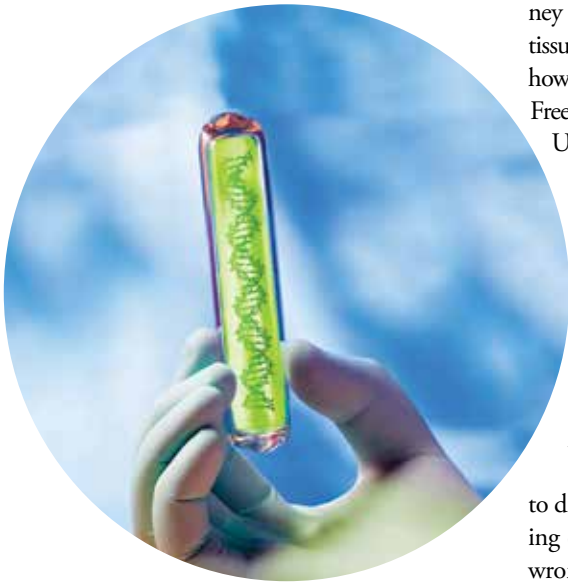


Kidney News

May 2017 | Vol. 9, Number 5

Gene Editing May Offer Clues, Future Treatments for Kidney Disease

By Bridget M. Kuehn



Using an array of cutting edge tools and techniques, researchers around the country have achieved an incredible feat. They have learned to grow living 3D, kidney-like structures called kidney organoids in the laboratory using human cells.

“What we are trying to do with the kid-

ney organoids is not only grow new kidney tissue, but learn fundamental things about how kidneys work,” explained Benjamin Freedman, PhD, an assistant professor at the University of Washington in Seattle.

These kidney organoids are grown from human stem cells, which can be coaxed into recreating some of the structures found in human kidneys. A powerful gene editing tool called CRISPR is often being used to insert kidney-disease-linked mutations into organoids allowing scientists to study how mutations contribute to disease.

Together these technologies promise to drive major advances in the understanding of normal kidney function, what goes wrong in kidney disease, and how it might be remedied. With further advances, the technology might one day allow scientists to grow transplantable kidney tissue in the laboratory, alleviating the shortage of kidneys for transplantation. But these potential advances are not without controversy. The CRISPR gene editing technology and its potential to modify human genes has sparked an ethical debate and led for some calls for limits on its use.

A powerful tool

Prior to the development of kidney organoids, scientists struggled to find a way to study living kidney tissue in the laboratory. For example, kidney tissue collected from the body quickly loses its structure under laboratory conditions and such tissue can't be used to recreate disease progression, Freedman said.

“The models we've had haven't been able to recreate the complexity of the kidney,” explained Freedman. But kidney organoids, while still much more primitive than a real kidney, are complex enough to recreate some of the kidney's key features. The CRISPR technique makes these organoids even more valuable by allowing scientists to customize their genetics.

Scientists have been cutting genes out of DNA or inserting genes into DNA using various techniques for 2 decades, said Benjamin Humphreys, MD, PhD, chief of the division of nephrology at Washington University School of Medicine. “But that technology was cumbersome and required a high level of expertise,” Humphreys explained. It also was expensive. A single

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Sickle Cell Trait Linked to Lower HbA1c, Higher Risk of ESRD

Two recent papers draw attention to some clinically significant health risks for patients with sickle cell trait (SCT)—an inherited blood disorder affecting up to 10% of African Americans.

African Americans with SCT have lower levels of hemoglobin A1c—which may place them at risk of delayed or missed diagnosis of diabetes and predia-

betes, according to a study in the *Journal of the American Medical Association* (*J Am Med Assoc* 2017; 317:507–515).

“These findings suggest that HbA1c may systematically underestimate past glycemia in African American patients with SCT and may require further evaluation,” according to the report by Mary E. Lacy, MPH, and Wen-Chih Wu, MD, of Brown University and colleagues.

The second study, reported in the *Journal of the American Society of Nephrology*, finds that SCT is associated with a twofold increase in the incidence of end stage renal disease (ESRD). That research was led by by Rakhi P. Naik, MD, MHS, of Johns Hopkins University and Marguerite R. Irvin, PhD, of the University of Alabama at Birmingham (*J Am Soc Nephrol* 2017; doi: 10.1681/ASN.2016101086).

Because testing for SCT is already widely performed in newborn screening and other settings, Naik, Irvin, and co-authors believe their findings “may have immediate implications for policy and

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Gene Editing

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experiment using older gene editing techniques might cost \$500 to \$5000 dollars, while CRISPR costs just \$30 (Miyagi A, et al. *J Am Soc Nephrol* 2016; 27:2940–2947).

The CRISPR technique commandeers a defense mechanism bacteria use to ward off viruses. In bacteria, CRISPR are repetitive sections of DNA that are used to store genes from viruses that have previously infected the bacteria. These viral DNA sequences allow the bacteria to seek out and destroy those sequences in future viral attackers. Scientists have learned to insert genes they want to target into these repeated sections of bacterial DNA to use this defense mechanism to find a gene in human DNA. When the CRISPR finds the targeted gene it uses an enzyme called Cas9 to cut the DNA and remove the target gene. It can also be used to replace the targeted gene with another one.

“The power of CRISPR is that it is a highly robust, precise, and cheap way to change genome sequences,” Humphreys said.

It is so easy to use that any laboratory can use it, and one of its fastest growing applications in kidney disease research is in developing customized organoids, Humphreys said. For example, scientists have used CRISPR to insert the mutated gene that causes polycystic kidney disease into the stem cells used to grow kidney organoids and these organoids grow cysts (Freedman BS, et al. *Nat Comm* 2015; 6:8715). The process can be carefully studied in the laboratory to better understand how the mutated gene causes this to happen and to test drugs that might stop or reverse the process, Freedman explained.

Hundreds of miniature organoids can also be produced and used to test the effects of numerous drugs simultaneously.

“You can do it on a scale you couldn’t do in animal models,” Freedman said.

Mice can also be genetically engineered to have mutations linked to kidney disease, but there are drawbacks to trying to study human diseases in mice. Mice are different from humans genetically and physiologically so they may not respond the same way humans will.

“Many findings in mice don’t carry over in humans,” explained Joseph Bonventre, MD, PhD, chief of the renal unit and director of the bioengineering division at Brigham and Women’s hospital in Boston. “They are good models, but there are situations where mouse models are not ideal.”

Organoids also open the door to personalized studies or drug testing. A kidney organoid could be grown with a genetic mutation thought to be causing a particular patient’s kidney disease. That would allow scientists to verify whether the suspect mutation, in fact, causes the disease and, if so, what might be done to modify its effects, according to Freedman.

“All of us have many mutations that could look like they could be causing disease,” explained Freedman. But sometimes the wrong culprit has been identified. Additionally, organoids would allow scientists to systematically test what various genes do in the kidney to find previously unsuspect-

ed genes that might contribute to kidney disease.

“We are at the dawn of the genetics era for kidney disease,” Freedman said. “Not only can we discover the genes—we will be able to fix those genes. It will take us into the next era of being able to understand kidney disease and how to treat it.”

Drawing the line

The ease of using CRISPR and its power to alter human genetics has, however, raised some ethical concerns about the use of the technology. For example, could the technology be used to create “designer babies” or lead to unexpected harms?

To address these emerging concerns, the National Academies of Sciences in 2015 hosted a summit and convened a committee of international research, regulatory, and ethics experts to address the need for oversight of such research. The committee released its report in mid-February 2017. The report clearly draws a line arguing that use of CRISPR in research should be limited to studies that aim to develop interventions that treat or prevent disease or disability, and should not be used to enhance humans.

“That has long been a concern [with gene editing],” said Jeffrey Kahn, PhD, MPH, director of the Johns Hopkins Berman Institute of Bioethics in Baltimore and member of the committee. “The tools are now better such that potential enhancement uses are closer in terms of the ability to do it. It’s more pressing.”

Drawing that line won’t always be easy, Kahn noted. Some applications of the technology will clearly fall into the treatment and prevention realm, for example, using CRISPR to edit the mutated genes that cause muscular dystrophy to boost muscle in affected individuals. But he noted that if the US Food and Drug Administration (FDA) approved such treatments it might be hard to prevent them from being used to boost muscle in individuals without the disease.

“It’s hard for the FDA to do that,” Kahn said.

For research using gene editing tools on most cell types, the committee found that existing safeguards and oversight of human research are sufficient. But the committee argued more oversight and discussion is necessary before gene editing of reproductive cells, which could result in genetic alterations in subsequent generations. Additionally, the committee argued that gene editing that could be inherited should only be done under a limited set of circumstances, for example, only when no other option for having a healthy genetic child is possible. It’s a more permissive stance than the call for a complete moratorium on inheritable gene editing that emerged from the 2015 meeting.

“What the report did is open up the door a crack to the possibility that under strict restrictions scientists could alter human embryos in select circumstances,” Humphreys said. “They made it very clear that a tremendous amount of research and discussion needs to take place.”

Although it is possible such technology could be applied to human embryos with

mutations that cause kidney disease, Freedman thought it was unlikely to be used for this purpose.

“I don’t see [CRISPR] germ line editing being of major utility in kidney disease,” Freedman said.

He explained that already parents affected by polycystic kidney disease could use in vitro fertilization and have their embryos screened for disease-causing mutations and choose not to have affected embryos implanted. But he said it is important to discuss these potential applications.

“It is good to have the conversations and to keep them in perspective with the general moral and ethical challenges that face society,” Freedman said.

Kahn and his colleagues hope their report provides guidance for governments around the world grappling with how to regulate these emerging tools. But he noted it is just the start of the process. Additional international meetings to discuss these issues are scheduled to take place in Beijing and the United Kingdom.

“It’s the beginning of that conversation,” Kahn said. “It’s a global discussion that’s ongoing.”

The CRISPR gene editing technology and its potential to modify human genes has sparked an ethical debate and led for some calls for limits on its use.

Potential treatments

Most ongoing work using CRISPR is still in the preclinical phase, but many in the field expect CRISPR-driven treatments for kidney disease may be on the horizon.

“We are in a time of very rapidly advancing knowledge concerning ways to manipulate and potentially correct genetic disease,” Humphreys said.

Currently, clinical trials are underway using CRISPR technology to edit mutations that cause blood diseases. Some genetic kidney diseases might also be targeted for treatment with CRISPR, noted Humphreys. Mutations that cause polycystic kidney disease might be one potential target for such gene therapy. Another potential target might be mutations in the APOL1 gene that contribute to kidney failure in African Americans. But first some major technical challenges must be overcome.

There is currently no efficient way to deliver CRISPR to the billions of cells in the kidney, explained Freedman. There are also still safety concerns that need to be fixed; for example, occasionally CRISPRs can miss their target and disrupt the wrong gene.

“We know gene editing technologies are getting better, but they do have off-target effects,” Freedman said. We don’t want to inadvertently cause disease when trying to cure disease.”

Another potential use of CRISPR is to enable scientists to grow transplantable kidneys in animals. For example, at a very early stage in development CRISPR could be used to turn off the genes that help grow a pig’s kidney, then human cells could be

transplanted and coaxed into growing a human kidney.

“It’ll be interesting to see how close you can get to growing a human organ in an animal,” said Freedman. “It could be a powerful source of organs.”

But doing that won’t be easy. The animal’s immune system is likely to attack the growing organ and a human’s immune system will likely reject an organ with traces of animal cells, Freedman said.

There are also concerns that transplanting organs grown in pigs into humans could transmit retroviruses embedded in the pig’s DNA to humans, noted Humphreys. But one laboratory has shown that CRISPR can be used to inactivate these viruses (Yang L, et al. *Science* 2015; 350:1101–1104). The CRISPR technology might also be used to edit immune genes in the pig or humans to prevent immune reactions, he said.

Organoids themselves might one day offer a source of kidney tissue for transplant. The vision would be to harvest cells from a patient with kidney disease, use CRISPR to correct any disease-causing mutation, then grow healthy transplantable kidney tissue in the laboratory. This could mitigate

the need for powerful immunosuppressive drugs since the cells would be the patient’s own and less likely to trigger rejection.

“In the long term, we would like to grow functional tissues and implant them back into the patient from which the organoid cells were derived,” Freedman said.

But Bonventre noted much work is still needed to develop organoids that integrate vasculature, nervous system cells, and immune cells.

“We need to have additional breakthroughs,” he said.

In the shorter term, Bonventre suggested that hybrid devices combining laboratory-grown tissue with mechanical systems might offer a rudimentary replacement kidney that is better than dialysis, even if it doesn’t completely replace all of the kidney’s abilities. Medications could be used to control potassium or pH, for example.

