ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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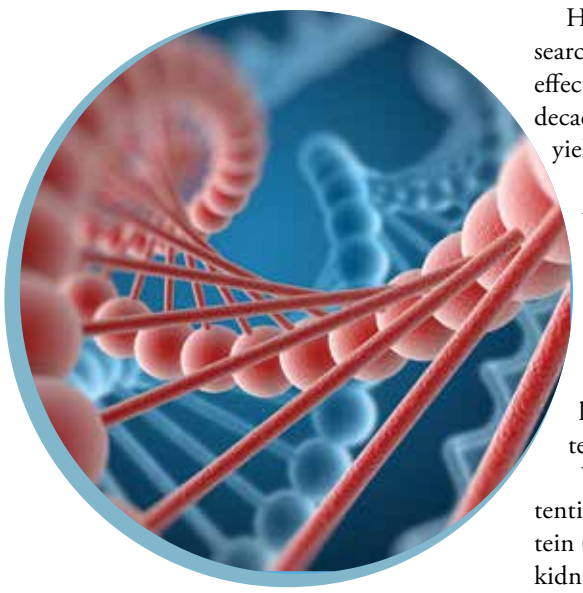
YAP Protein Emerging As Key Player in Kidney Health, Disease

By Bridget M. Kuehn



Necessity is the mother of invention for physician-scientists like Darren Yuen, MD, PhD, a nephrologist at St. Michael's Hospital in Toronto. Frustrated with the lack of treatment options for the progressive scarring in the kidney called fibrosis, he turned to his lab in search of a new antifibrotic agent.

His team is among a cohort of researchers who have studied the fibrotic effects of a protein called TGF-β for decades, but so far that work has not yielded new treatments.

"TGF-β hasn't panned out as a treatment target in kidney patients because it does a lot of things," Yuen said. That can make it hard to develop treatments that don't have troublesome side effects. So he decided to pivot his research to look at a protein called YAP that interacts with TGF-β.

Yuen is not alone in turning his attention to YAP. The Yes-associated protein (YAP) is emerging as a key player in kidney health and disease, with findings from multiple research groups converging on YAP as critically important. YAP is part of the Hippo signaling pathway that regulates cell growth and differentiation, with YAP activation linked to several malignancies, said Kirk Campbell, MD, a nephrologist and associate professor of medicine at the Icahn School of Medicine at Mount Sinai in New York.

"We're sort of at the beginning stages of investigating YAP signaling [in kidney disease]," said Campbell, whose work inspired Yuen to take a look at the protein's role in fibrosis. We are just scratching the surface."

Cancer connection

YAP is part of a network of proteins that are essential for normal development. During development, this network controls how large organs are by controlling how many cells grow and die (Wong JS, et al. *Am J Physiol Renal Physiol* 2016; 311:F241–F248). But in mature humans its role appears complicated.

The YAP protein can be turned off and sit quietly in the cell. But when it is turned on in adult cells, it travels to the nucleus and influences the expression of genes important for cell growth, multiplication, and survival. In some gastrointestinal cancers, an unusually high amount of YAP is produced, which may contribute to the cancer cells' success.

This dark side of YAP has made it

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Study Quantifies End Stage Renal Disease Risk in Living Kidney Donors

By Tracy Hampton

A newly developed method to quantify living kidney donors' risk of end stage renal disease (ESRD) postdonation may be helpful for individuals considering donation, for living donors wishing to understand their long-term risk, and for clinicians who monitor the long-term health of living donors. The risk calculator is described in a recent *Journal of the American Society of Nephrology* study.

Although research suggests there are minimal health consequences for individuals who donate a kidney, comprehensive studies are lacking. Long-term studies of living kidney donors have reported low rates of premature death and kidney failure (with an estimated overall ESRD risk to donors at 31 ESRD cases per 10,000 living kidney donors in the first 15 years postdonation), but personalized estimates based on donor characteristics are not available. Centers have developed ad hoc donor selection criteria on the basis of a single risk factor (such as a maximum body mass index cutoff) or a simple combination of risk factors (such

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Inside

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YAP Protein a Key Player

Continued from page 1

a target of cancer researchers who want to create anti-cancer drugs that turn off YAP, Campbell said. But treatments targeting YAP could have worrisome effects for the kidney because the drugs could make their way there during urine filtration and affect the survival of kidney cells.

