize the benefits of biopsy to their patients, then use the biopsy information to stratify their patients into disease subgroups so they can more effectively develop personalized treatment plans with their patients. Finally, and perhaps most importantly, patients must be made aware of how a kidney biopsy may help determine the best therapeutic approach for their particular disease subtype. These three inter-related cultural shifts are undeniably challenging to achieve in the health care system. However, if patients more clearly understand the importance of a kidney biopsy to their own treatment and disease management, they will be much more likely to request them from nephrologists, thereby driving the entire process of cultural change.

Currently, kidney biopsies have limited benefit to an individual, but a large benefit to research efforts aimed at improving treatments. The kidney biopsy procedure is risky; there are well defined complications. Therefore, ethical and participant safety considerations must be a primary concern. Individuals who choose to participate in research studies must be provided with clear information about the risks associated with undergoing a kidney biopsy. The risks should be reasonable relative to expected benefits to that individual and to society, and biopsies must be safely collected by trained professionals. Specific, validated protocols for tissue handling and interrogation should be developed and implemented to ensure that when a participant donates his or her tissue, it yields the greatest possible benefit to that individual, the patient community, and society as a whole. Ensuring these ethical and safety practices will encourage participation and inform patients of the potential benefits of biopsy collection to their own health care.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is launching the Kidney Precision Medicine Program (KPMP) in summer 2017, with the goal of ethically and safely obtaining and evaluating human kidney biopsies from research participants with AKI or CKD; creating a kidney tissue atlas; defining disease subgroups; and identifying critical cells, interstitial components, and pathways that can be targeted for novel therapies. Human kidney biopsies will be analyzed to identify new markers that will characterize cells, cell states, and molecular disease pathways. In an iterative process, the biopsies will then be evaluated with this new information, and regions of the tissue that remained unlabeled (dark areas) will be further interrogated to obtain additional novel molecular data enabling identification of new cell types and signaling cascades. The array of molecular, cellular, and tissue markers will then be linked to important patient clinical outcomes. The emerging kidney tissue atlas will be used as a foundation to better understand renal disease heterogeneity and can inform decision-making by pathologists, nephrologists, and patients with AKI and CKD.

Tissue interrogation is a central component of the KPMP workflow. Researchers have already been collecting mRNA, protein, and even some epigenomic data on partially fractionated (glomerulus, tubule-interstitium compartments) human kidney tissue; the KPMP will expand and extend these efforts to gain more depth of information at the single cell and single tissue compartment level. All resulting resources will be public, open, and transparent, and will be made available to everyone (e.g., patients, academic researchers, industry scientists). These findings and resources will help nephrologists better understand human kidney disease, and will invigorate kidney research, attract top talent from inside and outside nephrology, provide ample career development opportunities, and seed new investigator-initiated research. To achieve maximal success, the KPMP will foster partnerships among patients, academic researchers, private industry, advocacy organizations, and the NIDDK.

KPMP resources will undoubtedly be used by a variety of stakeholder groups. For example, a patient with diabetic nephropathy, or a family member of a patient with AKI, may request a kidney biopsy after learning about the benefits to his or her health and to the research enterprise; an academic researcher can use KPMP resources to evaluate whether a potential disease pathway or drug target is linked to a specific patient outcome; a pathologist who found a new object in a kidney biopsy could use the kidney tissue atlas for fine localization and correlate with a clinical outcome, further refining the disease scoring system; and a private industry scientist could utilize KPMP resources to identify and develop new human drug targets.

Our patient-centered, individualized vision for the future of nephrology drove us to keep the patient voice front and center in the design and implementation of the KPMP. Over time, we expect results and resources from the KPMP will drive the evolution of nephrology toward this future. An increased understanding of human kidney diseases is likely to catalyze the development of new therapies. Biopsy results will likely become more informative to clinical care as pathologists and nephrologists can better predict a drug's effectiveness based on an individual's specific renal pathophysiological profile. Ultimately, we predict that patients eager to better understand their disease subtype, specific prognosis, and individualized treatment will begin to demand a kidney biopsy.

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Catheters

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fections among dialysis patients. In the early years, a relatively small number of dialysis facilities participated. Today, though, thousands of facilities report to the CDC's National Healthcare Safety Network (NHSN) Dialysis Event Surveillance. This is in part due to requirements set in 2012 that all Medicare licensed outpatient dialysis facilities report access-related infections to the NHSN.

Also, in 2014, bloodstream infections were added to the Centers for Medicare & Medicaid Services' End-Stage Renal Disease Quality Incentive Program to assess dialysis facility performance.

In their recent analysis, Nguyen and his colleagues at the CDC summarized 2014 data submitted to the NHSN Dialysis Event Surveillance program. They noted that 6005 outpatient hemodialysis facilities reported data for a total of 160,971 dialysis events including 29,516 bloodstream infections (BSIs); 149,722 intravenous antimicrobial starts; and 38,310 episodes of pus, redness, or increased swelling at the hemodialysis access site. Across event types, pooled rates were highest for central venous catheters, lower for arteriovenous grafts, and lowest for arteriovenous fistulas.

The team found that 77% of BSIs were related to accessing patients' blood. Most—63% of BSIs and 70% of access-related BSIs—occurred in patients with a central venous catheter.

BSI and other dialysis event rates were also highest among patients using central venous catheters. *Staphylococcus aureus* was the most commonly isolated BSI pathogen (31%), and 40% of *S. aureus* isolates tested were resistant to the antibiotic methicillin. Vancomycin was the antimicrobial started in 76% of intravenous antibiotic initiations.

Hospitalization was an outcome for 22% of all dialysis events, including 49% among central venous catheter events, 36% among arteriovenous fistula events, 15% among arteriovenous graft events, and 0.4% among other vascular access events. Hospitalizations occurred in 48% of BSIs, 46% of access-related BSIs, 25% of vascular access infections and 11% of local access site infections. Death occurred in 1352 (0.8%) of all dialysis events. Two percent of BSIs and 1.6% of access-related BSIs resulted in deaths.

"We now have a clearer picture of the rates and types of infections hemodialysis patients in the United States are experiencing—nearly all US outpatient hemodialysis facilities are participating in CDC's NHSN Dialysis Event Surveillance," said Nguyen. "Our findings emphasize the need for hemodialysis facilities to improve infection prevention and vascular access care practices."

In an accompanying editorial, Dana Miskulin, MD, of the Tufts University School of Medicine, and Ambreen Gul, MD, of Dialysis Clinic Inc., noted that a major problem to the available data is that event reporting is based on an honors system, and dialysis units report their own information without any processes to ensure that events are reported accurately. "We make a plea to the dialysis community to 'clean up' the data, so that the Quality Improvement Program is fairer for all and to enable the full potential of these data, both for improving care now and for generating new evidence to provide future opportunities to improve care and outcomes, to be realized," they wrote.

The authors of the editorial also noted that the nearly 50% decline in rates of bloodstream and localized vascular access infections observed from 2006 to 2014 reflects improved practices; however, several red flags suggest that underreporting of events is likely. They also pointed to several unanswered questions, including whether outcomes are superior with catheter removal/replacement vs. 'treating through,' whether replacement over a wire is equivalent, and whether antibiotic locks have any role to play.

Duc Bui Nguyen, et al. National Healthcare Safety Network (NHSN) Dialysis Event Surveillance Report for 2014. *Clin J Am Soc Neph* 2017; 12(6).

Dana Miskulin and Ambreen Gul. Infection monitoring in dialysis units: a plea for 'cleaner' data. *Clin J Am Soc Neph* 2017; 12(6).

Findings

Ibuprofen May Increase AKI Risk in Ultramarathon Runners

Acute kidney injury (AKI) may be more frequent in ultramarathon runners who take ibuprofen, according to a randomized controlled trial in *Emergency Medicine Journal*.

The study included 91 athletes participating in 50-mile ultramarathon races in desert environments. Runners were randomly assigned to take ibuprofen 400 mg or placebo tablets every 4 hours during their race. Incidence of AKI was compared between groups: "risk" was defined as a 1.5-fold increase in creatinine and "injury" as a twofold increase. Runner characteristics were similar between groups; in the ibuprofen group, average total dose was 1200 mg.