“A combination of engineering and cellular systems will get us there in a way that requires little medication support,” Bonventre said. He said with enough resources he predicts there could be significant progress toward hybrid kidneys over the next 5 to 10 years.

Although much work remains before gene editing or transplantation of laboratory-grown tissue can be used to treat patients, scientists working in the field are optimistic that research using these technologies will lead to new therapies.

“In the long run, both organoids and editing will lead to new medications that are more effective and safer than transplants or dialysis,” Freedman said. ●

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Sickle Cell Trait

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treatment recommendations.”

Twofold increase in ESRD for African Americans with SCT

Naik and colleagues analyzed the association between SCT and ESRD in a sample of 9909 self-reported African Americans from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Sickle cell trait was present in 7.5% of the sample. Rates of other genetic variants associated with kidney disease were 12.8% for *APOL1* high-risk genotypes and 2.5% for hemoglobin C trait.

There were some significant baseline differences among groups: SCT carriers had a lower estimated glomerular filtration rate and higher urine albumin-to-creatinine ratio. Chronic kidney disease (CKD) prevalence was 36.8% in the SCT group, compared to 25.9% for individuals with hemoglobin C, and 25.1% for those with neither trait.

At a median follow-up of 6.5 years, ESRD incidence was 8.5 per 1000 person-years for those with SCT, compared to 3.9 per 1000 for those with hemoglobin C trait and 4.0 per 1000 for those with neither trait. On adjusted analysis, the hazard ratio for ESRD was 2.03 for individuals with SCT. Hemoglobin C trait was unrelated to ESRD incidence.

For individuals with *APOL1* high-risk genotypes, ESRD incidence was 6.6 per 1000 person-years. There was no interac-

tion between SCT and *APOL1* status. The association between SCT and CKD was stronger among those without hypertension: odds ratio 2.94, compared to 1.63 in those with hypertension.

“Our study demonstrates that SCT is not only a significant genetic risk factor for the development of ESRD in African Americans, but also that it confers a similar degree of risk for ESRD as *APOL1* high-risk genotypes, which are currently the most widely recognized genetic variant associated with kidney disease in this population,” Naik and colleagues write.

The findings suggest “an additional genetic basis” for the higher rate of advanced kidney disease among African Americans. While the mechanism of kidney damage is yet unclear, some evidence points to vascular damage and hypoxia in the renal medulla—the same pathway leading to nephropathy in patients with full sickle cell disease.

SCT linked to lower HbA1c

Lacy, Wu, and colleagues analyzed data on 4620 African American participants from two community-based cohort studies: the CARDIA Study and the Jackson Heart Study. The participants, mean age 52.3 years, made up to three study visits including concurrent measures of fasting glucose and HbA1c.

These measures were analyzed for association with SCT, which was present in 7.9% of those studied. Participants with SCT were older, had lower kidney function, lower HbA1c, and a higher reported rate of diagnosed diabetes.

On analysis using generalized estimat-

ing equations, mean HbA1c was 5.72% in those with SCT, compared to 6.01% in the non-SCT group. The average difference of 0.30% was present across a range of fasting or 2-hour glucose levels.

On adjusted analysis, SCT was associated with a mean 0.38% reduction in HbA1c at a given fasting glucose concentration. The difference was greater at higher fasting and 2-hour glucose concentrations.

The presence of SCT was associated with potentially missed cases of diabetes, defined as HbA1c of 6.5% or higher. Diabetes prevalence was 3.8% for participants with SCT versus 7.3% for those without. By comparison, rates of self-reported diabetes diagnosis were 17.2% and 14.7%, respectively.

The SCT group also had a lower prevalence of HbA1c of 5.7% to less than 6.5%, consistent with prediabetes: 29.2%, compared to 48.6% for those without SCT.

“These findings suggest that HbA1c may systematically underestimate past glycemia in African American patients with SCT and may require further evaluation,” Lacy and coauthors write.

The authors discuss some ways in which SCT might affect the accuracy of HbA1c. Red blood cells may be shorter-lived in people with SCT, thus reducing the time available for hemoglobin glycation. It’s also possible that the presence of HbS might interfere with common HbA1c assays. (The authors note that their study used high-performance liquid chromatography techniques that have not shown clinically significant interference in those with HbA1c).

The most common hemoglobin variant in the US population, SCT is found in 8%

to 10% of African Americans with SCT, compared to less than 1% of white Americans. The American Society of Hematology notes that SCT may be present in 1 to 3 million Americans, and in more than 100 million people worldwide.

The new studies suggest that the presence of SCT may signal some important clinical associations.

“These findings raise the possibility of benefit from incorporating information on hemoglobin variants into clinical guidelines for interpreting HbA1c values for screening and diagnosis of prediabetes and diabetes,” Lacy and colleagues write. They call for further studies to assess whether delays in recognizing prediabetes and diabetes could account for the reduced kidney function in African Americans with SCT.

In a previous study (*J Am Med Assoc* 2014; 312:2115–2125), Naik and colleagues found an increased risk of CKD, lower kidney function, and higher albuminuria in African Americans with SCT. The authors note that, in contrast to *APOL1* genotype, testing for SCT is routinely performed in newborn screening, athletic examinations, and pregnancy counseling.

“Genetic counseling about ESRD risks could allow for early CKD screening and risk factor modification such as smoking cessation, weight loss, hypertension/glucose control, and avoiding nephrotoxic agents,” Naik and coauthors write. They also raise the possibility that early intervention—including renal protective medications and disease-modifying sickle cell therapies—might be beneficial for African American patients at high risk for SCT-related kidney disease. ●

Findings

Osteoporosis Drugs for CKD Patients—Jury’s Still Out

Currently available data cannot establish the safety and efficacy of osteoporosis medications for patients with chronic kidney disease (CKD), concludes a meta-analysis in *Annals of Internal Medicine*.

A systematic review identified 13 randomized trials, including a total of 9850 patients, evaluating the clinical benefits and safety outcomes of osteoporosis medications in CKD patients. The medications studied were bisphosphonates, teriparatide, raloxifene, and denosumab. Outcomes of

interest were bone mineral density (BMD), fractures, mortality, and adverse events. Kidney transplant recipients were enrolled in six trials, postmenopausal women with CKD in four, and patients with CKD stage 3 to 5 or on dialysis in three.

There was moderately strong evidence that bisphosphonates slow BMD loss of the lumbar spine in kidney transplant patients. However, the effects in the femoral neck and other areas were unclear. There were conflicting or insufficient data on the ef-

fects of bisphosphonates on BMD in CKD patients who had not received a transplant. Bisphosphonates’ effects on fracture risk and safety outcomes were unclear.

There was low strength of evidence that raloxifene prevents vertebral fractures, but not that it increased BMD. Evidence on the effectiveness of teriparatide and denosumab was weak, with some data suggesting an increased risk of adverse outcomes.

Bone weakening and fractures are potential complications of CKD, leading to

recommendations for treatment with medications for osteoporosis. But the new review shows an overall weak body of evidence for the safety and effectiveness of osteoporosis medications across the spectrum of CKD. The authors discuss the need for further studies, especially in patients with CKD stage 3 to 5 [Wilson LM, et al. Benefits and harms of osteoporosis medications in patients with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2017; DOI: 10.7326/M16-2752]. ●

High Rate of AKI in Children with Diabetic Ketoacidosis

Nearly two-thirds of children with type 1 diabetes hospitalized for diabetic ketoacidosis (DKA) will develop acute kidney injury (AKI), suggests a study in *JAMA Pediatrics*.

The researchers reviewed all DKA admissions at a Canadian children’s hospital from 2008 to 2013. Complete medical records were available for 165 patients. The median age was 10.6 years; 54% were female. Three-fourths of patients were newly diagnosed with type 1 diabetes. Fifty-five

percent were transferred from another hospital and nearly one-fourth were admitted to the ICU. Median initial pH was 7.1 and serum bicarbonate level 7.0 mEq/L.

Based on Kidney Disease/Improving Global Outcomes criteria, 64.2% of patients developed AKI while in the hospital. Of affected children, 34.9% had AKI stage 1, 45.3% had AKI stage 2, and 19.8% had AKI stage 3. Two patients required hemodialysis.

On adjusted analysis, factors associ-

ated with the development of stage 2 or 3 AKI were serum bicarbonate less than 10 mEq/L, adjusted odds ratio (OR) 5.22; and higher initial heart rate, OR 1.22 per increase of 5 beats/min. Odds of stage 1 AKI were increased for children with an initial corrected sodium level of 145 mEq/L or greater, OR 3.29. There were no deaths in children with or without AKI.

The study documents a high prevalence of AKI among children with DKA admitted to a tertiary care children’s hospital.

This risk appears higher in children with laboratory evidence of volume depletion and severe acidosis. The authors call for prospective studies to clarify the risk factors and long-term implications of AKI in pediatric DKA—a group of young patients who already have a high long-term risk of diabetic nephropathy [Hursh BE, et al. Acute kidney injury in children with type 1 diabetes hospitalized for diabetic ketoacidosis. *JAMA Pediatrics* 2017; doi:10.1001/jamapediatrics.2017.0020]. ●

Patient Engagement

Kidney News Editorial Board member Edgar V. Lerma, MD, FASN, interviewed Kevin Fowler, recipient of a preemptive kidney transplant in 2004, and ASN President Eleanor D. Lederer, MD, FASN, about patient engagement in healthcare. Kevin is the Vice-Chair for the Kidney Health Initiative's Patient and Family Partnership Council, and is President of "The Voice of the Patient, Inc."



Kevin Fowler



Eleanor D. Lederer

What is patient engagement? How does a physician define it, and how does a patient define it? I would think that each has a different perspective of what it is and what it truly entails.

Kevin Fowler: To define patient engagement, we also need to define patient-centered care. In 2001, the Institute of Medicine (IOM) generated a seminal report, "Crossing the Quality Chasm" (1). In the report, the IOM defined patient-centered care as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions." Healthcare that is designed and delivered in a patient-centered manner provides an environment for patient engagement to flourish.

For a working definition of patient and family engagement, I use the definition given in *Health Affairs* (2): "Patient and family engagement as patients, families, their representatives, and health professionals working in active partnership at various levels across the healthcare system—direct care, organizational design and governance, and policy making—to improve health and healthcare. Although we use the term patient engagement for simplicity's sake, we recognize that those who engage and are engaged include patients, families, caregivers, and other consumers and citizens."

Dr Lederer: I suspect that there are many different ideas about what defines patient engagement, even among physicians, ranging from the most simple, adherence to a therapeutic regimen, to the most complex, patient-driven healthcare decision-making. Perhaps patients, too, have a similarly wide range of definitions of patient engagement.

Most patients and physicians probably envision some middle ground. I can speak most comfortably about the physician standpoint, because I have fortunately never really had a significant chronic illness. I see a wide range of patient engagement from nearly complete acceptance of decision-making by the physician to presentation of a list of questions and desired therapeutic options to be discussed. Patient engagement to me implies active interest in the disease process, therapies, and outcomes. It means that patients question my testing and recommendations to understand what is going on and how it will affect their lives. It means that the patient feels free to disagree with my recommendations and is willing to have a discussion.

What are the benefits of patient engagement to patients?

Kevin Fowler: There is evidence that patient engagement improves healthcare outcomes. I firmly believe my successful health outcomes are partially attributable to my engagement with my health. By being engaged, I feel that I have some control over my health. I influence the health dimensions within my control: adherence, wellness behaviors, specialty appointments, etc. I achieve a certain peace by controlling what I can control.

Most important, patient engagement shapes my priorities. Health is a priority in my life. I exercise routinely and meditate daily because I have learned how these behaviors enable me to weather and navigate the stormy seas associated with a chronic disease. Although our healthcare system does not reward these behaviors, I have seen their power to strengthen my physical and mental health.

Dr Lederer: The benefits of patient engagement are extraordinary. A patient who asks about medication side effects, looks up his/her disease on the internet, joins a support group, and engages in continuous follow-up provides the elements for an incredibly satisfactory and mutually beneficial relationship. A patient who understands the pros and cons of therapeutic choices and who understands that a therapy may not have the desired result in all cases allows for a safe and nonthreatening relationship.

What are the benefits of patient engagement to the greater nephrology community?

Kevin Fowler: In the short term, patient engagement would help nephrologists lower costs, improve outcomes, and achieve greater professional satisfaction while improving productivity and efficiency.