Kidney cells called podocytes, which make up a sieve-like device that filters protein out of urine, produce a lot of YAP and might be especially vulnerable to such YAP-targeted treatments. When podocytes are injured they are not replaced. This can cause gaps that allow proteins to leak out into urine. If enough podocytes are lost, focal segmental glomerulosclerosis (FSGS), a leading cause of progressive kidney failure, can develop.

To find out what would happen if YAP is shut down in podocytes, Campbell and his colleagues have silenced the gene that encodes it both in podocytes grown in culture in the laboratory (Campbell KN, et al. *J Biol Chem* 2013; 24:17057–62) and in healthy mice (Schwartzman M, et al. *J Am Soc Nephrol* 2016; 27:216–226). The podocytes in culture lacking YAP were more susceptible to injury. The mice too lost podocytes and began leaking protein in their urine, as well as developing other signs of FSGS.

"When [YAP] is deleted in podocytes, it leads to FSGS and progressive kidney disease [in mice]," Campbell said.

In the otherwise healthy cells used in Campbell's studies, YAP appears to boost podocyte survival, which raises concerns that YAP-targeted therapies in cancer or other diseases might have harmful effects on the kidneys.

"There is a concern that it is possible, based on our findings, that healthy podocytes may become injured if the function or expression of YAP were to be reduced [by YAP-targeted treatment]," Campbell said.

Friend or foe?

While Campbell's studies suggested that YAP may protect podocytes from dying, another recent study suggests injuring podocytes causes YAP levels to shoot up and contributes to further damage (Rinschen MM, et al. *Sci Signal* 2017;10:eaaf8165).

Markus Rinschen, MD, a nephrologist and scientist at the University of Cologne in Germany, and his colleagues didn't set out looking for YAP. They simply wanted to know what happens after an injury damages podocytes.

"We know podocytes are subjected to a lot of stress including mechanical, metabolic, and chemical stress," said Rinschen. "If the podocyte is injured [protein leaks in the urine], but how this happens is not completely understood."

So they intentionally caused a podocyte injury in rats and then looked at what happened to levels of various proteins in the cells to see if these changes could provide hints about the process.

"We found YAP with an unbiased analysis," Rinschen said. "YAP is one of the first proteins to increase before proteinuria develops."

As YAP shot up, so did the production of proteins that provide structure within cells. Too many of these structural proteins are known to contribute to fibrosis.

Complicating things, the study also revealed that overproduction of YAP post-injury in laboratory-grown cells only occurred when the cells were grown on a soft surface more similar to the conditions in the kidney. On a hard surface, the podocytes didn't respond by boosting YAP production after injury. Rinschen explained that podocytes respond to mechanical stress, and the hard surfaces may create mechanical pressure on the cells.

"They can somehow know how much pressure is there," he said.

Next, they treated the injured rats with a drug that blocks YAP from interacting with another protein in its network. The treatment ameliorated the podocyte injury and reduced the development of proteinuria.

"What seems to be the case is that YAP itself is some driver of the disease that is signaling back to rigidity," he explained.

So, is YAP helpful or harmful to the kidney? The answer is likely both, said Rinschen and Campbell.

"It's a double-edged sword," said Rinschen. YAP may both protect against cell death in podocytes and also be a part of the podocyte's stress response that can get out of hand, he said. Under stress, the podocyte boosts YAP production to ward off cell death, but overproduction of YAP affects other proteins it interacts with. This might boost fibrosis and stiffen the podocyte cell, triggering more stress and more YAP production.

"It may be a self-sustained response," he said.