Overall AKI incidence was 44%. On intention-to-treat analysis, AKI occurred in 52% of runners taking ibuprofen versus 34% taking placebo. The 18% difference exceeded the 15% noninferiority threshold. However, the number needed to harm was 5.5 ibuprofen-treated runners to cause 1 additional case of AKI.

Both categories of AKI were more frequent with ibuprofen: 38% versus 26% for "injury" (nonsignificant) and 14% versus 9% for "risk" (significant). Slower finishers were less likely to develop AKI: odds ratio (OR) 0.67. Greater weight loss was associated with a higher risk of AKI: OR 1.2 at a 1.3% reduction in body weight.

Studies have reported 34% to 85% rates of AKI in ultramarathoners. Although it has been suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) might contribute to these events, up to three-fourths of runners still take NSAIDs during races. The evidence for and causal nature of this association are unclear.

Despite the lack of statistical significance, this trial suggests an increased risk of AKI in ultramarathon runners who use ibuprofen. Taking NSAIDs during endurance running "could exacerbate renal injury," the researchers write. They note that associations of AKI with finishing time and weight loss suggest a role of dehydration [Lipman GS, et al. Ibuprofen versus placebo effect on acute kidney injury in ultramarathons: a randomised controlled trial. *Emerg Med* 2017; doi: 10.1136/emermed-2016-206353].

Filtration Markers May Predict ESRD and Mortality Risks

Concentrations of four markers of filtration, individually and in combination, are consistently associated with the risk of progression to end stage renal disease (ESRD), reports a study in the *American Journal of Kidney Diseases*.

Members of the Chronic Kidney Disease Biomarkers Consortium analyzed filtration markers and their association with 1-year change in measured (mGFR) and estimated (eGFR) glomerular filtration rate. The study included observational data on 317 patients from the Modification of Diet in Renal Disease study and 373 patients from the African American Study of Kidney Disease and Hypertension (AASK).

At 12- and 24-month follow-up visits, patients underwent measurement of creatinine, cystatin C, β-trace protein (BTP), and β2-microglobulin (B2M), along with mGFR. Associations with ESRD and all-cause mortality per 30% decline in mGFR or eGFR were analyzed for individual markers and for the average of four markers.

In both groups of patients, 1-year declines in mGFR, eGFR based on creatinine, and eGFR based on BTP were significantly associated with incident ESRD. The average of all four markers was also associated with ESRD. The only filtration marker more strongly associated with ESRD risk in both studies was decline in eGFRBTP.

Decline in eGFRCr was associated with all-cause mortality only in AASK: incidence rate ratio 4.17 per 30% decline. This was not significantly different from the associa-

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Findings

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tion with mGFR. None of the other filtration markers was associated with mortality. Increase in mGFR and eGFR was not significantly associated with ESRD or mortality risk.

Repeated assessment of filtration markers might help to predict clinical outcomes in chronic kidney disease. The new study provides initial data on clinical outcomes associated with change in concentration of some novel filtration markers.

The results suggest that declines in mGFR, eGFRCr, eGFRBTP are significantly associated with incident ESRD. The average of creatinine, cystatin C, BTP, and B2M is also "consistently associated" with progression to ESRD. The investigators conclude, "Measurement of BTP over time may offer additional information about future ESRD risk," [Rebholz CM, et al. Risk of ESRD and mortality associated with change in infiltration markers. *Am J Kidney Dis* 2017; doi: 10.1053/j.ajkd.2017.04.025].

Does Contrast Exposure Cause Contrast-Induced AKI?

Contrast media exposure is not a "primary pathogenetic factor" in the development of acute kidney injury (AKI) after primary angioplasty, reports a study in the open-access *Journal of the American Heart Association*.

The researchers analyzed 2025 patients with ST segment-elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention at an Israeli hospital between 2000 and 2015. Median contrast dose was 150 mL. Rates of AKI were compared with those of 1025 patients undergoing fibrinolysis or no reperfusion therapy, who were not exposed to contrast medium. Acute kidney injury was defined as a creatinine level of 0.5 mg/dL or a creatinine increase of greater than 25% within 72 hours.

Overall AKI rates were similar between groups: 10.3% in patients undergoing primary angioplasty and 12.1% in the comparison group. A propensity score-matched analysis including 931 pairs also found no significant difference: 8.6% and 10.9%, respectively.

A wide range of factors were independently associated with AKI after primary angioplasty: age 70 or older, treatment with insulin or diuretics, anterior infarction, baseline estimated glomerular filtration rate, and variables reflecting pump failure and reduced left ventricular ejection fraction. The dose of contrast agent was not a significant factor. A risk score developed from the primary angioplasty group had similar discriminatory performance for AKI in the angioplasty and comparison groups.

Acute kidney injury occurring after primary percutaneous coronary intervention is commonly reported as "contrast-induced" AKI. However, other factors may contribute to this risk; previous studies of this issue have lacked a control group of patients not exposed to contrast medium.

The new analysis suggests that contrast exposure is not the primary cause of AKI after primary angioplasty in patients with STEMI. The increase in adverse outcomes with AKI after angioplasty appears to be independent of contrast exposure. The authors conclude, "[A]ttempts to reduce AKI rates in STEMI patients likely require targeting mechanisms that are unrelated to contrast media" [Caspi O, et al. Acute kidney injury after primary angioplasty: is contrast-induced nephropathy the culprit? *J Am Heart Assoc* 2017; doi.org/10.1161/JAHA.117.005715].

Policy Update

NIH Gains in Appropriations Budget, but Falls Short of Need

By Zachary Kribs

On Thursday, July 13, 2017, the House Labor, Health and Human Services, Education, and Related Agencies Appropriations (LHHS) Subcommittee approved the Fiscal Year 2018 budget by a party-line vote. One of the largest of 12 annual appropriations bills, the LHHS bill provides a $5 billion reduction in funding to the Department of Health and Human Services as compared to enacted 2017 funding. However, the legislation provides for a few exemptions from the cuts, including a $1.1 billion increase for the National Institutes of Health.

Under the normal appropriations process as outlined by the Congressional Budget Act, the President presents their budget blueprint to Congress the first Monday of February. By mid-April, Congress completes action on the budget resolution, which sets topline spending levels for the government. Congress then begins to craft appropriations legislation, which specify exact funding levels for all discretionary programs. This process must be complete by the beginning of the fiscal year on October 1, otherwise the government runs out of money and shuts down.

However, this year, as in previous years, the budget process is far from on schedule. Congressional leadership in charge of determining the budget has yet to complete negotiations on topline spending levels, while appropriators, shrugging off normal order, are crafting appropriations legislation without the guidance of a budget resolution. Discrepancies between the appropriations bills and the budget resolution could further delay the budget process, and with just over a month of scheduled work days before the end of the fiscal year, many legislators are predicting the need for emergency funding measures like last year's series of continuing resolutions.

While the LHHS appropriations bill is a far cry from the Trump administration's budget proposal, whose drastic cuts the American Society of Nephrology (ASN) spoke out against earlier this year, the bill falls short of ASN's asks. A $1.1 billion increase for the National Institutes of Health is much more preferable than a $6 billion cut, but the amount is basically half of the $2 billion increase necessary to keep pace with medical inflation and sustain current research levels. Kidney diseases in particular deserve special attention. The government has already pledged $33 billion annually to support dialysis; greater emphasis on funding kidney research will foster breakthrough developments that would change the lives of the nearly 700,000 Americans living with kidney failure, and greatly reduce the burden kidney diseases place on the economy.

ASN will watch the bill closely as it moves through Congress. The legislation is scheduled for a full markup by the House Appropriations Committee on Wednesday, July 18, and will then be voted on in the full House floor before being sent to the Senate. Many amendments are expected to be made, and ASN will continue to advocate for both a $2 billion increase and the establishment of a Special Kidney Program to address the outsized toll kidney diseases place on the American public.

Cuts Proposed for NIH Funding for Facilities and Operating Costs

By Ryan Murray

In addition to the "proposed" sweeping reduction to the National Institutes of Health (NIH) budget, which is not expected to be supported by Congress, President Trump's fiscal year 2018 budget includes significant reductions to NIH support for costs associated with conducting federally supported research, causing concern within the medical research community.

The total cost of federally sponsored research includes both direct and facilities and administrative (F&A) expenses (previously referred to as "indirect costs"). Direct costs are used to cover portions of researcher salaries and necessary equipment and supplies, while F&A costs refer to necessary research infrastructure and operating expenses that the university provides to support research.