In the long term, it would raise expectations for patients. As patients advance across their level of being actively involved in their own care, they will learn that the field of nephrology innovation has stalled. Studies looking at improving quality of life for dialysis patients and transplant recipients have been limited, and 5- and 10-year mortality outcomes remain unchanged. Moreover, the treatments for kidney disease have been very limited. For example, although I am at least the 4th generation in my family with polycystic kidney disease (PKD), there are still no approved treatments for the disease. Since my children have a 50% chance of inheriting PKD, I want them to face a brighter future.

What are the potential downsides of patient engagement?

Kevin Fowler: There are some patients for whom their condition limits their ability to be engaged. For example, a patient with a severe stroke may have limits placed on their cognitive functioning or their ability to communicate. In these situations, patient

engagement may occur through their caregiver. In other situations, there are patients who have no fixed limits on their engagement, and they choose not to engage. As the saying goes, "You can lead a horse to water, but you cannot make it drink." I have seen situations like this. Even after a major health event, some patients do not view their health as a priority.

Dr Lederer: The potential downsides of patient engagement, at least in my mind, are nearly nonexistent. Some physicians may become irritated when patients come in with information that they have gleaned from the internet, Dr. Oz, or neighbors. Some patients have very strong feelings about how they view the medical profession. They may wish to use only "natural" remedies. They may not wish heroic, cumbersome, or expensive therapies for a variety of reasons. I view these events as opportunities for education and deepening the relationship, developing trust, and education.

What organizations are leading the way in patient engagement?

Dr Lederer: There are several organizations that are promoting patient engagement. There are support groups and foundations for many illnesses, including kidney diseases, where patients interact and where more seasoned and knowledgeable individuals mentor newer members in disease process, questions to ask the doctor, side effects of medications, and the like. The Kidney Health Initiative (KHI), a partnership between the American Society of Nephrology and the Food and Drug Administration, has actively engaged patient groups to develop patient-centered projects to guide clinical trials in aspects of kidney diseases that are important to patient quality of life, not simply medically defined outcomes, such as cardiovascular death. Death, of course, is a key outcome, but patients with kidney diseases on the whole have a deeper appreciation of their mortality than we give them credit for, and often, they are asking for relief from day-to-day symptoms, not freedom from death.

Kevin Fowler: I recommend two organizations and one periodical:

- The Institute of Patient and Family Centered Care (IPFCC): The IPFCC was formed in 1992, and its mission is to integrate Patient and Family Centered Care into healthcare organizations. This will help you think about creating a sustainable environment and strategy for patient engagement.
- Kidney Health Initiative: KHI's Patient Family Partnership Council is integrating the IPFCC principles in order to develop a patient engagement strategy for kidney disease patients.
- *Health Affairs* February 2013 issue: The entire issue is dedicated to patient engagement.

What do you think is key to successful patient engagement? What are the various ways and means by which successful patient engagement is carried out?

Kevin Fowler: The foundation for patient engagement exists in the trust between the patient and their physician. Trust is developed based upon mutual respect, honest and clear communication, and alignment on the care plan. I have had excellent relationships with my various specialists. I have viewed my physicians as coaches and teachers. Patient engagement occurs when both the patient and the care team are aligned on treatment goals—it's about teamwork, learning, and activation.

Dr Lederer: Enabling patient engagement takes many forms. The first step is the establishment of an open line of communication in the office, by phone calls, and by electronic medical record–assisted messaging. Making yourself or another member of the healthcare team available for quick consultation is another way to communicate to the patient that “we want you to be part of your medical care.”

What are some of the barriers to patient engagement?

Kevin Fowler: Strategically, the number one barrier is that healthcare has never been designed for patients. While the Patient Protection and Affordable Care Act has made great strides in placing the patient at the center of care, the US has a long way to go.

The delivery of kidney care in the US also has a long way to go. Although passage of Medicare ESRD legislation in 1973 assured dialysis access to all patients, the policies have provided reimbursement incentives for ESRD rather than prevention or care coordination. This has not really changed in almost 44 years.

In the short term, the number one priority to increase patient engagement is for patients to understand their GFR. As everyone knows, less than 90% of patients with CKD stage 3 know their kidney function. This has to be improved as soon as possible if we want to truly have meaningful conversations about patient engagement. Granted, there are limitations with the CKD classification system. However, from a public health perspective, it is unacceptable that patients at risk for kidney disease do not know their kidney function.

Dr Lederer: I identify two significant barriers to patient engagement. Time is the first. Office visits are rushed. It is only human to feel hassled if you are running behind in clinic and a patient or family member pulls out a legal pad full of questions. Days can be long. Coming back to the office and seeing a list of patient phone calls to answer can be daunting. The second barrier is the invisible wall that patients and physicians erect to detach themselves from each other. How many times a day in clinic do I hear a patient say, “I didn't want to bother you with this” or “I know you are really busy but...?” And I can't help but think to myself: Why are you afraid to ask your questions? Are you worried that I will consider you a “difficult” patient? This barrier takes time to crumble and comes only with trust. Once that trust is established, then even if you forget to answer a patient's phone call, the response by the patient is not “you are too busy for me”; the response is more likely to be “she just forgot, I will call again.”

How have you benefited from patient engagement?

Kevin Fowler: Tremendously!

Although I was given the best treatment option with a preemptive kidney transplant, my kidney function has exceeded the expectations of my transplant nephrologists. I believe that is partially attributable to my lifestyle changes posttransplant. On average, I exercise 30 minutes daily five days a week. I practice daily meditation, and I write in a journal. I developed these habits after struggling with depression posttransplant. Through trial and error, I learned that these habits create strong mental health while maintaining optimal cardiovascular function. I learned through experience that strong mental health is key when dealing with the uncertainty of a chronic disease.

When I was diagnosed with prostate cancer, my physician recommended that I pursue surveillance rather than active treatment. I asked my physician for a second opinion, and asked him to take my case to a Tumor Board. The Tumor Board then recommended treatment. This led to another odyssey because I was receiving conflicting opinions on the best treatment option. Ultimately, I made my treatment selection with the help of a transplant nephrologist outside of my health system. I arrived at this decision by asking lots of questions, and leveraging all of my contacts.

Patient engagement has enriched my practice immeasurably. When patients are willing to talk about why they agree or disagree with a decision that you have made, you begin to learn who they are and vice versa.

—Dr. Lederer

How have patients benefited from patient engagement? Discuss some examples.

Dr Lederer: Patient engagement has enriched my practice immeasurably. When patients are willing to talk about why they agree or disagree with a decision that you have made, you begin to learn who they are and vice versa. In my experience, patients who take a greater part in their decision-making are more invested in their care. I see that commonly with dialysis decisions. I like to start discussing renal replacement therapies early and repeatedly, emphasizing that I want the decision to be theirs, not mine. When the time comes for fistula formation, peritoneal dialysis catheter placement, or evaluation for kidney transplantation, the patient with whom I have discussed these options on several occasions seems much more accepting of the next steps. I have had many patients come to me with side effects of medications that they were experiencing and had researched on the internet or the medication information insert. We were able to change the medication to something that they tolerated better instead of having the patient simply stop the medication.

Why did you become engaged in your health?

Kevin Fowler: Growing up, I saw my mother suffer on dialysis. While my mother suffered greatly, she approached it with a wonderful spirit.

When my primary care physician diagnosed me with PKD and informed me that I would eventually experience renal failure, I thought I would have to start dialysis first. That prospect scared me deeply.

When I had my first appointment with my nephrologist, he suggested that I have a preemptive kidney transplant, and thus avoid dialysis completely. When he thought I would be a good candidate for preemptive dialysis, I thought I had won the lottery. I learned that less than 3% of kidney transplants are preemptive. Combined with the fact that our children were 4 and 6 at the time of my transplant, I was very motivated to live a healthy lifestyle, and to see my children grow up.

Over time, I learned that there is still a lot that is unknown about transplantation. Armed with that knowledge, I have learned to trust my instincts. For example, on several occasions, I have not felt well due to oncoming fever. Rather than waiting for the fever to develop, in consultation with my transplant team, I have been admitted to the hospital for the treatment of infections. In this way, the infections were resolved early without severe consequences.

Why did you become engaged in your patients' health?

Dr Lederer: I became engaged in my patients' health when I began to realize what having a chronic illness meant to patients and family. When I began to understand what the day-to-day coping with a chronic illness really meant. When I learned what going to the emergency room really meant for the patient and family members: hours waiting in a queue on hard plastic chairs and uncomfortable stretchers.

I have had patients tell me that, after they take their diuretic, they don't leave the house for 2 hours. They don't take their diuretic before a clinic visit, because they would have to stop by the side of the road several times.

I have had diabetics tell me that they don't go out to eat with their friends anymore, because they get dizzy when they stand up, they perspire heavily whenever they eat, and more often than not, a meal is followed by sudden vomiting or diarrhea.

Many of my dialysis patients tell me that they have one good day a week, the only day of the week that is not a dialysis day or the day after a dialysis day.

What is your advice to patients?

Kevin Fowler: Preserving my health is one of the top priorities in my life, and my behaviors support this priority. If you have some form of kidney disease, my question to each patient is where does your health stand as a priority? Unfortunately, we take our health for granted until we have a major event.

If you have kidney disease, I suggest making your health one of your top priorities. If you do not become your own advocate for your health, no one will. During my journey I have felt overwhelmed at several junctures. I have been able to stay the course because my health is not just about me but also about my wife Kathy and our children.

Continued on page 8

Patient Engagement

Continued from page 7

I encourage patients to view their nephrologists and care teams as their coaches. I still prepare for my medical appointments with questions for the doctor. When physicians understand that you are engaged with your health, you build respect with your care team and establish the expectation about how you want to be treated. Physicians respect this investment in time because it enables them to help you even more.

What is your advice to physicians?

Kevin Fowler: Recognize that we are in a period of major change in healthcare. Technology is enabling healthcare to be transformed from a paternalistic system to one in which the patient will be the driver of the healthcare system. Granted, we are many years away

from this vision being achieved. Nonetheless, we are in the early stages of this healthcare evolution.

I will give the same counsel that I gave to the FDA at the Patient Focused Drug Development Meeting for transplant recipients. Patients are not a monolithic group but differ in their emotional needs, level of patient activation, unmet medical needs, etc. Many healthcare professionals are under the false impression that an app is the solution to patient engagement. With the exception of one app, I have found virtually no value in apps for my patient engagement.

For any nephrologist seriously interested in patient engagement, the first priority should be understanding their patient population. The patient insights will prove to be invaluable in developing effective patient communication strategies. I have seen too often to count priorities placed on patient engagement solutions first without a deep understanding of the patient community. Patient

insights will inform a patient engagement strategy.

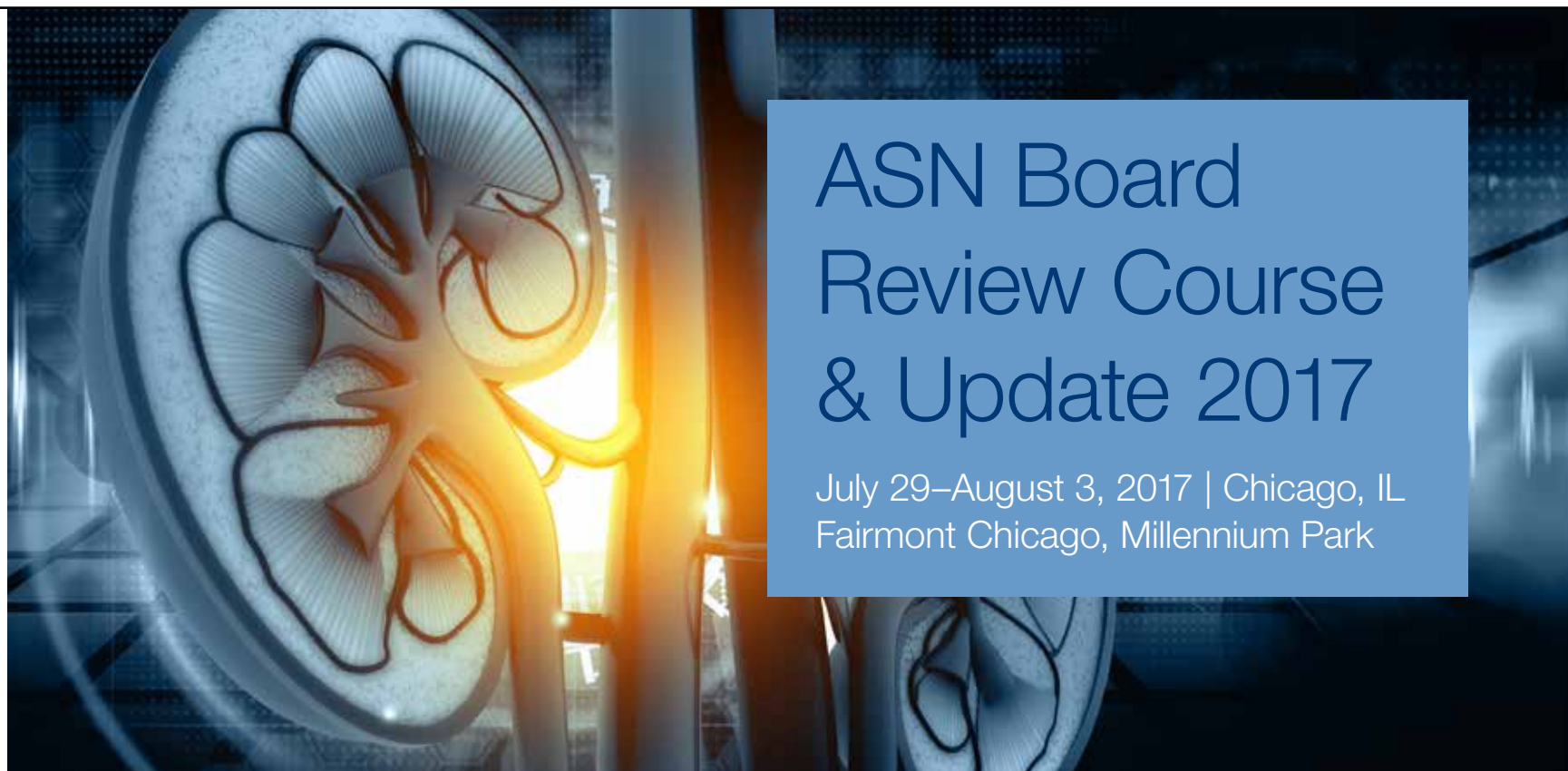
As a physician, what is your advice to physicians? To patients?