Whether YAP is helpful or harmful might also depend on the health of the cell. Campbell explained that his experiments were done in healthy podocytes while Rinschen's were done with podocytes that were injured.

"It's a pro-survival molecule," Campbell said. "It's possible that too much of a pro-survival signaling molecule could be bad in the context of disease."

YAP and fibrosis

Fibrosis plays an important role in kidney failure in chronic kidney disease. But most kidney diseases don't present until they are in a late stage of progression and fibrosis has already begun, leading to more fibrosis.

"It's a self-perpetuating cycle," Yuen said.

Yuen's work has focused on stopping that cycle and hopefully slowing or arresting kidney disease. His work on YAP has focused on what it does in fibroblasts, the cells that produce the bulk of the scar in the kidney. Just like Rinschen, he and his colleagues have shown that YAP's effects depend on the stiffness of the surfaces around it (Szeto SG, et al. *J Am Soc Nephrol* 2016; 27:3117–3128). When fibroblasts are grown on a hard surface, which may recreate some of the mechanical stress that fibroblasts experience during fibrosis, YAP is turned on. But when the cells are grown on a soft surface, YAP is sequestered away from the nucleus. With YAP out of the picture, TGF-β's ability to activate the production of the profibrotic proteins Smad 2 and Smad 3 were muted, suggesting that YAP signaling is necessary for TGF-β's harmful effects.

Next, Yuen and his team tested whether a drug called verteporfin that targets YAP might help shut down fibrosis. They induced fibrosis in the kidneys of mice and found it did reduce YAP, Smad 2/3, and fibrosis. The findings raise hope that it might be possible to develop a YAP-targeted therapy for fibrosis.

"My hope is that these types of therapies would provide a new opportunity to treat patients already presenting with some kidney disease-related fibrosis," Yuen said.

Although verteporfin is currently used to treat humans with macular degeneration, Yuen noted, it has downsides that make it unlikely to ever be used as a kidney disease therapy. For example, it is administered as a one-time intravenous infusion in patients with macular degeneration. It's also designed to be light-activated, which wouldn't be beneficial as a chronic treatment for patients with kidney disease. But Yuen said verteporfin might be used as a model to create a YAP-targeted drug for kidney disease.

First, Yuen said, scientists must better understand what YAP does in other kidney cells and in the rest of the body. This would be crucial to avoid unintended harmful effects in the kidney and elsewhere.

"We have to be careful," Yuen said. "We have to learn more of the context of how YAP works in the kidney. If we better understand the context, we may still be able to develop targeted therapies."

Rinschen was more circumspect about the clinical implications of his team's research on YAP so far, and noted much more work is needed to understand YAP's role in kidney health and disease.

"We are far from any clinical applications," Rinschen said. "We should view this as a pathological principle rather than a drug target."

He advocated for more unbiased research looking at the dynamics of kidney disease and the interactions of many proteins during the process.

"We need to think in a broader way concerning kidney disease," Rinschen said. "What happens first? What is triggering what? How do these proteins interact?"

Campbell agreed that more work is needed to understand the big picture.

"We have identified a molecule that has a role in podocyte homeostasis under normal and disease conditions," Campbell said. "The molecule is part of a larger pathway with a number of different players that tightly regulate its function. It will be important for us to understand the role not just of YAP, but of related molecules that could potentially be harnessed for therapeutic benefit in [kidney disease]."