Despite F&A costs as a percentage of federal funding remaining relatively unchanged at approximately 27% for more than a decade, they have become a popular target among politicians looking to reduce federal expenses because of a misconception by the public that F&A costs do not support research. F&A expenses are essential research costs including but not limited to personnel support, physical infrastructure, energy and utility expenses, costs of regulatory compliance, and other government-mandated expenses. These expenses are necessary to conduct high-quality medical research. A reduction in F&A costs would make research unaffordable for many institutions and lead to a reduction in critical biomedical research.

The proposed reduction in F&A costs can be achieved through two routes. Congress could pass a statute that caps the F&A costs an institution can be reimbursed for; this, however, is seen as unlikely due to the bipartisan support for medical research.

The more likely route is a lengthy process in which the Office of Management and Budget could issue new guidance. This process would occur over several years and would require public comment on the proposed guidance. The American Society of Nephrology has encouraged the administration to support medical research and reconsider its proposal on F&A costs, and will continue to track this issue.

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Biomarkers in Acute Kidney Injury and Beyond

By Justin Lee Loy, MD, and Joseph Mattana, MD

At present, the renal community suffers from a limited array of noninvasive tools in routine clinical use that can accurately and rapidly identify acute kidney injury (AKI) and generate useful prognostic information to help guide current therapy and anticipate major subsequent events, some of which may require substantial interventions, such as initiating renal replacement therapy.

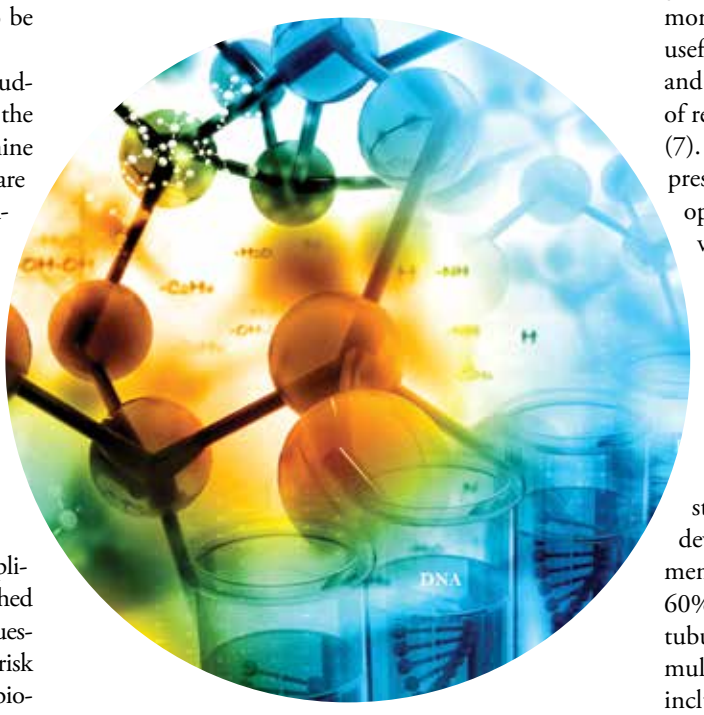
Similar to cardiology and the use of troponins in acute myocardial infarction, there is an urgent need for new biomarkers to help guide the treatment of patients with renal disease. The study of biomarker applications in renal disease continues to cover a broad spectrum of clinical conditions, including AKI, chronic kidney disease (CKD), and ESRD, including dialysis and transplantation. Within each of these entities, multiple potential applications continue to be evaluated.

In AKI, for example, biomarkers have been studied in terms of early identification of AKI given the well known limitations of changes in serum creatinine in signaling an acute decline in GFR. Biomarkers are also being studied in terms of their predictive capability, for example, to predict the risk of AKI resulting in a need for renal replacement therapy or to predict the risk for development of CKD. In the latter scenario, this may result either from a failure of renal function to return to baseline or perhaps is a result of renal damage, which may not be detectable on the basis of serum creatinine and urine protein measurements but is nevertheless sufficient to result in a course leading to CKD and ESRD.

New biomarkers may have great potential application in CKD as well. For patients with established CKD, among many critically important clinical questions are the risk of progression to ESRD and the risk for cardiovascular morbidity and mortality; hence, biomarkers continue to be investigated for potential utility to address these issues. For patients with ESRD who are on dialysis, the ability to manage the disproportionate cardiovascular morbidity and mortality from which these patient suffer might be aided substantially if biomarkers that could help guide therapy and prognosis were available. For patients with ESRD who undergo renal transplantation, there are numerous clinical issues for which biomarkers that are being actively studied could have an enormous effect, including early detection of allograft dysfunction and differentiation of acute rejection from other causes of allograft dysfunction, including BK virus nephritis, with the goal of reducing the need for allograft biopsy (1). Another major area of investigation has been using biomarkers to help generate an immunologic profile of the transplant patient and guide immunosuppressive therapy to help prevent over- or undertreatment to prevent rejection (2). Here, we will briefly highlight a few examples of clinical scenarios and the potential value of having improved biomarkers.

AKI—radiocontrast nephropathy

Ischemic AKI has served as an important model in which to study new biomarkers, and progressive insights continue to be obtained into the roles of biomarkers as early and accurate indicators of ischemic AKI. There is ongoing investigation into many other aspects of biomarkers, including their mechanistic contribution to AKI as well as their ability to provide prognostic information to facilitate anticipation of the need for renal replacement therapy and more individualized therapeutic interventions. For example, findings from the Translational Research Investigating Biomarkers and End Points for AKI Consortium in patients undergoing cardiac surgery have provided strong support not only for the potential for biomarkers to identify AKI at earlier time points but also to identify patients at risk for other adverse outcomes (3). The scope of AKI biomarker research has continued to extend well beyond ischemic AKI.



The past year has seen ongoing work on biomarkers in the setting of AKI from various nephrotoxins, including radiocontrast, liver disease, multiple myeloma, hypertensive renal injury, and urinary tract obstruction, among others. Despite the introduction of low- and iso-osmolar radiocontrast, the incidence of contrast-induced AKI remains a common clinical problem likely due to several factors, including an increase in radiographic procedures being performed and an aging population with increased frequency of comorbidities, such as diabetes, CKD, and atherosclerotic disease (4).

The pathophysiology of contrast-induced AKI is thought to be the result of renal ischemia compounded by renal vasoconstriction (5). Contrast-induced AKI has been associated with prolonged hospitalization and represents an independent predictor of unfavorable outcome (6). Currently, contrast-induced AKI is still diagnosed using changes in serum creatinine with its inherent limitations, including its variable production rates among diverse individuals; its secretion in the proximal tubule, which can be altered by drugs; and the time required for a rise in serum creatinine to become evident and thereby indicate the development of an acute reduction in GFR and renal damage. The time required for an elevation of serum creatinine and the resultant delay in the diagnosis of AKI not only limit any opportunity to potentially avert the development of renal damage but also may contribute to prolonging hospital stays in patients undergoing serial serum creatinine measurements who did not develop AKI and in whom a biomarker could have answered this question shortly after the procedure was done.

The term subclinical AKI refers to a change in biomarker level alone without evident simultaneous loss of kidney function. This condition has been associated with increased risk of adverse outcomes in long-term follow-up. One promising biomarker to detect contrast-induced AKI earlier is neutrophil gelatinase-associated lipocalin (NGAL). NGAL and, more specifically, urinary NGAL were shown to be useful in early diagnosis of contrast-induced AKI and in prognosis of AKI (i.e., prediction of initiation of renal replacement therapy and hospital mortality) (7). They can be readily measured by ELISA, but presently, further studies are warranted, because the optimal test (blood or urine), timing, and cutoff value still need to be clarified.

AKI in oncology

AKI in the setting of cancer and cancer therapy is a well known and common clinical problem. Examples of groups at high risk for AKI are patients with acute lymphoma or leukemia undergoing induction chemotherapy. One study reported at least one third of such patients developing AKI, with those requiring renal replacement therapy experiencing a mortality of more than 60% (8). Although years ago cisplatin-induced acute tubular necrosis was a predominant AKI scenario, multiple new agents introduced over recent years, including antiangiogenesis drugs, tyrosine kinase inhibitors, and mAbs, have vastly expanded the spectrum of mechanisms of renal injury.