Dr Lederer: I am an unapologetic champion for patient engagement. It enriches the relationship between patient and physician, gives the patients more autonomy and control over their lives, and likely leads to better outcomes. ●

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Policy Update

By David L. White, Rachel Nell Meyer, and Zachary Kribs

A “tumultuous” 2017 in Washington

The first four months of 2017 have been nothing short of tumultuous in the Washington world of health care policy. As a result, the American Society of Nephrology (ASN) Policy and Advocacy Committee (PAAC) members are engaged on numerous policy fronts from efforts to repeal the Affordable Care Act (ACA) to the executive order on immigration and its travel ban to President Donald J. Trump’s budget proposal to cut funding for the National Institutes of Health (NIH) by nearly 20%.

It would be easy to view the current Washington environment as chaotic and feckless, but there has been a great deal more accomplished and moving forward than meets the eye. While ASN and the American Association of Kidney Patients (AAKP) hosted their fifth consecutive Kidney Health Advocacy Day (KHAD) 2017 on March 29, this year was anything but “business as usual.” The ASN PAAC also met for a day-long session on March 28 before KHAD. The following are highlights of what ASN took to Capitol Hill and is currently working on.

Fighting for NIH Research Funding

ASN refused to roll over on massive proposed NIH cuts and delivered that message to over 50 congressional offices during KHAD 2017 and is continuing to do so nearly daily—often with peer societies.

The battle for fiscal year (FY) 2018 was set in early March when the White House released an outline of its forthcoming budget request. The budget proposal contained a heavy-handed \$54 billion worth of cuts to non-defense programs to pay for a similar increase in military and security spending.

In the proposed budget, the Department of Health and Human Services (HHS) received the largest cut, a whopping \$15.1 billion, or 17.9% of its budget when compared to the previous year. HHS is also home to the National Institutes of Health (NIH), which would receive a proportionately large cut of \$5.8 billion, nearly 20% less when compared to the previous year. Applied equally across the NIH, this cut would mean a \$332.8 million reduction in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) budget. Further complicating matters, the Trump Administration unexpectedly requested new spending cuts for all non-defense spending in FY 2017 on March 21.

ASN’s response to these proposed cuts in total was unequivocal in rejecting them and making a strong case for increased research funding. ASN President Eleanor Lederer, MD, FASN, “condemned” the proposed NIH cuts in a public statement issued by ASN on March 17.

Instead, ASN is asking for:

- Special Kidney Program for NIDDK: \$150 million per year for 10 years (new funding)
- \$2.165 billion for NIDDK (in FY 2018)
- \$2 billion increase for NIH (over FY 2017)

Many congressional offices have expressed openness to the idea of raising NIH funds despite President Trump’s budget proposals. More to come.

Protecting and Encouraging Living Organ Donation

ASN and American Association of Kidney Patients members know the value of kidney transplantation and are fighting to protect the rights of living donors and hopefully make the pathway to living donation easier. When both groups joined together for KHAD 2017, they delivered a strong endorsement for the Living Donor Protection Act (H.R. 1270), while asking for cosponsors and passage of this critical legislation. The ASN PAAC has made enacting the Living Donor Protection Act a top legislative priority for ASN in the 115th Congress.

Rep. Jaime Herrera Beutler (R-WA) and Rep. Jerry Nadler

(D-NY) introduced the legislation with the goals of protecting the rights of living donors and ensuring Americans are educated about living donation. The current organ shortage and wait-times to transplantation are growing, as evidenced by the more than 100,000 Americans currently on the wait list. Every 14 minutes a patient is added to the kidney wait list, and 13 Americans die each day waiting for a kidney.

The Living Donor Protection Act of 2017 offers three solutions to alleviate some of the barriers to transplantation faced by patients, their families, and potential living donors:

- Protects donors by ensuring they are not denied or given limited coverage or higher premiums by life, disability, or long term care plans.
- Secures jobs by allowing living donors to take time off work to recover from donation surgery without losing their jobs.
- Educates Americans about living donation by requiring that the HHS Secretary update informational materials regarding new protections for living donors.

The bill is already gaining cosponsors from both sides of the aisle in the House of Representatives. ASN, AAKP, and other kidney and transplant advocacy groups are collaborating to identify a lead Democrat and a lead Republican to introduce the bill in the Senate. Several Senate offices with whom ASN and AAKP met indicated their interest in cosponsoring the legislation when it was introduced.

“ASN commends Congresswoman Herrera-Beutler and Congressman Nadler for their leadership in introducing the Living Donor Act of 2017,” said ASN President Eleanor Lederer, MD, FASN. “More than 40 million Americans have kidney disease, and transplantation is the optimal therapy for those whose kidneys fail. ASN is proud to endorse this important legislation, which will help eliminate barriers and increase access to transplantation.”

CHRONIC Care Efforts Have Bright Prospects

After two years of ASN, the Alliance for Home Dialysis, and other stakeholders working with the Senate Finance Committee and the Finance Committee Chronic Care Working Group, the leadership of both the Finance Committee and the Working Group have introduced the Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act (S. 870), a bipartisan bill to strengthen and improve health outcomes for Medicare beneficiaries living with chronic conditions.

ASN strongly supports the legislation’s proposal to designate the dialysis facility as an originating site for telehealth services for home dialysis patients. Home dialysis—in the form of peritoneal dialysis (PD) or home hemodialysis (HHD)—is an important treatment option that, for some patients, offers significant clinical and quality of life advantages. By expanding home dialysis patients’ flexibility to use telehealth technology to interface with their nephrologists, this bill may help increase access to this important treatment option for patients with kidney failure.

As highlighted by a January 2017 Government Accountability Office (GAO) report, nearly 40 million Americans—roughly 17% of the US adult population—live with kidney diseases. Of these individuals, over 680,000 live with kidney failure, a life-threatening condition that must be managed by dialysis or a kidney transplant. Patients with kidney failure are among the most complex and most expensive patients in medicine, costing Medicare over \$103 billion annually.

“The policies outlined in the CHRONIC Care Act of 2017 that permit the utilization of new and innovative technologies like telehealth, and the elimination of barriers to coordination of care, will provide for improved outcomes of individuals managing kidney diseases, and will also reduce the burden of kidney diseases on the economy,” wrote ASN President Eleanor Lederer, MD, FASN, in a letter to Senate sponsors. ●

ASN Policy and Advocacy Committee Interns in Their Own Words

I had the great opportunity to attend my first ASN public policy committee meeting this month in Washington, DC. The meeting started with a briefing about the current state of health care in the US, as well as a discussion about many hot topics affecting people with kidney disease and the physicians who treat them. The topics discussed felt vital and relevant to what I read about in the news and what I experience in my daily practice. I then had the great opportunity to participate in my first Hill Day. It was exciting to be a part of Team Clambakes and Crabcakes, an homage to our home states of Massachusetts and Maryland. As part of the team, I had the opportunity to learn the art of advocacy from the extremely skilled and eloquent Deidra Crews, MD, Dan Weiner, MD, Mallika Mendu, MD, and David White, our dialysis and transplant veteran. I found my time in Washington to be extremely interesting and exciting. It has definitely inspired me to further pursue my interests in public policy.

This experience highlighted to me the importance of physician involvement in legislation. In the same way that we educate our students, residents, and fellows, it is critical to take that next step to educate our senators and representatives so that patient care and innovation do not suffer.

Lauren Stern, MD, Assistant Professor, Boston University School of Medicine, and ASN Policy and Advocacy Committee intern

As an intern on ASN’s Policy and Advocacy Committee (PAAC) for the year 2017, I participated in Kidney Health Advocacy Day (KHAD) on March 29, 2017. My 1-day experience on Capitol Hill during KHAD was, so to say, equivalent to spending 2 years at a graduate public policy training program—from learning best practices of policy stakeholder engagement during the advocacy training session prior to heading to Capitol Hill, to working alongside seasoned policy experts from the ASN Policy and Advocacy Committee and the American Association of Kidney Patients to present our policy requests to congressional staffers, to sharing our experiences with the kidney community on social media. While these experiences will, no doubt, further my long-term desire to voice the importance of kidney disease to policy makers, sharing our KHAD experiences on social media was probably the most gratifying, at least from the immediate vantage point. Using hashtags pertaining to our key legislative items such as #KidneyAdvocates (general), #YouOnlyNeed1 (Living Donor Protection Act), and #FundKidneyCures (Kidney Research Funding) to tweet about KHAD events and to share our photos, we were able to mobilize the nephrology community to join the urgent fight. I look forward to participating in upcoming ASN advocacy events!

Joseph Lunyera, MBChB, MSc, postdoctoral associate, Duke University School of Medicine Division of General Internal Medicine, and ASN Policy and Advocacy Committee intern



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ABSTRACTS

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Fellows Corner

How to Make Handwashing a Fun Experience For Patients in the Dialysis Unit

By Cheng Chu MD



Cheng Chu, MD

Bloodstream infections (BSI) among hemodialysis patients are among the most challenging problems in dialysis units, and are associated with significant morbidity and mortality (1).

Approximately 37,000 vascular access-related BSIs are estimated to have occurred among US hemodialysis patients with a central venous catheter in 2008, with an average cost per hospitalization of \$23,000 (2,3). A number of factors appear to have contributed to these high rates, and they apply to both dialysis staff and patients; proper gowning and gloving, hand sanitation, high catheter rate, and appropriate skin antisepsis are examples. An overlooked and perhaps the most important modifiable risk factor in this equation is patients' personal hand hygiene. Despite recommendations by the Centers for Disease Control and Prevention (CDC) that all hemodialysis patients should wash their hands pre- and post-hemodialysis, this is not always the case. The potential for cross-contamination between dialysis equipment and vascular access from unclean hands is both real and preventable.

Infection control efforts to date

In 2009, the CDC sponsored a collaborative project to prevent BSIs in 17 outpatient hemodialysis facilities by implementing a set of core interventions (4). Among these interventions, dialysis units were required to perform monthly hand hygiene audits with feedback of findings to clinical staff. After 15 months of intervention, there was a sustained 32% decrease in overall BSIs and a 54% decrease in vascular

access-related BSIs (6). Based on these results, the CDC now recommends a set of bundled interventions to be implemented in all outpatient hemodialysis facilities (Table 1).

Hand hygiene in dialysis facilities

One of the challenges I see in our dialysis facility is that hand washing is perceived as a mundane and repetitive exercise, with no stimulation and little feedback on the quality of the hand washing technique. This often contributes to patients going through the motions, or wholeheartedly skipping the practice altogether.

The reality is that patients are just like everyone else in the workplace: They want to be "patted on the back" for the good job they are doing, and they want acknowledgment from the provider that they are making improvements in their own healthcare decision-making. Only through a cycle of repetitive positive reinforcement can we expect a significant change in behavior that will lead to better healthcare outcomes. There is also evidence to support educational

activities along with feedback of observed hand washing sessions to improve hand hygiene compliance in dialysis units (6).