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

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

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427 Keynote 427:
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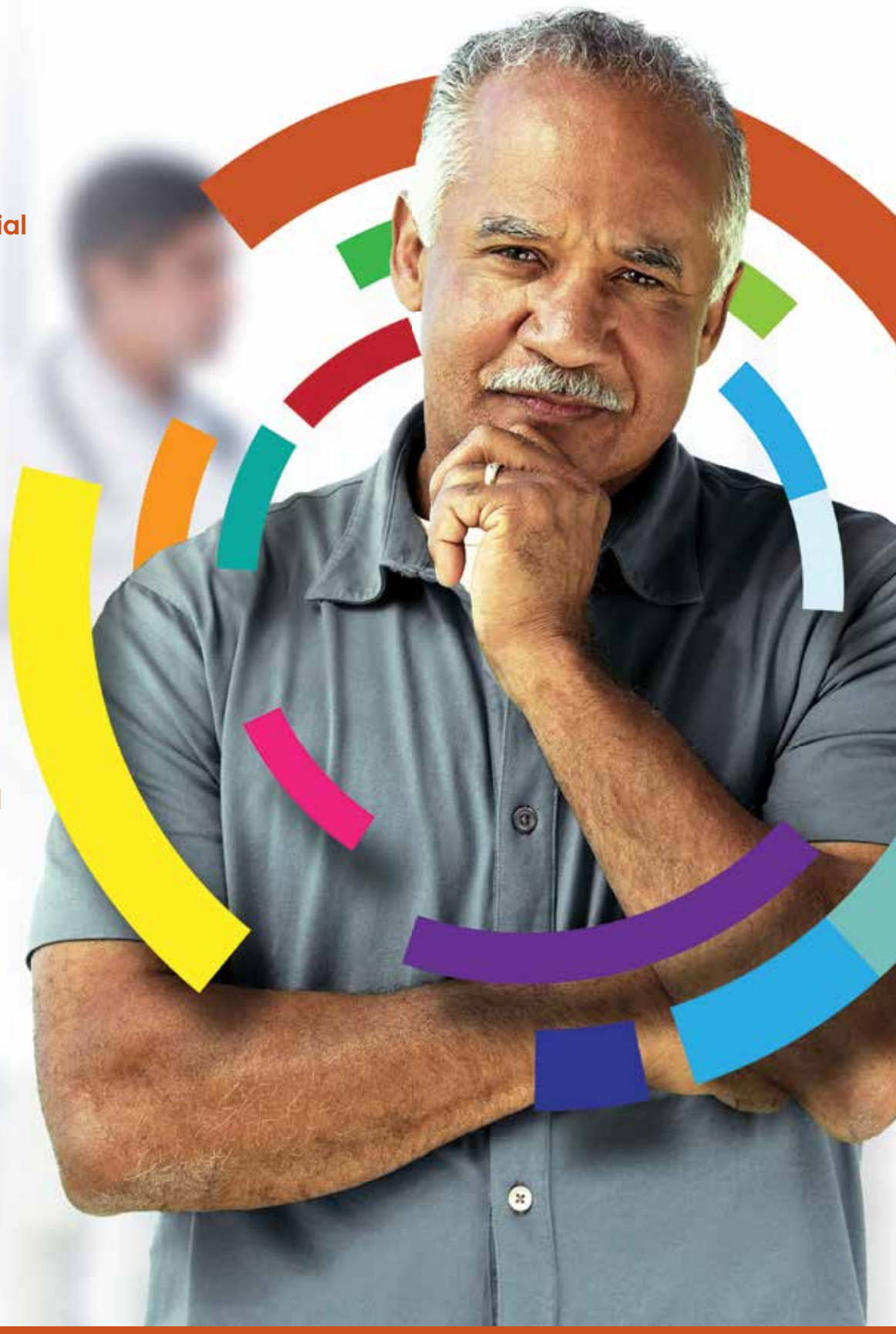
  - Have not received prior systemic therapy for advanced disease



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Findings

Living Donors Still "at the Top of the List" for Kidney Transplant

Early experience under the revised kidney allocation system (KAS) shows continued quick access to high-quality deceased-donor organs for prior living donors (PLDs), reports a study in the *American Journal of Transplantation*.

Using Organ Procurement and Transplantation Network data, the researchers compared access to deceased donor kidney transplants for two groups of PLDs. The study compared prevalent and incident cohorts of 50 patients for the year before KAS implementation in December 2014, and 39 patients for the year after implementation. Transplant rates per patient-year and waiting times were assessed, along with the Kidney Donor Profile Index (KDPI) of the transplanted kidneys.