The growth of these oncologic therapies with a growing list of mechanisms of renal injury has presented a great challenge to nephrology and an urgent need for improved means of prevention, identification, and therapy for AKI in cancer patients. It is worth emphasizing that the consequences of cancer therapy–induced AKI can extend far beyond the acute injury itself, regardless of whether a need for renal replacement therapy results. Some patients will experience only a partial recovery or no recovery at all and are left with permanent parenchymal damage. For those not requiring permanent renal replacement therapy, they can still be left with a reduced GFR and multiple attendant complications, including an increased risk of development of ESRD.

An additional vexing problem facing patients and their oncologists and nephrologists may be the need to delay or abandon certain chemotherapeutic agents when renal damage occurs, with the potential to thereby worsen oncologic outcomes. One area in which biomarker research has been carried out is AKI in the setting of cisplatin chemotherapy. Cisplatin is part of many chemotherapy regimens, and significant nephrotoxicity is most commonly the re-

sult of tubular toxicity. Several biomarkers, such as kidney injury molecule-1 (KIM-1), urinary NGAL, and L-type fatty acid binding protein (L-FABP) have been investigated. Urinary NGAL has been shown to be significantly elevated before the rise in serum creatinine, and also, it predicted residual kidney dysfunction weeks later (9). These are promising developments, but further research is needed.

Biomarkers in drug development and nephrotoxicity

It should also be noted that, in addition to the potential for clinical utility of new biomarkers for monitoring for adverse effects of drug therapy, such as oncologic therapies, biomarker research should have a great effect on the field of drug development. Monitoring for renal toxicity is critical to the process of drug development. Biomarkers that can identify nephrotoxicity early in the course of AKI can potentially help protect study participants from developing major acute renal complications as well as permanent renal damage, while potentially allowing for greater testing of drugs where such concerns exist. It should also be noted that this is an area where collaboration between academic institutions and pharmaceutical research companies may be especially productive.

Chronic kidney disease

Research on the use of biomarkers in CKD and the risk of developing CKD also continues, with various applications being explored. The risk of development of CKD in patients who suffer an episode of AKI is an important clinical question, but serum creatinine levels after an AKI event may not be able to identify all patients at risk for CKD.

In one study of children undergoing surgery for congenital heart disease with cardiopulmonary bypass, when those with AKI were compared with those without AKI 7 years later, those who had suffered AKI had higher levels of IL-18 and L-FABP, despite having comparable renal function and urine protein excretion (10). There is also great interest in the potential application of biomarkers in predicting outcomes in CKD, such as cardiovascular events and progression to ESRD. The list of agents being studied in this domain is growing and includes some that have been well studied in AKI, such as NGAL and KIM-1 (11), and others, including soluble tumor necrosis factor receptors and fibroblast growth factor-23. In addition to AKI and the subsequent risk of development of CKD, another potential area where there may be utility of new biomarkers is the ability to predict later development of CKD in patients who undergo nephrectomy. For example, patients undergoing nephrectomy for renal cell carcinoma who had overexpression of miR-193b-3p were found to have a high risk of developing CKD (12).

Potential future applications of biomarkers

The clinical relevance of the growing body of biomarker research has not been unquestioned. For example, the lack of effective interventions in the clinical setting to ameliorate or reverse the course of AKI has served as an argument against the value of having biomarkers that can detect AKI at earlier time points than can be achieved with serum creatinine measurements and urine output. A counterargument is that, in parallel with biomarker research regarding identification and prognostication of AKI, there is ongoing research investigating mechanisms of renal injury and recovery in AKI and therapeutic maneuvers that could ultimately be developed to treat AKI. Such interventions will almost certainly require an accurate determination of the time of onset of injury and detailed information during the subsequent time course. It is noteworthy that some unsuccessful clinical trials of agents to accelerate recovery of AKI, agents that worked well in animal models, have likely been hampered by lack of accurate knowledge of this time course and the inability to detect early AKI by relying on serum creatinine levels. After such therapies are available, it can be argued that having biomarkers for the early identification and prognostication of AKI should be invaluable.

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Are Kidney Transplant Centers **Financially Viable Anymore?**

By Uday Nori, MD

In the March issue of *Kidney News*, a study by Axelrod et al. (1) was featured that analyzed the costs of kidney transplantation. The study found that costs are increasing substantially, mostly because of the increased complexity of transplant recipients and a lack of changes in the reimbursement model by payers.

This article will highlight several other points that contribute to the increasing costs and will focus on the unintended effects of the current regulatory environment, as well as review some of the historical aspects of kidney transplantation regulation. Specifically, the combination of increasing regulation by the Centers for Medicare & Medicaid Services (CMS), stagnant payments for kidney transplantation, declining living kidney donor participation, and the increased role of multidisciplinary teams in the management of transplant recipients have all contributed to higher costs of kidney transplantation. Although individual centers' data are not published in the literature, it is likely that these rising costs may make kidney transplantation nonviable financially.

Background

In 1972 the US Congress passed legislation authorizing the ESRD Program under Medicare. Since then, the number of patients with ESRD has skyrocketed, from 10,000 patients in 1972 to 469,950 in 2013. Although ESRD represents <1% of all Medicare patients, it has become the single most expensive disease paid by Medicare, accounting for $30.9 billion in 2013, or 7.1% of the overall Medicare-paid claims costs. Kidney transplantation (included under the ESRD definition) accounted for about $3.5 billion.

Over the years, several attempts have been made to contain costs, improve quality of care, and bring forward best practices. The National Organ Transplantation Act of 1984 (to ensure best use of organs and fairness to those awaiting transplantation) created the Scientific Registry of Transplant Recipients, which is obligated to publicly report data on performance of transplant programs and organ procurement organizations in the United States. Other efforts included the Organ Donation Breakthrough Collaborative in 2003, with the goal of increasing the number of organ donors in the United States, and in 2007, the Transplant Growth and Management Collaborative designed specifically for transplant centers to share best practices from high-performing centers. The goals of these efforts were intended to 1) increase the number of donors, 2) increase the number of organs transplanted per donor, 3) reduce deaths on the waiting list, and 4) improve outcomes.

Current paradigm

In March 2007, CMS issued final regulations regarding conditions of participation (CoPs) for hospital-based kidney transplant programs. The regulations became effective on June 28, 2007.

Key among many of the new requirements is adequate 1- and 3-year graft and patient survival as reported in the preceding 30-month cohorts in the 6-month program-specific reports. This information is derived from a comprehensive survival model on the basis of national donor, recipient, and transplant data, and is adjusted for the composite risk. A lower observed versus expected survival rate for an individual transplant center would lead to various levels of censure, including termination of the center's transplant license. At the time of its announcement, CMS believed that transplant programs would likely have little difficulty complying with these guidelines and that the cost to each transplant center would be less than $56,000 in the first full year after implementation of the new guidelines and less than $21,000 for each subsequent year.

This new initiative by CMS with its emphasis on outcomes was consistent with a trend in recent years of efforts by various groups—including government, insurance companies, and business groups—to improve the quality of medical care. Because health care in the United States consumes 17% of the gross domestic product, the perception was that the health care industry had performed an insufficient job of improving outcomes and reducing costs.

Consequences of the new Conditions of Participation

Within the first 12 months of implementation of the new CMS rule, several large transplant programs were flagged for lower observed versus expected outcomes. Studies have found that programs serving a high-risk patient population were more likely to be flagged by the Scientific Registry of Transplant Recipients for poor outcomes. Such publicly available data were reported in the mainstream media (e.g., *LA Times*) in harsh terms.

The CMS policy was the center of much controversy and debate, mainly having to do with the statistical models that were used. It was felt that large, urban transplant centers were the target of flagging, because they had a higher-risk population and therefore, more aggressive management protocols. These reports led to an exaggerated perception of the programs' struggle and failure in the public eye. They also eroded the public's confidence, as well as community and industry partnerships.

Programs reported a loss of referrals, because private insurance payers were using the program-specific reports to identify centers of excellence and directing patients away from programs with poor posttransplant outcomes. Programs that entered into systems improvement agreements with the CMS reported significant expenses related to the process, disruption of their program activities, and a decline in transplant volumes.

Being under the threat of termination made the noncompliant programs more conservative in their patient selection, and they removed many patients from the waitlist. There is some evidence that the patients affected by this approach are from disadvantaged backgrounds: living in low-income areas farther away from the centers, and lacking high school education.