Quality improvement project

Imagine my surprise when I came across a product known as Glo-germ, which is marketed as a fun and effective way of training hand cleanliness in the workplace. Glo-germ comes in a liquid or powder form that is applied to the hand and glows under ultraviolet (UV) light (simulates germs). The idea is to have patients apply the liquid uniformly on both hands, and then ask them to wash their hands as they normally would along with soap and water. Poor handwashing technique will leave residual stains on the hand, often unseen by the naked eye, but will illuminate under UV light and this illumination can be used as a surrogate measure for quality of the hand wash (Figure 1). As a pilot quality improvement project, I enrolled 20 hemodialysis patients from our dialysis facility and scored them on a scale of 0 to 4 based on the amount of residual illumination that remained

after the initial hand wash. In addition, I recorded the total time spent on each hand washing session. This was followed by a five-minute session of patient education on proper hand washing techniques, demonstrating thoroughness in using soap, deep hand rubbing, and coverage of finger wedges. Many patients were surprised at how poorly they performed on the initial hand wash. A second observation of the same patients occurred one week later with measurement of the same performance indices.

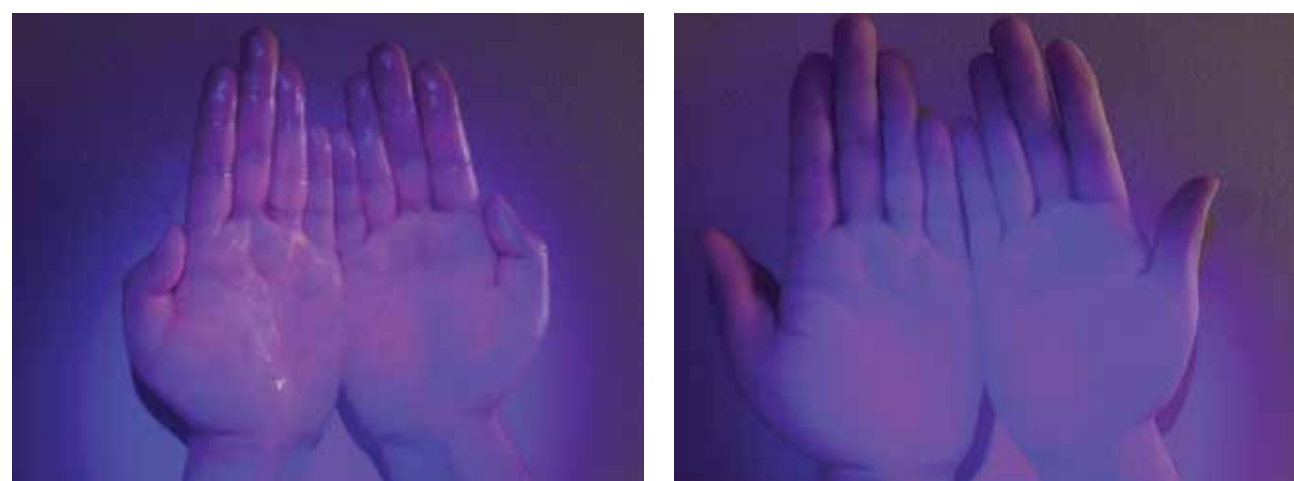
I was not surprised that at one week follow-up, patients were more engaged with the process and displayed better hand washing technique. Many of the patients enjoyed playing with Glo-germ product and were eager to show what they had learned from their previous sloppiness. There was a statistically significant improvement in both hand stain score (i.e., cleaner hands) and time spent with hand washing (Figure 2). Obviously, the project was limited by the small sample size, and larger studies with longer

Continued on page 12

Table 1: CDC recommendations to decrease bloodstream infections in dialysis facilities

Surveillance and feedback	Catheter reduction
Hand hygiene	Chlorhexidine for skin anti-sepsis
Vascular access observation	Catheter hub disinfection
Staff and patient education	Antimicrobial ointment

Figure 1: Demonstration of successful hand washing technique using Glo-germ



A. Poorly washed hands with high residual illumination

B. Well washed hands with no illumination

Fellows Corner

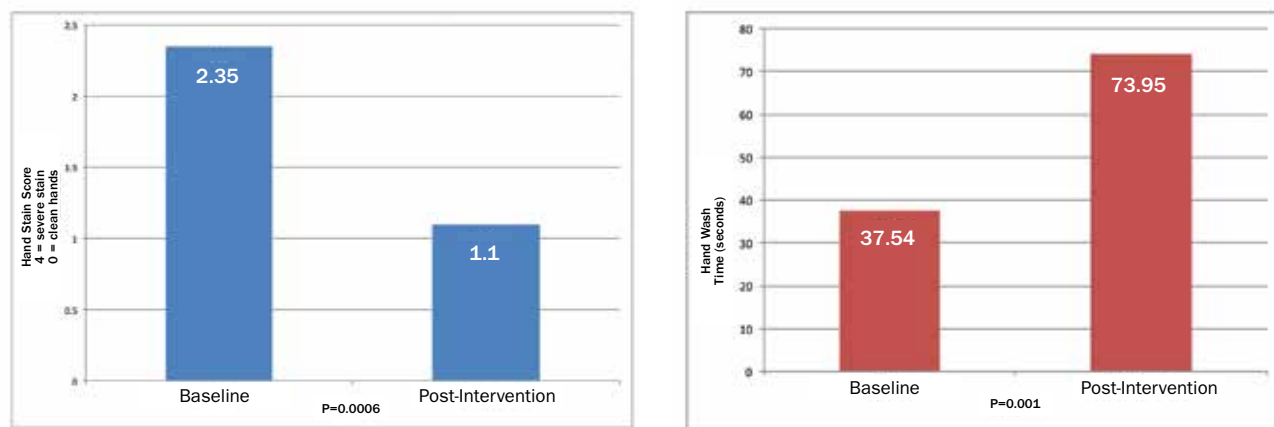
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intervention periods are needed to demonstrate a decrease in infection rates in dialysis units. However, I believe that at the very least, the project has raised awareness of the inadequacy of personal hand hygiene among our dialysis patients, and that more time and energy needs to be devoted to this simple task. ●

Cheng Chu, MD, is a second year nephrology fellow at Saint Louis University.

Dr. Chu was invited to share this research as a part of the Nephrologists Transforming Dialysis Safety (NTDS) initiative. Created through a partnership of the CDC and the American Society of Nephrology, NTDS aims to engage nephrologists as dialysis facility team leaders to target zero infections by actively pursuing the elimination of preventable infections in dialysis facilities through adherence to recommended infection prevention practices, appropriate screening and detection of infections, implementation of clinical protocols, and collaboration with state

Figure 2: Effectiveness of educational intervention on hand washing adequacy



A. Hand stain scores before and after intervention

B. Duration of hand washing before and after intervention

and federal healthcare-associated infection programs.

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Decreasing the Kidney Discard Rate

This article is the second in a series of *Kidney News* articles addressing ways to increase kidney donation on the basis of the deliberations at a December 2016 Rogosin Institute Roundtable on increasing the rate of kidney transplantation.

The first article in this series addressed five ways that the rate of kidney transplantation in the US could be increased to save more lives and provide a better quality of life to those patients with kidney failure: 1) decreasing the need for transplant through health promotion and disease prevention, 2) increasing the supply of deceased donor kidneys, 3) decreasing the kidney discard rate, 4) increasing living donation, and 5) increasing kidney paired donation.

Of these, one immediate and practical solution is to decrease the discard rate of donor kidneys: 20 percent of kidneys procured are never used. Here, we interview 3 experts about why this discard rate is so high and what might be done to decrease it. These panelists include a transplant surgeon (Sandip Kapur, MD), a transplant recipient and patient advocate (Kevin Fowler), a pre-transplant coordinator (Christa Lawson), a nephrologist who is vice chair of the board of a dialysis company (Doug Johnson, MD), and a clinical services director of an organ procurement organization (Deana Clapper).

Why do you think the kidney discard rate in the US is 20 percent?

Kapur: Because of the shortage of organs available for transplant, we are often forced to “push the envelope” when accepting potential organs for transplant. For example, we will consider using kidneys from patients with a history of hypertension or diabetes. At times, these kidneys do not show the presence of significant disease on biopsy, and we are able to transplant the organ(s). Other times, we are forced to discard the organs due to evidence of disease. In other instances, potentially transplantable organs take a long time to be allocated and/or transported to the transplant site, prolonging the cold ischemia time to an unacceptable level.

Johnson and Lawson: We consider the high discard rate to be due in significant part to an unfortunate and unintended consequence of the 2007 Centers for Medicare & Medicaid Services (CMS) Conditions of Participation for transplant programs. The regulations that were put in place to protect individuals receiving a transplant are actually decreasing access to kidney transplantation, because transplant centers have become more conservative in their evaluation of deceased donor kidneys due to fears that use of these kidneys will impair their patient and graft survival outcomes and thereby result in increased oversight or penalties from the CMS.

Clapper: Tennessee Donor Services has been investigating the discard rate over the last year. Tennessee Donor Services has the highest donors per million of any organ procurement organization at 52 donors per million in 2016. Unfortunately, we also discarded 149 kidneys in 2016 compared with 59 kidneys in 2006. Why is this? We have been under the same leadership since the CMS Conditions of Participation was implemented in 2007 and have not changed our process for deceased donor kidney evaluation. We continue to only retrieve kidneys that we consider to be transplantable and work aggressively to see that each recovered kidney is transplanted. In our view, each recovered kidney represents a potential life transformed. However, the potential for CMS audits of and penalties for those transplant centers (especially the lower-volume centers) with outcomes that are not as good as the regulations require makes these centers more apt to discard a higher-risk kidney.

Fowler: I think the high discard rate is a symptom of the fact that the US health care system has not been designed for the patient or the end user of the service. We are in the early stages of a shift from paternalistic health care to one with greater patient collaboration.

What role does federal government oversight of the kidney transplant program play in this high discard rate?

Kapur: Federal oversight has led to risk aversion at some transplant centers due to fears of increased scrutiny if outcomes with the more marginal organs are suboptimal.

Fowler: Although federal oversight is necessary and critical, I believe that it has had a negative effect on risk taking and innovation in transplantation, a field that works on the basis of risk taking and innovation. The commitment to innovation has saved the lives of thousands of people like myself. I believe innovation has stalled because transplant centers are not rewarded for innovation and risk taking but instead, fear being penalized.

Johnson and Lawson: The goal of the new standards for graft and patient survival for kidney transplant centers CMS implemented in 2007 was to improve transplant outcomes. However, we have seen transplant centers become more conservative in their acceptance of kidneys with a high Kidney Donor Profile Index (KDPI) score since the implementation of these standards. Although the standards have been revised twice in the past year, which is a credit to CMS, we continue to see more conservative behavior from transplant programs. In our opinion, transplant centers will be more likely to use higher-risk deceased donor kidneys (those with a KDPI > 85) if the results for these transplants do not adversely affect the program’s evaluation by the CMS.

Schold et al. (1) evaluated the association between transplant center evaluations and kidney transplant volume in 2013. Schold looked at the Scientific Registry for Transplant Recipients performance reports from January 2007 to July 2009 and found that 46 centers had at least one occurrence of a lower than expected patient or graft survival. Of these 46 centers, 72 percent had a decrease in kidney transplant volume, with a mean de-

cline of 22.4 transplants. Centers with low performance scores also had a decrease in the number of standard and expanded criteria donors and the use of kidneys with extended cold ischemia time (Figure 1) (1).

Schold et al. (2) updated this analysis in 2016 and evaluated the effect of a low-performance score evaluation for a transplant center. Although the outcomes for these transplant centers did improve after such an evaluation, this improvement in quality came at a cost, with an increase in times to patient removal from the waitlist (+28.6 removals per 1000 follow-up years, $p < 0.001$) and a decrease in transplant rates (-11.9/1000 follow-up years, $p < 0.001$).