There was no significant difference in transplant rates from before to after KAS implementation: 2.27 versus 2.29 for prevalent candidates and 4.76 versus 4.36 for incident candidates. Median waiting time to transplantation for prevalent PLDs was 83.2 days in the pre-KAS cohort and 102.6 days in the post-KAS cohort. This increase was neither clinically nor statistically significant.

Median KDPI for prevalent PLDs was 23% in the pre-KAS cohort versus 31% in the post-KAS cohort. Ninety-five percent of kidneys transplanted in PLDs in the post-KAS cohort were in the range of KDPIs transplanted in children during the same period. Despite a sharp decrease in waiting time for high-priority candidates with calculated panel reactive antibodies of 98% to 100%, PLDs still had much shorter waiting times.

Although living kidney donation is generally a safe procedure, the number of PLDs who later require kidney transplantation is "not negligible." The new KAS was designed to maintain high-priority for kidney transplantation in special populations, including children and PLDs.

This early evaluation suggests that PLDs are still "at the top of the list" for access to kidney transplantation under the revised KAS, with very short waiting times for high-quality organs. The authors call for continued assessment to ensure that PLDs' access to transplantation does not decrease unexpectedly [Wainwright JL, et al. The impact of the new kidney allocation system on prior living kidney donors' access to deceased donor kidney transplants: an early look. *Am J Transpl* 2017; 17:1103–1111].

Higher Rates of Metabolic Abnormality but Normal Weight in Minority Patients

The percentage of Americans with normal body weight but cardiometabolic abnormalities is higher in racial/ethnic minority groups—especially South Asians and Hispanics, reports a study in *Annals of Internal Medicine*.

The researchers determined the prevalence of the metabolic abnormality but normal weight (MAN) phenotype and associated factors in five US racial/ethnic groups. Data on 2622 white, 803 Chinese American, 1893 African American, and 1496 Hispanic adults were drawn from the Multi-Ethnic Study of Atherosclerosis; information on 803 South Asian subjects came from the Mediators of Atherosclerosis in South Asians Living in America study. The MAN phenotype was defined as at least two of four cardiometabolic abnormalities: high fasting glucose, low high-density lipoprotein cholesterol, high triglycerides, and hypertension.

The prevalence of MAN was 21.0% in whites compared to 32.2% in Chinese Americans, 31.1% in African Americans, 38.5% in Hispanics, and 43.6% in South Asians. The differences remained significant on adjustment for demographic and behavioral factors and ectopic body fat.

The researchers performed further adjustment for a significant interaction between age, sex, and race/ethnicity with body mass index (BMI). Values equivalent to the MAN prevalence observed in whites with a BMI of 25.0 were 22.9 in African Americans, 21.5 in Hispanics, 20.9 in Chinese Americans, and 19.6 in South Asians.

The results suggest that US patients in racial/ethnic minority groups have a higher rate of cardiometabolic abnormalities at normal body weight, compared to their white counterparts. The researchers conclude: "Using a BMI criterion for overweight to screen for cardiometabolic risk may result in a large proportion of racial/ethnic minority groups being overlooked" [Gurjal UP, et al. Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: a cross-sectional analysis of two cohort studies. *Ann Intern Med* 2017; DOI: 10.7326/M16-1895].

Confounders Obscure Link between Preeclampsia and ESRD

The roles of obesity and pre-existing kidney disease make it difficult to assess the true nature of the association between preeclampsia and end stage renal disease (ESRD), concludes a report in the *American Journal of Kidney Diseases*.

The researchers used the US Renal Data System to identify 34,581 women who gave birth in Olmsted County, Minn., between 1976 and 2010. Forty-four women with confirmed ESRD were matched for year of birth, age at first pregnancy, and parity to two controls. In the cases, median time from last pregnancy to ESRD onset was 17.7 years.

Pregnancies affected by preeclampsia were confirmed by review of medical records. The association between preeclampsia and ESRD was analyzed, with attention to shared risk factors such as previous kidney disease, obesity, diabetes, and hypertension.