As a result of these negative trends, several new amendments to the current system are being designed and discussed.

Other costs to transplant programs

In its CoP, Medicare also recommended use of dedicated professionals such as social workers and clinical coordinators to evaluate and manage transplant patients. To meet the demands of data acquisition, monitoring, analysis, and reporting, additional personnel are hired by the programs. Similarly, there is increased reliance on transplant-trained physicians from nephrology, infectious diseases, endocrinology, etc., to help manage transplant recipients. Hiring these multidisciplinary teams adds costs to the programmatic infrastructure.

Since 2005, there has been a steady decline in living donor transplants. The causes for this decline remain elusive. Even the novel paired donor exchange program, which gained popularity after 2009 and contributes to as much as 25% of all living donor transplants at some centers, is not able to match the peak achieved in 2005. Successful donor exchange programs are resource intensive and have complex logistics. Medicare reimbursement has not changed over the past 10 years, regardless of the increase in complexity of the patients. The logistics and staffing to maintain such programs require substantial costs to transplant centers and most likely result in net loss over time. The only major incentive for programs to perform these transplants is to provide a life-saving service to an otherwise disadvantaged population and avoid having to utilize deceased donor kidneys for these patients.

Many experts in the field believe innovative treatments such as "desensitization treatments" have been relatively stagnant because of the new regulations. These treatments can potentially provide more access to high-risk individuals but carry the risk of worse than expected outcomes and are therefore not favored.

In summary, the current regulatory environment has affected the function of kidney transplant programs in some adverse ways. Because it is widely acknowledged that transplantation is superior to dialysis both in terms of quality of life and cost savings to the community, revision in the regulations is highly desired. A reimbursement system on the basis of a risk-adjusted payment model is likely to benefit the various stakeholders in the transplantation field (2, 3).

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Practice Pointers

How Do Patients with FSGS Present?

By Ellen McCarthy, MD

Focal segmental glomerular sclerosis (FSGS) is the most common primary glomerular disease, resulting in heavy proteinuria and leading to ESRD. The term FSGS refers to a morphologic pattern of injury rather than a distinct disease. Sclerotic lesions are present in <50% of all glomeruli on light microscopy (hence focal), with <50% of the glomerular tuft affected (hence segmental). FSGS can be primary or secondary to a variety of physiologic, anatomic, or environmental factors. Primary FSGS is characterized by rather acute onset of heavy proteinuria, with other features of the nephrotic syndrome, renal impairment, and resistance to treatment in many patients. The incidence of FSGS as cause for ESRD is increasing (1). Spontaneous remission rate is low (<5%) and progression to ESRD within a few years (5 to 8 years) of diagnosis is common (50%) in patients who do not respond to therapy (2).

There are several histologic variants described in the Columbia classification: FSGS not otherwise specified (NOS), collapsing, tip, perihilar, and cellular variants (3). In spite of initial hopes, this classification, although useful, has not consistently correlated with natural history or response to therapy. FSGS NOS is the most commonly seen variant. In general, collapsing variant has the worst prognosis, whereas tip lesion has the best prognosis and is often responsive to immunosuppressive therapy.

How can one differentiate primary FSGS from secondary FSGS?

FSGS describes the histologic appearance of glomeruli and is nonspecific with regard to etiology of primary or secondary in origin. Differentiating primary from secondary FSGS is important, in that doing so will have significant implications in treatment of patients (4). Primary FSGS is a diagnosis of exclusion, and the onus is on the clinician to carefully examine the clinical, biochemical, and pathologic data to rule out secondary FSGS.

FSGS can be secondary to acquired or congenital reduced renal mass (single kidney, oligomeganephronia, renal dysplasia, etc.), adaptive changes (such as increased body mass), genetic mutations, drug toxicity, infections, or the course of other glomerular diseases. Nephrotic syndrome, defined as proteinuria greater than 3.5 g/24 hours and hypoalbuminemia, is more commonly seen in patients with primary FSGS. Patients with secondary FSGS are more likely to have nephrotic-range proteinuria without the marked hypoalbuminemia and edema of nephrotic syndrome. Patients with primary FSGS and those with HIV-associated nephropathy, collapsing glomerulopathy, or drug toxicity, including toxicity of pamidronate, often have nephrotic syndrome and rapid progression of renal failure, whereas other forms of secondary FSGS may have only proteinuria and exhibit a slower course. Hypertension may be seen more commonly in patients with secondary FSGS.

Important data are obtained from kidney biopsy, in that tip and collapsing lesions are seen in primary FSGS, whereas perihilar lesions more commonly characterize secondary FSGS. However, no histologic subtype is diagnostic for primary FSGS, and secondary causes must be excluded, irrespective of subtype. On electron microscopy (EM), diffuse foot process effacement characterizes primary FSGS, whereas sporadic or patchy foot process effacement is more common in secondary FSGS. It is, therefore, important that EM be obtained if at all possible in patients with suspected FSGS.

The pathologic processes occurring in primary and secondary FSGS are likely different as well. Primary FSGS is believed to result from diffuse podocyte injury with podocyte loss and formation of synechiae. Secondary FSGS is characterized by glomerular and podocyte hypertrophy, with podocytes becoming attenuated in covering a larger area of the basement membrane, although with preservation of foot processes.

Treatment differs in primary versus secondary FSGS. Patients with secondary FSGS should be treated conservatively, with an emphasis on good BP control, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, weight loss if above healthy weight, smoking cessation, low-sodium diet, and control of hyperlipidemia with a statin in particular. These same measures should be taken in patients with primary FSGS in addition to immunosuppressive therapy if indicated. Patients with secondary FSGS do not respond to immunosuppressive therapy and are exposed to potential harm if treated unnecessarily with these medications.

What are important familial forms of FSGS in adults?

Just as a wide variety of nongenetic factors can lead to the histologic lesion of FSGS, a broad range of genetic mutations can also lead to FSGS (5). Inherited forms of FSGS consist of autosomal recessive disorders that usually present in infancy or early childhood and autosomal dominant disorders that usually have a later onset. Although there are patients with recessive disorders not presenting until adulthood, most familial FSGS encountered in adults is caused by autosomal dominant disorders. The most common mutation leading to FSGS in adults is in the gene for inverted formin 2. FSGS can also be caused by mutations in the actin crosslinking protein α-actinin-4 or the cation channel TRPC6. Patients with genetic forms of FSGS rarely respond to immunosuppressive drugs, although information about response to treatment is largely anecdotal. Recurrence of proteinuria after renal transplantation is uncommon.

Although not a Mendelian form of FSGS, variants of the apolipoprotein A1 gene confer increased risk of developing FSGS. These variants are found in patients of African descent. Homozygotes or compound heterozygotes for the G1 or G2 allele have a seven- to tenfold increased risk of developing FSGS.

What are important familial forms of FSGS in adults?

The goal of nonspecific and specific therapies in both primary and secondary FSGS is to minimize proteinuria. Achieving complete remission is ideal, although even partial remission portends a better renal outcome (6). Treatment guidelines for primary FSGS were recently published by Kidney Disease Improving Global Outcomes (KDIGO) (7). Treatment for primary FSGS in adults is largely on the basis of controlled trials done in children and consists of immunosuppressive therapy. Initial treatment consists of high-dose corticosteroids for up to 16 weeks or until complete remission; about 50% of adult patients respond to corticosteroid therapy. Calcineurin inhibitors (CNIs) can be used in patients resistant to or intolerant of corticosteroids. The role of alkylating agents in treatment of adults with FSGS has not been substantiated; likewise, the use of mycophenolate mofetil has not been substantiated. Rituximab has been studied in small uncontrolled series in adults with mixed results. Despite the fact that the KDIGO guidelines report that there is insufficient evidence to support recommending alkylating agents, rituximab, or mycophenolate mofetil in adults with FSGS, it is possible that there may be a role for these agents as well as others, including galactose or adrenocorticotropic hormone, in patients who are resistant or intolerant of recommended therapies.

What is the pathogenesis of FSGS?

FSGS is a podocytopathy, and injury to the podocyte (glomerular epithelial cell) is thought to be the central and initiating event in disease development (8). The nature of the initial insult is unclear, but in some patients, it may be related to a circulating injurious substance or substances, or perhaps, absence of a protective substance.