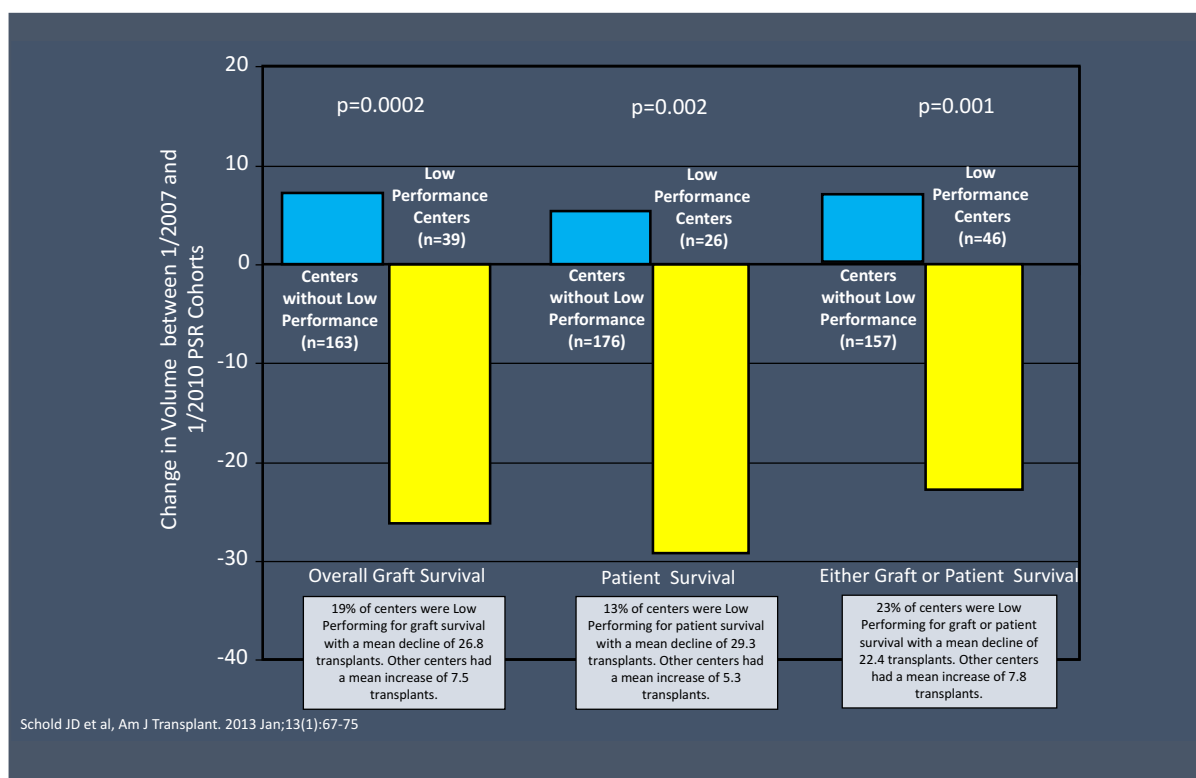
Should some kidneys be discarded, and if so, what justifies discard of a donated kidney?

Fowler: If a potential kidney offers only risk to the patient, the answer is very simple. However, there are a lot of gray areas that need to be discussed between the potential recipient and transplant team. Let me provide an example. If I were to (God forbid) lose my transplanted kidney in 10 years and I had the option of receiving an extended criteria kidney, I would probably accept the potential risks of an extended criteria kidney rather than the known risks of going on dialysis. Because my chances of dying on dialysis in 5 years would be pretty high, I would be willing to take the risk with the suboptimal kidney for the potential benefit that I could gain.

Clapper: Yes. Some kidneys have to be discarded. In my opinion, if no kidneys are discarded, then it is likely that the organ procurement organization is not retrieving the maximum number of potentially transplantable kidneys. We believe that the optimal discard rate is about 15 percent.

Kapur: I agree. Some kidneys must be discarded, because they simply do not meet the standards. Donors with chronic conditions may have scarring of their kidneys that lead to their discard. Kidneys showing poor function when the organ is placed on a perfusion pump, with anatomical issues, or with surgical damage may also have to be discarded.

Figure 1. Change in transplant volume associated with centers’ receipt of low performance evaluation. Abbreviation: PSR, program-specific report. Reprinted with permission from Schold et al. (1).



What can be done to reduce the discard rate?

Fowler: An informed and educated patient population should be able to participate in discussions regarding the risks and benefits of extended criteria donor kidneys. The presence of the patient voice, absent to a great extent in such discussions to date, could take pressure off the transplant centers, organ procurement organizations, and federal oversight agencies.

Kapur: We need to educate transplant centers to take individual donor factors into account rather than just using the “label” that the KDPI score provides (see Bae et al. [3]). In addition, improving current inefficiencies in the allocation system, particularly for the more marginal organs, may help to reduce discard. Providing more opportunities for “open offers” would allow centers to match a marginal organ with the most appropriate recipient without adding to the cold ischemia time. Also, widespread knowledge of a potential “weekend effect” (the risk that fewer kidneys will be used on weekends, because professional staff is either unavailable or not sufficient; see Mohan et al. [4]) might increase awareness of this issue in the transplant community and stimulate corrective action. Every kidney is priceless, and losing one because of inconvenience or logistical issues does not make sense.

Johnson and Lawson: We think that a pilot demonstration should test the use of kidneys with a KDPI score >85 for beneficiaries with close monitoring but without the repercussions of increased scrutiny by CMS of the graft or patient survival outcomes for the transplant program. We simply need to know more about the use of these high-KDPI kidneys. If this pilot was part of a Comprehensive ESRD Care initiative (i.e., in the End-Stage Renal Disease Seamless Care Organization [ESCO]), recipient survival outcomes could be compared with those of dialysis patients. The ESCO presents a great opportunity to carry out this evaluation. We should seize it.

The evidence that transplantation is more advantageous to the patient than hemodialysis, even when transplant center performance is not the highest, is already available. Schold et al. (5) evaluated the Scientific Registry for Transplant Recipients performance reports for July 2003 to December 2010. They found that, even at the lowest-performing transplant centers, the adjusted hazard ratio for patients receiving a transplant was vastly superior to that of those waitlist patients receiving dialysis. Patients receiving a transplant at the lowest-performing centers had an adjusted hazard ratio of 0.40 compared with patients on a waiting list (Figure 2).

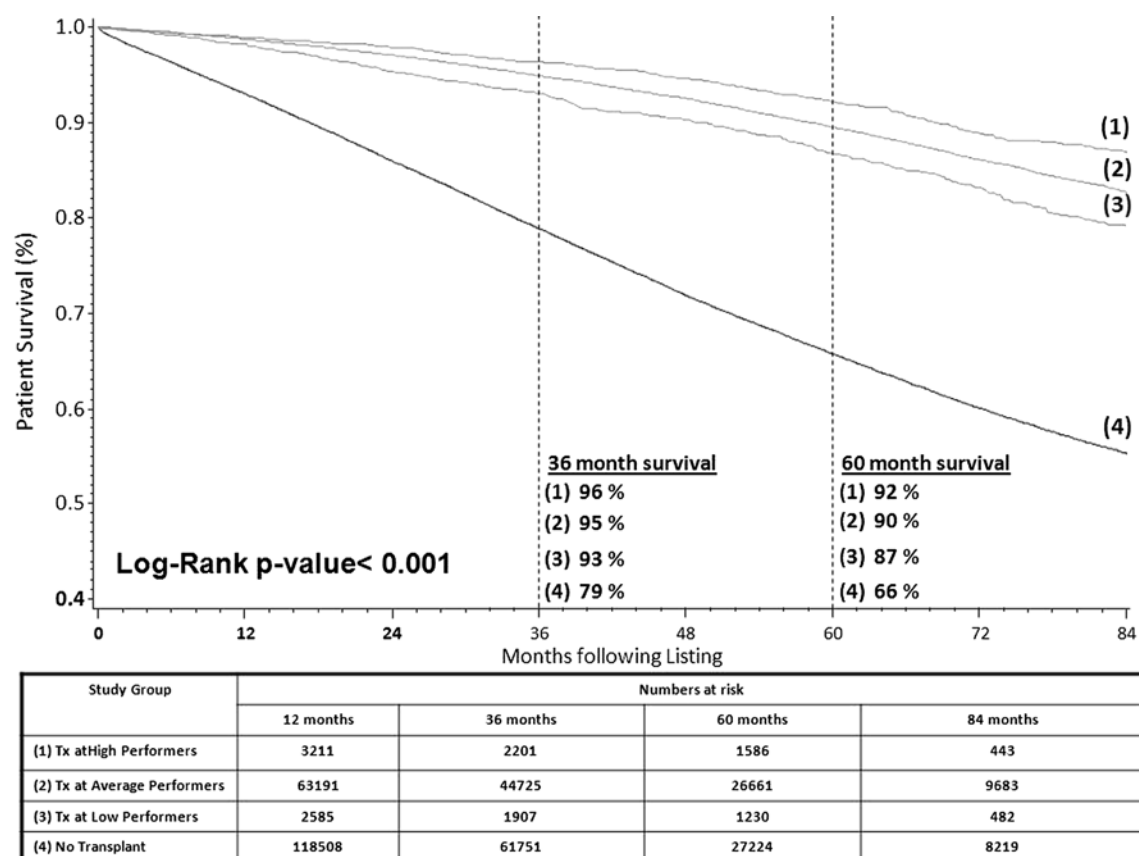
We note, in addition, that patients who receive a kidney transplant in the first year and a half on dialysis have superior survival compared with those who need to wait longer to receive a kidney transplant (6). In other words, the sooner that we can get dialysis patients transplanted, the better.

Is there a role for recipient education in reducing the discard rate?

Kapur: Perhaps. Educating patients about the risks and benefits of high-risk organs, including high-KDPI kidneys, is critically important. Transplant professionals should work to help patients understand the potential benefit of high-risk organs versus the risk of remaining on dialysis.

Johnson and Lawson: Absolutely. The patient should have the right to decide to accept a kidney with a higher-risk KDPI score. It is important to clearly discuss the potential risk of receiving a kidney with a higher-risk score but also very important to allow the patient to have the opportunity to accept this kidney.

Figure 2. Kaplan–Meier plot of patient survival after listing by transplant status and center quality on the basis of deceased donor transplantation at a transplant center with a given performance at the time of listing. Abbreviation: Tx, transplantation. Reprinted with permission from Schold et al. (5).



Fowler: Yes. There is a lack of patient education on the meaning of the assessment of deceased donated kidneys and the risks that they present: standard criteria, extended criteria, etc. Transplant centers are stretched thin now and do not have the capacity to educate patients on this aspect of transplantation. My suggestion would be to assign authority and accountability for patient education to one entity. In this way, it would be easier to measure the progress of patient education efforts.

Is there any research being done that could reduce the discard rate in the future?

Kapur: Recent analyses of the effect of the new kidney allocation system (KAS) and its outcomes might help to influence centers to improve their transplant numbers. We need to know just how well the new KAS system is working in terms of risk scores and outcomes.

Johnson and Lawson: We would like to implement a pilot allowing use of kidneys with a KDPI score >85 (mentioned above) in Dialysis Clinic Inc.’s six ESCO locations, encompassing a total of 2350 patients. If our pilot program is approved, we hope that the ESCOs could be a means to allow more patients on dialysis to benefit from a kidney transplant by using kidneys that have a higher likelihood of being discarded. If the outcome data show that this approach is beneficial to patients in relation to both survival and quality of life, it is our hope that this process could be applied across the country.

In summary, the donor kidney discard rate is too high. Decreasing this discard rate is both practical and achievable in the near future. Doing so will not only benefit patients in terms of quality of life and survival but also decrease health care costs. Achieving the desired lower rate of discard requires multiple efforts that include pilot relaxation of the current KDPI standards in a controlled manner with data collection and analysis; encouragement and not penalization of transplant center efforts to increase use of expanded criteria donor kidneys, now called high-KDPI kidneys (again with

data collection); education of patients regarding the risks and benefits of high-KDPI donor kidney use and involvement of patients in the decision-making process; evaluation of ways to improve the new KAS to improve its efficiency and therefore decrease cold ischemia time; and use of “open offer” solutions to ensure maximal use of a donated kidney at any given transplant center. The call is clear: we must and can do better, but we need to do it together!

Next in the series is “Progress and Plans for the UNOS Kidney Transplant Learning Center. ●

Christa Lawson is the care coordinator/transplant coordinator at Reach Kidney Care in Mount Juliet, TN. Doug Johnson, MD, is vice chair of the board of Dialysis Clinic, Inc. Deana Clapper is in clinical services at Tennessee Donor Services. Kevin Fowler is the president of The Voice of the Patient. Sandip Kapur, MD, is professor of surgery and chief at the division of transplant surgery, Weill Cornell Medicine, New York-Presbyterian Hospital/Weill Cornell Transplant Center.