Nine of the 44 women with ESRD had evidence of kidney disease before their first pregnancy, a rate of 21%, compared to just 1 of 88 controls. Medical records review identified preeclampsia in 18% of cases versus 5% of controls, for an unadjusted odds ratio of 4.0. The association between preeclampsia and ESRD was unaffected by adjustment for race, education, diabetes, and hypertension before pregnancy. However, it was weakened and became nonsignificant after adjustment for obesity.

Registry-based studies have suggested that hypertensive disorders of pregnancy are a risk factor for ESRD. However, because of shared risk factors, the nature of the association between these two conditions has been unclear.

The new study suggests a fourfold increase in ESRD associated with preeclampsia. However, it also provides evidence of a possible confounding effect of obesity. In addition, 20% of women with ESRD already had evidence of kidney disease before their first pregnancy. While the causal pathway is still unclear, the researchers conclude: "Preeclampsia may identify women early in life who are at future risk for kidney disease" [Kattah AG, et al. Preeclampsia and ESRD: the role of shared risk factors. *Am J Kidney Dis* 2017; 69:498–505].

TRF-Budesonide Reduces Proteinuria in IgA Nephropathy

A targeted-release formulation of budesonide—designed to deliver drug to the distal ileum—reduces proteinuria in patients with IgA nephropathy who don't respond to first-line treatment, reports a trial in *The Lancet*.

The phase 2b NEFIGAN trial included patients with confirmed IgA nephropathy and persistent proteinuria at 62 European nephrology clinics. All patients were on optimized renin-angiotensin system (RAS) blockade, which continued throughout the study. After stratification by baseline urine protein creatinine ratio (UPCR), patients were randomly assigned to TRF-budesonide, 8 or 16 mg/d, or placebo. The main efficacy outcome was change in UPCR from baseline to 9 months of treatment.

On planned interim efficacy analysis in 149 patients, the combined TRF-budesonide groups had a mean 24.4% reduction in UPCR, compared to an increase of 2.7% in the placebo group. The 16 mg/d dose group had a significant 27.3% reduction in UPCR, while the 21.5% reduction in the 8 mg/d group fell short of significance.

The reduction in proteinuria was associated with changes in 24-hour urine protein and albumin excretion and urine/albumin creatinine ratio. These changes were sustained throughout the study, including a 3-month follow-up phase. The researchers write, "This persistence of effect following cessation of treatment suggests a disease-modifying effect."

On safety analysis in 150 patients, the overall incidence of adverse events was similar across groups. Of 13 serious adverse events, 2 were considered possibly associated with TRF-budesonide: one patient had deep vein thrombosis and another had unexplained decline in renal function.

For patients with IgA nephropathy who have persistent proteinuria despite optimized RAS blockade, high-dose systemic corticosteroids are the recommended treatment. The pathogenesis of IgA nephropathy is thought to involve mucosal B-lymphocyte activation and proliferation in Payer's patches. The TRF-budesonide evaluated in NEFIGAN targets the distal ileum, which has a high density of Payer's patches.

At a 16 mg/d dose, TRF-budesonide added to optimized RAS blockade reduces persistent proteinuria in patients with IgA nephropathy. The researchers conclude: "TRF-budesonide has the potential to become the first disease-specific treatment for IgA nephropathy, with a risk-benefit profile supportive of its use early in the course of disease" [Fellström BC, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomized, placebo-controlled phase 2b trial. *Lancet* 2017; DOI: http://dx.doi.org/10.1016/S0140-6736(17)30550-0].