Podocyte injury is first seen on EM in the form of foot process effacement and cell body attenuation. Injury may then lead to cell death and/or detachment from the glomerular basement membrane (GBM), a resultant decrease in podocyte number, and subsequent mismatch between podocytes and GBM to be covered. Podocyte depletion is a critical event in the pathogenesis of FSGS. Some weeks to months after the initial insult, tuft adhesion between parietal epithelial cells and denuded GBM is seen by light microscopy. It has been suggested that misdirected filtration then can occur between the glomerular capillary and the area outside Bowman's space and along the tubular basement membrane. The role of parietal epithelial cells in FSGS, whether protective or injurious, is currently actively debated.

The podocyte is a terminally differentiated cell, and therefore, hypertrophy (not proliferation, which is quite limited) is the response to increase in glomerular size seen in obesity and reduced nephron number, such as that seen in patients with history of low birth weight. Glomerular hypertrophy as well as increased fluid flow shear stress that occurs in glomerular hyperfiltration may each play an important role in development of secondary FSGS.

What is the role of circulating factor or factors in recurrent FSGS?

Proteinuria recurs in renal allografts of about 30% of patients with primary FSGS in native kidneys. The risk of recurrence in subsequent allografts is over 80% if there has been a previous recurrence (9). There are several observations that strongly implicate a circulating substance that initiates disease recurrence in these patients: 1) proteinuria may be seen within minutes or hours of transplantation, 2) plasmapheresis or immunoadsorption may reduce recurrent proteinuria, 3) injection of patient serum or plasma or fractions thereof into experimental animals results in increased proteinuria, 4) proteinuria that spontaneously resolved was seen in a neonate borne of a mother with FSGS, and 5) absence of proteinuria in a second recipient who received an allograft from an initial recipient with native FSGS and rapid recurrence of proteinuria after transplantation. The identity of possible circulating factors has been earnestly sought for decades. Possible candidates include T cell-derived mediators, soluble urokinase-like plasminogen activator receptor, or cardiotrophin-like cytokine factor 1 (10).

Risks of recurrent FSGS include young age and rapid progression to advanced chronic kidney disease. There are intriguing data to suggest that presence of circulating factor(s) before transplantation may predict recurrence.

Recurrent FSGS can lead to graft failure, although aggressive treatment may prolong the life of the allograft.

What is the treatment of recurrent FSGS?

Treatments that can be effective for primary FSGS, such as angiotensin blockers or CNIs, have not shown great efficacy in the treatment of recurrent FSGS. Plasmapheresis has been the cornerstone in treating recurrent FSGS as well as prophylaxis against recurrence in both children and adults (11). It is considered standard of care currently, despite lack of randomized, controlled trials. Plasmapheresis is generally well tolerated and safe. Plasmapheresis alone will not induce remission in most patients and must be used in conjunction with other interventions. Such interventions include aggressive use of CNIs.

Rituximab is emerging as a promising agent in treating recurrent FSGS, although thus far, data are limited to small studies and numerous case reports. Published reports suggest a 79% response rate when rituximab is used in recurrent FSGS. It is postulated that the direct effect of rituximab on the podocyte via modulation of sphingomyelinase activity accounts for the benefit seen in decreasing proteinuria. Randomized, controlled trials are needed to elucidate the role of rituximab in treatment of recurrent FSGS in adults and children. Agents, such as CNIs and rituximab, may alter podocyte responses as well as act on the immune system. Study is ongoing to understand the mechanism of these agents.

Future directions

Several areas in the diagnosis and treatment of primary and recurrent FSGS are in need of high-quality randomized, controlled trials. It is of vital importance to distinguish primary from secondary FSGS, because many subsequent treatment decisions are on the basis of this initial dichotomy. Accurate categorization would prevent exposing patients to immunosuppressive drugs who are unlikely to benefit from them. Identification of accurate and reliable biomarkers would enhance our ability to determine whether a patient has primary or secondary FSGS and enable appropriate therapy. Likewise, identification and characterization of causative factors in the circulation would ultimately allow for diagnosis, treatment, and prevention of recurrence. The recommended treatment protocols for FSGS in adults are largely on the basis of studies done in children. Verification of applicability to adults seems important. It is crucial to be able to predict which patients are at risk for recurrence of FSGS to institute preventive and/or therapeutic measures in a timely fashion. Finally, evidence-based treatment protocols for recurrent FSGS are needed. These gaps in our understanding of FSGS pose an exciting challenge for those of us who study the condition and care for those patients afflicted with FSGS (Table 1).

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Table 1: Treatment of FSGS

Treatment target	Intervention	Primary FSGS	Secondary FSGS	Recurrent FSGS after transplant
All FSGS				
Hemodynamic changes	ACEI, ARB, PGE2 receptor blockade	Yes	Yes	Yes
Hemodynamic changes and vascular metabolism	Normalize systemic BP, stop smoking	Yes	Yes	Yes
Hemodynamic changes, inflammation	Treat metabolic syndrome, obesity, hyperlipidemia	Yes	Yes	Yes
Podocyte injury				
Podocyte integrity	Calcineurin inhibitor	Yes		Yes; protect synaptopodin and actin cytoskeleton
Podocyte integrity, immunosuppression	Prednisone, ACTHAR gel	Yes		Yes; glucocorticoid and melanocortin receptors
Immunosuppression	Mycophenolate	Yes		Potential (often used in routine immunosuppression)
Podocyte integrity, immunosuppression	Rapamycin	Potential		Potential; inhibit mTOR, protect autophagy
Podocyte integrity, immunosuppression	Rituximab	Yes		Potential; inhibit sphyngomyelinase
Circulating Focal Sclerosis Permeability Factor (FSPF)				
Down-regulate synthesis of FSPF	Immunosuppression/cytotoxic agents/stem-cell transplant	Potential		Potential
Remove FSPF	Plasmapheresis, plasma exchange, or lipopheresis	Potential		Yes
Bind or block FSPF/interaction with receptor	Galactose; a specific antibody or cytokine trap	Potential		Potential
Inhibit signaling such as Jak/STAT activation	Kinase inhibitor	Potential		Potential

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, PGE2 = prostaglandin E2, FSPF = FSGS permeability factor.

Meet the new *JASN* Editor-in-Chief: **Josephine P. Briggs**

Josephine P. Briggs, MD

ASN has named the new editor-in-chief of the *Journal of the American Society of Nephrology (JASN)*: Josephine P. Briggs, MD. Dr. Briggs, who is Director of the National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH), will serve in the editorship for six years beginning Jan. 1, 2018.

Asked about her outlook and plans for *JASN*, Dr. Briggs said: "The scope of the journal should continue to be the entire range of renal research from the most basic—structural biology, cell biology, kidney physiology—through the entire translational process—and extending to the most applied, including observational studies, epidemiology, clinical trials, and health services research." She said she considers *JASN* the premier influential specialty journal in nephrology and plans to enhance the journal's eminence with a focus on publishing the best primary research in the field.

Dr. Briggs' credentials in clinical medicine, research, and editorial work are notable. After earning her medical degree at Harvard Medical School, she completed her residency training in internal medicine and nephrology at the Mount Sinai School of Medicine, New York, NY, where she was also a fellow in clinical nephrology. She worked as a research scientist for seven years at the Physiology Institute at the University of Munich in Germany.

Dr. Briggs joined the NIH in 1997 as Director of the Division of Kidney, Urologic, and Hematologic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases, where she oversaw extramural research activities. In 2006, she accepted a position as Senior Scientific Officer at the Howard Hughes Medical Institute, and in 2008 returned to NIH in her current director position, according to her NCCIH biography. She is also a member of the NIH Steering Committee, the most senior governing board at NIH. Earlier, she served as interim director of the NIH Precision Medicine Initiative Cohort Program, a new model for research with a goal of enrolling at least 1 million participants.

Dr. Briggs has participated in the editorial boards of *Seminars in Nephrology, Hypertension, Kidney International, and the American Journal of Kidney Diseases*. She also served as deputy editor of the *Journal of Clinical Investigation*. Dr. Briggs's research interests include the renin–angiotensin system, circadian regulation of blood pressure, and policy and ethical issues around clinical research.