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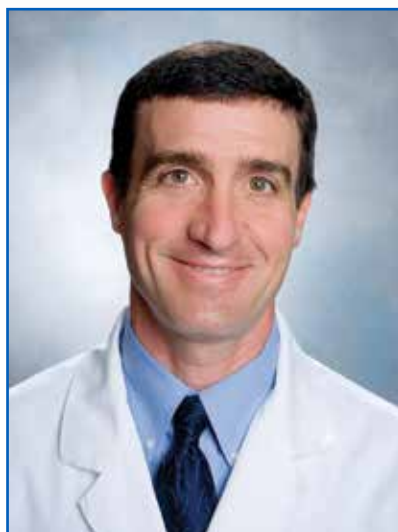
Distinguished Conversations

It was my pleasure to interview Gary Curhan, MD, ScD, for our Distinguished Conversation series. At the time of this interview, he was completing his 6-year term as Editor-in-Chief of the *Clinical Journal of the American Society of Nephrology*. Gary has already enjoyed a highly distinguished career as professor of medicine at Harvard Medical School and Harvard School of Public Health. He will be continuing to pursue his major research interests including the epidemiology of nephrolithiasis, risk factors for renal function decline, epidemiology of hearing loss, novel risk factors for cardiovascular disease, health effects of analgesic use, novel risk factors for hypertension, and the epidemiology of gout. These interests have led to more than 350 and counting peer-reviewed publications. He has served on the Advisory Council for the NIH National Center for Complementary and Alternative Medicine and has served on numerous NIH Study Sections. He has been continuously funded by NIH for over two decades, and is an active mentor, with his own training grant, and was a founder and Co-Director of Harvard's PASTEUR program for student research mentoring.

—Richard Lafayette, MD, *Kidney News* Editor-in-Chief



Richard Lafayette, MD



Gary Curhan, MD, FASN

Dr. Lafayette: Congratulations on completing your six years as Editor-in-Chief of *CJASN*. It is a tremendous accomplishment to have served in this role. You have been able to create terrific new features and maintain the journal as the home of clinical nephrology.

What are your plans now?

Dr. Curhan: Thank you very much. It's definitely been an exciting six years. My plans now are to use my "free" time to return to my research activities and mentoring. I've continued to do research but as you know, *CJASN* took a fair amount of my attention. But fortunately, I work with a large number of really talented investigators in a number of areas related to nephrology such as nephrolithiasis and some other areas such as primary hyperparathyroidism and hearing loss.

Dr. Lafayette: Do you have a new grand venture in store, or are you sort of reordering your life back to how you left it before *CJASN*?

Dr. Curhan: I am looking at what the next steps are. I have been reading some different books, such as "Designing your Life: How to Build a Well-Lived, Joyful Life," written by a group at Stanford. I am trying to make sure my compass is still pointing me in the right direction.

Dr. Lafayette: That sounds great. Coming back to *CJASN*, were there any early learning points when you were first starting out that may have suggested being Editor-in-Chief would be different from what you had first expected? What do you think could have helped you better prepare for the role, perhaps by way of advice for the incoming editor?

Dr. Curhan: I was very fortunate to have been involved with *CJASN* from the very beginning, as I had worked as an associate editor under the founding Editor-in-Chief, Bill Bennett, MD, FASN. I learned a lot from his leadership style as well as from the two deputy editors at that time, Mohammed Sayegh, MD, and Harold Feldman, MD, FASN. That interaction gave me an appreciation for the involvement and effort required to be an associate editor. But I clearly underestimated the time and energy it takes to be a dedicated Editor-in-Chief. I also initially underestimated the importance of the editorial team, but quickly learned how fortunate and very lucky I was to have been able to work with a talented group of individuals.

The deputy editors during my term, Kirsten Johansen, MD, and Paul Palevsky, MD, FASN, had a tremendous, positive impact on the topics and quality of the journal. The 11 associate editors were also outstanding, and we relied on them heavily for decisions about original manuscripts. And I cannot overstate the importance of having our own managing editor, Shari Leventhal. When I started, the managing editor was handling both *CJASN* and *JASN* and doing a great job, but the leadership at ASN realized the rapid growth of each journal would require individual managing editors. Shari made a huge positive difference.

So what else do I wish I had known earlier? How to juggle the constant deadlines and huge number of manuscripts, while at the same time trying to focus on making the process as easy as possible for authors, keeping the quality high, and selecting the best original and invited manuscripts. So I wish I'd known and understood more about these issues earlier on, but I learned quickly.

We launched a number of important series that Paul Palevsky developed, including Renal Physiology and Renal Immunology. The time and effort it took for what I thought was going to be just a series of review articles was really much more extensive, and that was because of the high standards Paul set. We also standardized the images because we envisioned—and I think it's happening—that these would be used for a long time, not just by our readers, but also by fellows, residents, and medical students.

Dr. Lafayette: I think the community very much appreciates the continuity of the outstanding quality of the content and images. That's probably why you get so many submissions, and why special sections have been so greatly appreciated. Looking back at your time as Editor-in-Chief, what do you consider your main accomplishments during those six years? Of which accomplishments are you most proud?

Dr. Curhan: There were several obvious, and some less obvious, accomplishments that I will talk about in no particular order.

From the beginning, my priority was to improve the quality of the journal. Bill Bennett had done a great job launching *CJASN*, which was extremely challenging, but under his leadership it rapidly became a source for submission of high quality articles. This strong foundation allowed us to continue to raise the bar to improve the quality of manuscripts accepted, both original and invited.

We also devoted a lot of time to presentation to make sure the information was presented in a way readers could easily understand. We aimed for clear, high-quality figures.

We paid a lot of attention to the review process to ensure we had high quality reviews by experienced reviewers.

Another aim was to improve the author's experience. As an author myself, I know what it's like to be on the other end and how frustrating and aggravating it can sometimes be to try to submit a manuscript and deal with a website that isn't completely understandable or sometimes gives contradictory instructions. So we made the submission process as easy as possible. Shari often provided personal support to authors along the way.

I wanted to make sure the journal was educational. The first thing I did as Editor-in-Chief was to redesign the cover. My goal was to select a new image every month that didn't necessarily relate to what was inside, but just to remind people of the importance of images and to use them to educate. Along with the cover image, we included a short case vignette and discussion of the diagnosis—this was something that made the journal more appealing.

We received outstanding invited material and launched a number of innovative series, such as Renal Physiology, Renal Immunology, Ethics, Public Policy, Attending Rounds, and the Medical Director series. Our expectation was that these series would not necessarily be cited, but we knew they would be of interest to our audience and widely read. Downloads of these series far exceeded our expectations. In fact, for the Medical Director series, one of the large dialysis organizations requested and received permission to require that all of their medical directors read the series.

We also launched eJournal Club, an idea of David Goldfarb's. The goal was to have ongoing interactions between authors and readers—not just a one-time letter to the editor—but a back-and-forth discussion among a group.

Ming Chawla, MD, did an unbelievable job designing the original *CJASN* app, and *JASN* followed suit. We added biostatistical editors to emphasize the importance of careful analysis. And we had a really diverse editorial team and editorial board. From the beginning, I wanted to have transparency so everyone involved with the journal—myself, deputy editors, associate editors, and the editorial board—completed detailed disclosure forms, and these were posted online for anyone to see.

I am particularly proud of the survey that found that *CJASN* was the most read nephrology journal. That was always a priority—not just to publish articles, but to have a journal that people would want to read.

Dr. Lafayette: What were the things that didn't go as smoothly? What could have been done differently that you can now reflect back on with either a chuckle or as something for the new group to take on?

Dr. Curhan: There is always room for improvement, and I think change is often for the better. I think it was wise to implement term limits for the Editor-in-Chief's role for the ASN journals, and I am sure that the new team will continue to improve on what was done before.

The main challenges are time and resources. All of us involved with the journal have other full time jobs, so time is very precious, as well as the limited resources. What I would have liked to have done was have a larger editorial team so we could have done more things and done them faster.

As far as what I would have done differently . . . there are all sorts of different metrics by which you can judge success, and I think we could have used more frequent internal assessments. I am not talking about impact factor, as I personally don't think it is really the best measure of quality. The example I always give is that if you publish a really bad article that gets cited a lot as being a bad article, that makes your impact factor go up—that doesn't seem like the ideal system.

If we had more time, we would have had more broad discussions and would have ideally have had even more series, but the time and resources really limited what we could do.

Dr. Lafayette: To extend on that and look more globally, where do you think we are today in terms of medical publishing, especially in nephrology?

Dr. Curhan: I think it is an exciting time. Since I was a fellow a long time ago, the number of high quality manuscripts has continued to increase both nationally and internationally. There are also more journals, but perhaps now there are too many. It is unclear to me right now about quality control for some of the for-profit journals. This increase in the number of journals can lead to a substantial burden on the pool of reviewers. There is a limited number of high-quality reviewers, but with an increasing number of manuscripts and journals, the competition for these reviewers becomes greater.

There are innovative approaches to using electronic or online versions of the journal. Up-to-Date uses embedded links and other approaches; in my mind there's no reason those couldn't and shouldn't be used in online versions of journal articles.

Another aspect is ongoing discussions, such as what we tried with the eJournal Club. Despite being an innovative approach, it unfortunately didn't take off the way David and I had hoped it would. There is so much competition for people's eyes, and it's very challenging to engage people in ongoing thoughtful conversations about articles. Although a large number of people enrolled in eJournal club, the number of those who actively contributed was less than we had hoped.

This is an area where perhaps a different model will foster ongoing engagement between authors and readers.

Dr. Lafayette: There has always been a desire to learn how we can keep nephrologists interested and provide them with an opportunity to further their own knowledge while constantly improving kidney practice. With board recertification as it is now, what is your opinion about the best way to share new knowledge and update community standards available for nephrologists? How do you give nephrologists a sort of carrot-and-stick to keep them up to date?

Dr. Curhan: As a clinician, I want to have information that is readily available, interesting, and presented in a way that will help me and my patients. Are journals the only way to do that? I don't think so. Journals play many different roles, and I think each journal needs to decide what roles it will fill. Doing too much with a journal may cause it to lose its way. At *CJASN*, we had criteria about what it was that we wanted to do. We hoped that at least some of the items we published would be of interest to everyone, and that others would be of interest to various subgroups. For example, some investigators were more interested in the original articles and some clinicians or medical students were more interested in the invited material. It varied by month and topic, but having a clear overall strategy about who the audiences are and what it is you are trying to provide for them helps keep a journal on track.

As consumers, I think nephrologists are going to have to look at the different resources available to them. I hope *CJASN* serves a lot of their needs, but it cannot and should not serve up everything everyone wants. We primarily targeted the journal to clinical nephrologists and clinical investigators.

As far as the status of renal research, I think it is an exciting time. There are a lot of young fellows and junior faculty who want to pursue academic careers, and new drugs are being developed. Hopefully, there will continue to be an increasing number of private companies developing new treatments, and not just medications, but devices as well. I hope NIH funding will increase—that will be very important to help maintain interest and continuity in renal research.

Dr. Lafayette: I agree, and we'll certainly continue to advocate our government to continue to support research.

You mentioned medical students. We are at a particular time when there is some concern about a lack of interest in nephrology as a career, and trying to get medical students and residents interested in our field has become more of a challenge. What are your general thoughts about that challenge and what do you think journals like *CJASN* can do to help?

Distinguished Conversations

Continued from page 17

Dr. Curhan: Yes, the challenge is clear, as we see each year with the Match, particularly with the number of graduates in the US and elsewhere who show an interest in the field. I think there is still much work that needs to be devoted to expanding the level of interest. There is a lot of misunderstanding about how exciting and vibrant nephrology is, and I know a lot of people are trying to work on that.

We hope our efforts to make *CJASN* content understandable to a broad range of readers made the journal attractive and interesting to students, residents, and senior practitioners. Selecting exciting, cutting edge topics such as new drugs and devices can help expand interest in nephrology. And inserting links (such as an original article that links to the Renal Physiology series) can make it easier for a reader to not have to go to a completely different book but to rather use published peer-reviewed material, allowing them to go back and forth between the original article and the more general article that might help improve their understanding of renal physiology. These approaches take time and effort, but the opportunities are certainly there.

And, of course, we need to find other creative ways to engage young people, including using social media. Getting the message out there in this manner and making sure content is readily accessible can help a lot.

Dr. Lafayette: You were there as an associate editor when *CJASN* was started, at a time when ASN already had a very successful journal, *JASN*. It was always going to be interesting how the two journals either acted separately or found common ground. What was your experience of working together at ASN to keep the two journals successful? Was there a partnership or competition for scientific and review articles?

Dr. Curhan: The ASN Council made a very wise decision to launch a second journal because clearly there was a need. The high quality material that *CJASN* was receiving and publishing confirmed that *JASN* alone could not publish everything, particularly a large number of clinical investigation manuscripts. I also believe that competition is good, even among friends. So having the journals separate, and they were indeed completely independent publications, was the wise thing to do. But at the same time, working with Karl Nath, who was Editor-in-Chief of *JASN*, was a particularly special aspect of my term. Karl is just a wonderful individual, and we've had a very collegial relationship. We worked together on several items such as the apps and had several interactions with the publisher. I hope that relationship will continue for the new editors of *CJASN* and *JASN*. Healthy competition, as well as collaboration, would help both journals.

Dr. Lafayette: The *CJASN* Editor-in-Chief does have sort of broad power to influence the journal—the type of science it covers and the articles it attracts. During your stay as an epidemiologist, some may say there was a lot more epidemiology in *CJASN* than before. How does one strike that balance of moving toward the information you are passionate about vs. perhaps wanting to stay broad and cover the whole field? Is that ever a challenge, or is it an opportunity as well?

Dr. Curhan: That was something I was concerned about when I was preparing to take over as Editor-in-Chief. I wanted to make the journal as broad as possible so it would be of interest to our readers. Epidemiology is just one way to do that. At the same time, there has been huge growth in the number of epidemiologic studies compared with physiologic studies, so if anything, we were trying harder to get other types of studies—not just epidemiology, but, for example, health services research studies, clinical trials, and physiologic studies. But as we know, there is just not the same number of submissions from these other areas.

We also wanted more studies about transplantation, pediatric nephrology, and other areas, but *CJASN* is dependent on the types of articles that are submitted. I like to think we reviewed the articles based on their quality and not just the type of article. We worked very hard to find associate editors with a broad range of backgrounds, and they played a very critical role in the decision-making process. While there were some epidemiologists, the vast majority were not. I insisted that all associate editors be clinical investigators and practicing clinical nephrologists because I knew that would bring a unique perspective to the journal.

There are probably more epidemiology-type studies in *CJASN* than other types, but I doubt the relative number is any different from that in the nephrology journals focused on clinical investigation.

Dr. Lafayette: Is there anything else you would like to comment on concerning your viewpoints about nephrology in general, medicine in general, or your tenure at *CJASN*?

Dr. Curhan: One area we did not talk about was print vs. electronic publication. From the beginning, when I was first asked whether or not by the end of my tenure we would still have print publications, I wasn't sure. If you asked me now about whether we will still have print publications at the end of the next six years, I would say the transition is going to happen at some point. I don't know exactly when, but there are many reasons why it's appropriate to have paper versions, yet these are becoming less and less so. Electronic versions of journals don't solve everything, and there are plenty of electronic journals that I can't say I am impressed with. Just the fact that they're electronic does not mean that the quality is better. I would hope when this journal does eventually switch over to being all electronic, that the same standards are met, including limits on word count.

Electronic publication does open up some other possibilities: figures and tables and the ways they can be manipulated, results that may allow a reader to say, "What happens if I remove this aspect or that aspect?" These facets of electronic publication may be for the future, but I can easily imagine how as investigators we could have multiple versions of the same table or figure.

Other possibilities are creative figures or videos, with embedded links. Already, abstracts show up when you hover the mouse over the references, but I can imagine that one day related articles might pop up, not just to what's on PubMed, but also to related books and educational materials. I think there are opportunities, but bringing them to pass will take a lot of time and effort.

And as long as there are people who prefer the paper version, I think there is every reason to keep publishing a paper version. ●



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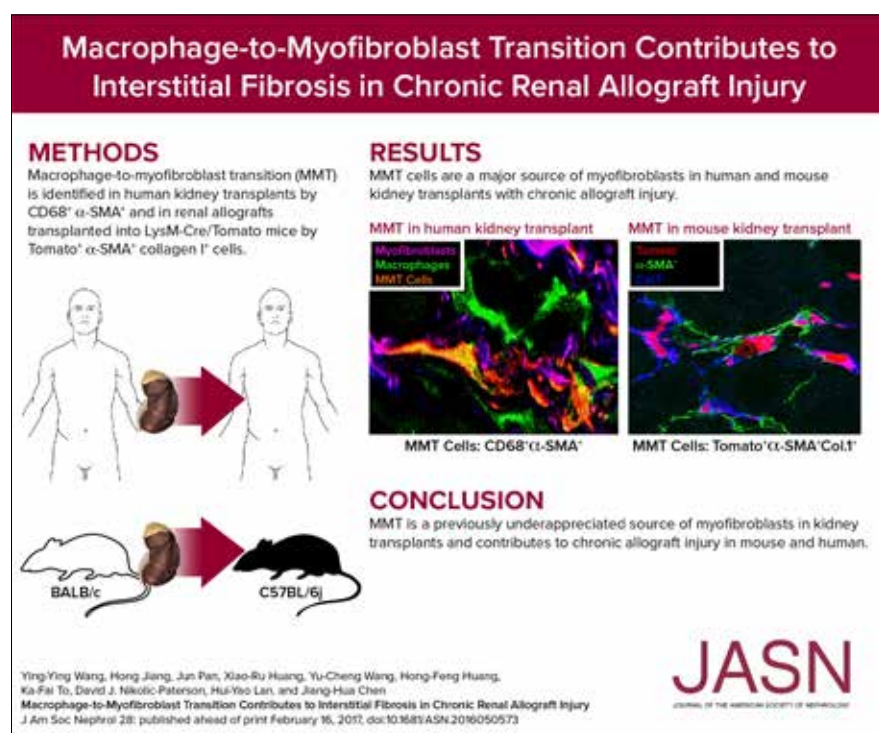
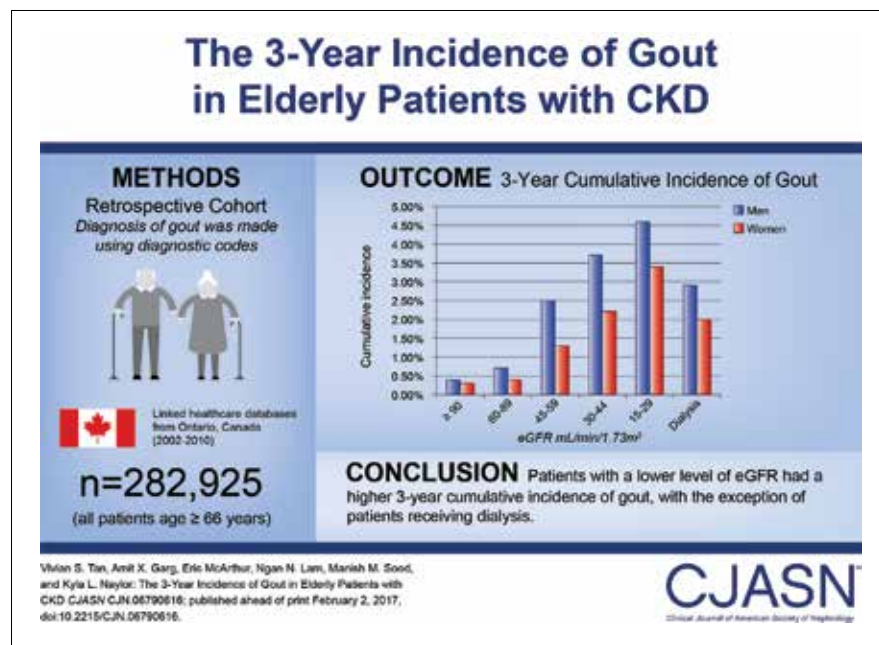
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The speakers, Alan S. Kliger, MD, Priti R. Patel, MD, MPH, and Leslie P. Wong, MD, MBA, FASN, will delve into the growing threat of the infection crisis in the United States and will provide tools and strategies proven to reduce infection rates.

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Industry Spotlight

Treatments for Uremic Pruritus Underway

Cara Therapeutics (Stamford, CT) released positive data about its uremic pruritus product, intravenous CR845, which targets peripheral kappa opioid receptors.

Cara noted that Part A of the Phase 2/3 trial achieved reduced itching and improved quality of life, the trial's primary and secondary endpoints. The company intends to meet with the US Food and Drug Administration to finalize clinical study design for Part B of the trial as well as begin patient enrollment later in 2017, noted Cara Therapeutics President and Chief Executive Officer Derek Chalmers, PhD. Part B will include up to

240 participants and involve CR845 treatments just after each patient undergoes dialysis.

Other therapies for uremic pruritus are available or under development. In 2016, the *Canadian Journal of Kidney Health and Disease* published a review of the efficacy of gabapentin. The authors found the drug effective for uremic pruritus but noted "adverse events are common." They advised starting at a low dose of 100 mg orally after hemodialysis and titrating to the desired effect to provide safe and effective outcomes (Lau T, et al. Gabapentin for uremic pruritus in hemodialysis patients: a qualitative systematic review. *Can J*

Kidney Health Dis 2016; 3:14).

Another drug, pregabalin, also is under study. An observational, longitudinal study was conducted to assess the effectiveness of 75 mg pregabalin posthemodialysis for treatment-resistant uremic pruritus. The team saw a reduction of 12 points based on the 5D-Itching scale on day 2 after using pregabalin (Khan TM, Aziz A, Suleiman AK. Effectiveness of posthemodialysis administration of pregabalin (75 mg) in treatment resistant uremia pruritus, 2016; 8:74-76).

Other therapies for uremic pruritus include systemic ultraviolet light and oral antihistamines. ●

FDA roundup

Keryx Pharmaceuticals (Boston) announced that the US Food and Drug Administration (FDA) will review its drug Auryxia (ferric citrate) for use in patients who have iron deficiency anemia and non-dialysis-dependent chronic kidney disease (CKD). Ferric citrate is a phosphate binder indicated for controlling serum phosphorus levels, typically in patients with CKD who are on dialysis.

A review for the new use of the drug should be complete by Nov. 6, 2017, according to Drugs.com.

The supplemental New Drug Application (NDA) is based on data from a 2-week controlled, phase 3 trial in 234 adults with non-dialysis-dependent CKD. Patients enrolled in the trial were intolerant to or had an inadequate response to previous treatment with oral iron supplements. Patients did not receive any intravenous or oral iron, or erythropoiesis-stim-

ulating agents. In the study, treatment with Auryxia demonstrated significant increases in hemoglobin levels of >1 g/dL at any point during the 16-week efficacy period for the majority of patients (52.1%; n = 61/117), which was deemed a clinically meaningful result.

AstraZeneca received disappointing news from the FDA: a complete response letter regarding AstraZeneca's NDA for ZS-9, sodium zirconium cyclosilicate. This is a second FDA rejection for the treatment, an insoluble, non-absorbed compound with a structure that was designed to preferentially capture potassium ions. The compound was initially rejected by the FDA in May 2016, "on the back of certain manufacturing issues," *Pharmatimes.com* reported. The drug is being developed by ZS Pharma, a subsidiary of AstraZeneca.

The FDA also has offered nonbinding recommendations to the pharmaceutical industry about how to move forward in developing drugs that prevent delayed graft function after transplantation. An FDA guidance report recommends that trials for drugs to treat the condition should be an active treatment versus placebo design, because there is no approved drug for preventing delayed graft function. The FDA also recommended a preapproval safety database of 300 patients or more who are using the investigational drug. The Regulatory Affairs Professional Society noted that the trials should collect specific information on the type of donors (i.e., donation after brain death, cardiac death, or living donor), the type of organ recovery, organ storage and transport conditions, and post-transplantation immunosuppressive therapy used. ●

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BRIEF SUMMARY OF PRESCRIBING INFORMATION



Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information].

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively [see Adverse Reactions (6.1) in PARSABIV full prescribing information]. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV [see Dosage and Administration (2.4) in PARSABIV full prescribing information]. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV [see Dosage and Administration (2.2) in PARSABIV full prescribing information]. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary [see Dosage and Administration (2.2) in PARSABIV full prescribing information].

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range [see Dosage and Administration (2.1) in PARSABIV full prescribing information].

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia [see Warnings and Precautions (5.1) in PARSABIV full prescribing information]
- Worsening Heart Failure [see Warnings and Precautions (5.2) in PARSABIV full prescribing information]
- Upper Gastrointestinal Bleeding [see Warnings and Precautions (5.3) in PARSABIV full prescribing information]
- Adynamic Bone [see Warnings and Precautions (5.4) in PARSABIV full prescribing information]

Clinical Trials Experience

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

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased ^a	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia ^b	0.2%	7%
Paresthesia ^c	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

^a Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

^b Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

^c Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [¹⁴C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [¹⁴C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [¹⁴C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

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

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken [see *Warnings and Precautions (5.1) in PARSABIV full prescribing information*].



PARSABIV™ (etelcalcetide)

Manufactured for:

KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.

One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: <http://pat.amgen.com/Parsabiv/>

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Indication

Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™.

Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone. Parsabiv™ (etelcalcetide) prescribing information, Amgen.