Her longtime interest in communicating findings effectively to fellow physicians, scientists, and other health care providers also extends to informing the public. In 2014, Dr. Briggs received the ASN John P. Peters Award in recognition for her many and varied contributions to improving the lives of patients and to fostering the understanding of the kidney in health and diseases. She was also the recipient of the Department of Health and Human Services 2014 Secretary's Award for Distinguished Service.

Fellows Corner

Political Musings on a March

By Rob Rope, MD

On January 21, 2017, I, as a blessed research fellow without call responsibilities, participated in a local Women's Day march. The messages of the day, in the context of the last few months of political rancor, had led me to consider how our country's political and social trajectory might affect a patient's health.

Ask a nephrologist what the top causes of CKD are, and you will assuredly hear, "diabetes and hypertension," perhaps followed by a comment about the proverbial hypertension chicken and egg. But what drives diabetes and hypertension? One might say obesity, but what about poverty and social disparities? What about the growing distance between food production and ingestion, or the discovery of "vanishing caloric density"? What about our demanding work culture and love affair with the car? Or our failing education system, which contributes to poor dietary and lifestyle choices? What about the growing connections between climate change and kidney disease (1)?

Political and societal changes are intimately linked to the diseases we see today (e.g., the rise of diabetes and obesity or the historical reduction of disease related to poor sanitation or violent and traumatic deaths). So, what is the number needed to treat or harm for these changes compared to prescribing lisinopril or paying for frequent hemodialysis? I do not know if there is an answer, but I certainly have many questions. Should politics, in its broadest sense, inform my life as a physician? Should what I support as a person, through my actions, discussions, and votes, be influenced by the experiences of my patients as well as that of myself and my family? Should medical students learn about politics and policy alongside physiology, cultural competency, and ethics? After all, our health is affected by policy and our culture, not just our blood pressures and statins.

If providers are to set examples for their patients by eating right, not smoking, and exercising, should we also advocate for sociopolitical changes? Should we be emphasizing renewable energy, implementing green nephrology principles, advocating for a living wage or universal healthcare, and addressing work-life imbalances or the failures of "renal rehabilitation" (2,3)? Many in our country value, by character and/or necessity, hard work and productivity. Should we advocate also for such quaint values as mindfulness, community service, or home-cooked meals?

I wonder, for example, if raising the minimum wage would mean more of our patients could afford healthier food, or perhaps work less and thus afford the time to prepare food at home or go for a walk. Advocating prevention, taking a holistic view of health, and effecting change through political action may improve outcomes more effectively in the long term than focusing on disease management. What if that meant prioritizing the war on poverty, overhauling our education system, or changing our capitalist culture?

In some cases, the connection between politics and our patients' health is less opaque. To me, obstetric nephrology means preeclampsia and decisions regarding immunosuppression in pregnancy. I have never seen, and hope never to see, acute renal failure from septic or hemorrhagic illegal abortions (4). The legal right to birth control and safe abortions has made this possible in the US and many developed countries. On a different note, the experience of an undocumented immigrant in California, with access to outpatient ESRD care, is in stark contrast to one in Texas who is ineligible for outpatient treatment and therefore shows up to the emergency department routinely for emergency dialysis (5). Politics, not medicine, made that choice.

After the truly noble advocacy of patients and providers, our government made a historic decision to cover ESRD care broadly in this country. This not only allowed the extension of life-saving therapy, but also arguably created the specialty of nephrology as we now know it.

The questions and musings presented here aside, politics and advocacy are like medicine: there is something for everyone. Of note, a recent perspective in the *New England Journal of Medicine* outlines some issues to consider if you are interested in joining a legislative advocacy organization (6) (also see Table 1). In the end, what motivates you? Is there time in your life to reach out? I am looking for time in mine, although certainly not always finding it. However, if we as providers can't do it, with our higher education and financial security, how can we expect our patients to?

Rob Rope, MD, @renalpolitics, is a former Stanford fellow and former editor of the Kidney News *Fellows Corner column.*

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Table 1: Resources to stimulate potential advocacy engagement

Medical organizations	• Physicians for a National Health Plan – http://www.pnhp.org/ • Physicians Committee for Responsible Medicine – http://www.pcrm.org/ • American Medical Association – https://www.ama-assn.org/
Renal organizations	• American Society of Nephrology – https://www.asn-online.org/policy/ • Renal Physicians Association – http://www.renalmd.org/Our-Advocacy-Work/
Environment and nephrology	• Green Dialysis Network (http://www.greendialysis.org) • UK-based Center for Sustainable Healthcare, Green Nephrology Network

The inclusion of these resources is not an endorsement on behalf of the writer or ASN. Rather they are included as potential educational resources for readers.

Industry Spotlight

Diabetes Drug News

New research shows that an existing type 2 diabetes drug also significantly decreases the risk of other serious conditions. A study published in the *New England Journal of Medicine* demonstrated that the drug canagliflozin, in addition to helping to treat 2 diabetes, also seems to significantly lower the risk of cardiovascular disease (CVD) and kidney disease in patients with diabetes, *Reuters* reported.

Renal-related events specifically were to be measured as part of a post-approval safety exploration of canagliflozin (brand name Invokana and Invokamet, Janssen Pharmaceuticals, a Johnson and Johnson company). The published research combined the new CANVAS-Renal Study, designed to be compared directly with data from the original CANVAS study of 2009 before canagliflozin had achieved FDA approval. The renal outcomes were progression of albuminuria and "the renal composite," a compilation of measures including a 40% reduction in eGFR sustained for at least two consecutive measures, the need for renal replacement therapy (dialysis or transplantation), or death from renal causes.

Progression of albuminuria occurred less frequently among participants assigned to canagliflozin than among those taking placebo (89.4 vs. 128.7 participants with an event per 1000 patient-years). The composite outcome of sustained 40% reduction in eGFR, the need for renal replacement therapy, or death from renal causes occurred less frequently among participants in the canagliflozin group than among those in the placebo group (5.5 vs. 9.0 participants with the outcome per 1000 patient-years).

With regard to the drug's safety, in late May 2017, the FDA issued a Drug Safety Communication about the increased risk of leg and foot amputations with canagliflozin.

A new trial will test a drug candidate in people with type 1 diabetes and diabetic kidney disease (DKD). GKT831 is the lead drug candidate of French biopharmaceutical company Genkyotex. Labiotech.eu noted that an earlier trial of GKT831 for DKD had focused on both the liver and the kidney. The new, dedicated kidney trial will take place in Melbourne, Australia, at the Barker Heart and Diabetes Institute.

Elias Papatheodorou, CEO of Genkyotex, explained to Labiotech that "regarding DKD, we feel that we did not dose long enough. Instead of 12 weeks, we will be treating for 48 weeks. We will also test a higher dose, since we saw a very good safety profile." As part of the study, patients will receive 200 mg of oral GKT831 or placebo twice daily for 48 weeks, the company announced.

Cancer Drug Roundup

Now that positive results from Phase 3 clinical trials have been reported, the European Medicines Agency (EMA) has recommended approval for tivozanib through the EMA's Committee for Medicinal Products for Human Use (CHMP), as treatment for advanced renal cell carcinoma (RCC). The drug, brand named Fotivda (AVEO Pharmaceuticals, Cambridge, MA) could receive a final decision for approval by late August or early September 2017. The US Food and Drug Administration approved the drug in 2013.

EUSA Pharma, a specialty pharmaceutical company based in Hemel Hempstead, UK, that has a distribution network in approximately 40 countries around the world, is poised to distribute tivozanib throughout Europe, South America, and South Africa.

"Tivozanib's unique tolerability profile together with the longest progression-free survival, reported in a Phase 3 first line RCC study, have the potential to fill an unmet patient need for better tolerated treatment in this disease," said Michael Bailey, president and chief executive officer of AVEO. Bailey also noted that the AVEO drug may be on track to become part of a future combination therapy in a Phase 2 trial with Opdivo (nivolumab, Bristol-Myers Squibb, New York, NY).

Bailey said that if the European Commission grants marketing approval for tivozanib, this outcome "would trigger a $4 million research and development reimbursement payment from EUSA (to AVEO)" with possible additional payments of up to 12 million.

The National Health Service in England and Wales has joined Scotland in approving the use of cabozantinib for advanced kidney cancer. The drug, marketed as Cabometyx in the United States, is the second drug for the company Exelixis (South San Francisco, CA).

In late June, researchers reported results of a head-to-head comparison of cabozantinib with everolimus (Afinitor, manufactured by Novartis Pharmaceuticals in East Hanover, NJ). They noted that cabozantinib improved rates of progression-free survival, objective response rate, and overall survival compared with everolimus among patients with advanced renal cell carcinoma regardless of nephrectomy status, according to Phase 3 results of the METEOR trial presented at the American Society of Clinical Oncology Annual Meeting.

An *Investor's Business Daily* profile on Exelixis noted the company was confirming the effectiveness of its breakout compound for treating kidney cancer, posting first-time operating profit, and retiring the majority of its debt.

In late June, AstraZeneca and Hutchison China MediTech announced they had initiated a global late-stage clinical trial of the experimental drug savolitinib in a relatively rare type of kidney cancer. The Phase 3 study will test savolitinib in c-MET-driven papillary renal cell carcinoma.

AstraZeneca will pay China MediTech (Shanghai) $5 million, *Reuters* reported.

FDA nixes Pfizer's Epogen biosimilar and requests a fix

For the second time in 2017, Pfizer has received a disappointing letter about its progress toward FDA approval for a biosimilar product similar to the drug Epogen. The root of the problem lies with manufacturing facilities that may produce the biosimilar, not with the safety or biosimilarity to Epogen, Pfizer notes.

In February 2017 Pfizer received a letter from the FDA that warned about particulate matter (cardboard) in some batches of other drugs manufactured in its facility in McPherson, KS, in 2016. The company responded by taking steps to address the concerns.

On May 25, Pfizer received good news: the FDA Oncologic Drugs Advisory Committee (ODAC) voted to recommend the company's proposed biosimilar for approval. "The ODAC's recommendation was based, in part, on the FDA's briefing materials, which concluded that proposed biosimilar epoetin alfa is highly similar to its reference product, Epogen and Procrit (epoetin alfa), and supports a demonstration that there are no clinically meaningful differences in terms of the safety, purity and potency of the product," Pfizer said.

Regarding the reference product for the biosimilar, a generic form is not yet available. Epoetin is manufactured and marketed by Amgen as band name Epogen. Johnson & Johnson subsidiary Janssen Biotech sells the same drug under the name Procrit, per a product license agreement.

Pfizer announced in late June, however, that it had received an FDA Complete Response Letter (CRL) about the company's Biologics License Application (BLA) for its proposed epoetin alfa biosimilar. This CRL relates to matters noted in the FDA's original warning letter issued in February, following a routine agency inspection of Pfizer.

"The issues noted in the Warning Letter do not relate specifically to the manufacture of epoetin alfa," Pfizer wrote in its announcement about the CRL. "This facility was listed as the potential manufacturing site in the BLA (Biologics Licensee Application) for the proposed epoetin alfa biosimilar."

Fierce Biopharma reported that "the agency couldn't approve the biosimilar because the potential manufacturing site in the BLA for the biosimilar was "the same Hospira unit plant which was responsible for an FDA rejection of Glatopa, the highly anticipated long-lasting generic version of Teva's Copaxone."

Cricket Health and American Kidney Fund to Deliver Education, Support

A new program sponsored by a company that develops technology-based solutions for chronic kidney disease (CKD) will give 100 patients access to new formats for care and education.

Cricket Health, based in San Francisco, along with support from the American Kidney Fund, says it will enroll patients through mid-August into the pilot program. The patients and those close to them can connect with multichannel educational content, virtual healthcare opportunities, and an online community of peers. The partners have designed the program so that CKD patients may better understand their treatment options and plan ahead to ensure an orderly transition to advanced care, for those who progress to end-stage renal disease.

"The lack of timely and comprehensive CKD education represents an enormous missed opportunity to increase rates of home dialysis therapies and kidney transplantation among eligible patients," said Vince Kim, co-founder of Cricket Health. "We are excited to work with a leading advocate like the American Kidney Fund to enhance the quality of life for these patients and demonstrate a better way to provide patients the tools and resources necessary to make enduring decisions about the care and management of their disease."

Cricket Health intends to roll the program out to more patients in the future, based on results of this pilot program, the company announced. The program, called Health Options Patient Education (HOPE), lets patients share information with their caregivers, families, and friends. Multi-channel content—such as video, chat, and written information—accounts for differing styles of learning.

Cricket Health states its goal is to reduce the clinical, psychosocial and economic burdens associated with chronic kidney disease. Cricket Health was co-founded in 2015 by CEO Arvind Rajan, a former senior executive at LinkedIn, and Kim, a former general partner at Aberdare Ventures, a healthcare technology venture capital firm.

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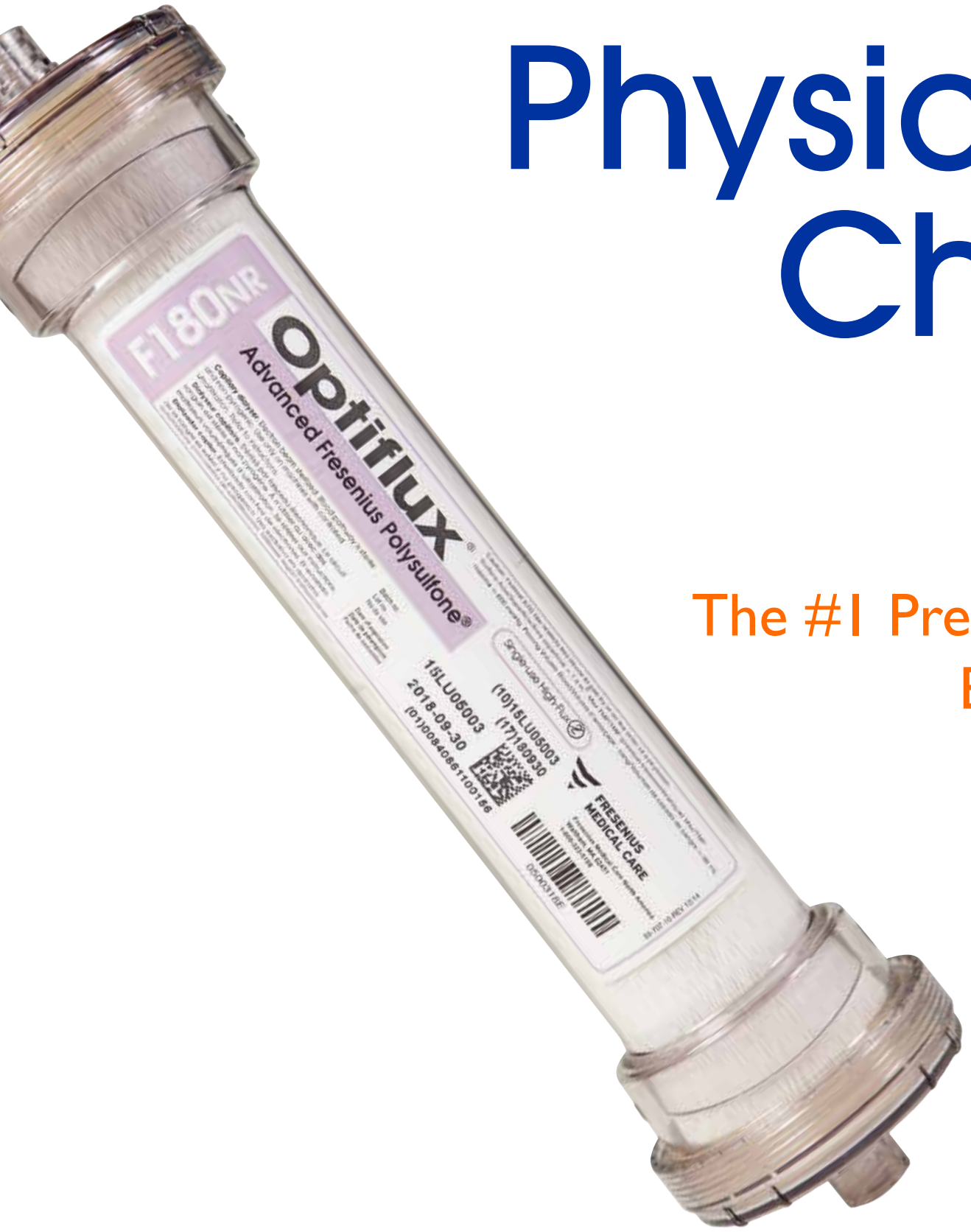

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