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ASN President, *CJASN* Editor-in-Chief Discuss Scientific Publishing, Broadening Reach

ASN President Eleanor D. Lederer, MD, FASN, recently interviewed Raj Mehrotra, MD, FASN, the new Editor-in-Chief of the Clinical Journal of the American Society of Nephrology (CJASN) *about scientific publishing and his plans for* CJASN. *Following are excerpts from their conversation. To listen to the full podcast, please visit http://asn.kdny.info/qpOr30blv7Y.*

Eleanor D. Lederer, MD, FASN

Raj Mehrotra, MD, FASN

DR. LEDERER:

During a recent ASN Communities chat, you were asked about your biggest surprise upon becoming Editor-in-Chief of *CJASN*. You responded to the effect that you realized you had no idea of the huge breadth of research going on. If someone like you—who is so energetic and keeps up with the clinical literature as well as you do—realizes you aren't keeping up, what will happen to the rest of us, who don't have your energy?

DR. MEHROTRA:

It's an important question, and I take a broader view than just scientific publishing. The way we consume news and information during the past 20 years has changed dramatically. We have 24-hour cable news, Facebook, and other social media. I would argue that scientific publishing has not kept pace with how we live our lives now compared to 20 years ago and need to innovate in order to best communicate information to people with so many demands on their time. Something I find helpful is to utilize an electronic table of contents for journals that publish things of interest to me. Even then, I am often so inundated with email that I would be wrong if I said I read things carefully every time.

CJASN has started a few more initiatives in the past few months to grab the attention of individuals who are so busy otherwise. We have started to produce podcasts. Our hope is to have podcasts for at least two articles published in *CJASN* every month. We also recently introduced the visual abstract, which is like a single PowerPoint slide that summarizes the key message from a paper. We hope the visual abstracts will be made available through the website and social media.

How we communicate information through social media is also very critical. There's a way in which you and I consume information and then there are the ways those now growing up in the medical world—fellows and young faculty—consume information. We need to test our assumptions about things that could potentially be effective forms of communication that we are not presently thinking about. I hope to test those assumptions in the next year or two.

DR. LEDERER:

Young people today often use "T.L.D.R" online, meaning "too long, didn't read." I think this is a direct outgrowth of the phenomenon you've described. People are now accustomed to getting their news in teeny chunks in a way that's relatively easy to digest. Even TV news is all little bitty two-minute blurbettes on what's going on. And you have to wonder how many people are actually reading the two- or three-page *New York Times* articles that can actually be quite excellent and groundbreaking.

I think a challenge for people looking at medical literature today is that it's designed so you can read the abstract at the top and get your little sound bites. However, if you're really interested, you have to dig to find: How did they do this? What was the population that they were looking at? What kinds of statistics did they use to analyze it?

One of the sequelae of the new way of disseminating news and information that has gotten a lot of press lately is that we have become sort of holed-up and siloed in the types of information we want to get or are willing to listen to or look at. For the practicing nephrologist, that's got to be a challenge as they try to keep up with everything. You and I, in academics, may focus on our chosen fields. So you know everything there is to know about peritoneal dialysis, but I don't know as much about it. On the other hand, I probably know as much as anybody about phosphate metabolism, but that may not be an area that you are as interested in and do not read about as much. But the general nephrologist cannot do this. They see many problems and try to keep up. That's why a journal like *CJASN* is important—it appeals to general practicing nephrologists. The challenge is: How can you present articles in the most effective way? How can you highlight what is most important or groundbreaking for a general nephrologist who is reading the journal to try to keep up?

DR. MEHROTRA:

I completely sympathize with the "T.L.D.R." acronym, which you just introduced me to. In thinking about this and how I would share my vision for the journal, I'd partition it into two parts: communicating original research, and value-added features that put our knowledge in context.

Original research is very important because the information can be presented in a manner such that if another investigator wants to replicate the findings, they have all the information they need in that paper.

The value-added features are where one has to be very careful because I do not believe that there are many people who read papers that are 3000 or 5000 words, except maybe fellows who want to use review articles to help them make presentations.

We have changed direction in that regard and the phrase I like to use is "bite-sized pieces" that allow people to readily consume information, but in no more than 1500 words. That may even be too many, but at least it is moving in the right direction.

I think a lot of the information we consume, even scientific publishing, is viewed on handheld devices, not even desktops anymore, and nobody's going to scroll all the way down an article unless they can readily consume it. The challenge for journal editors is to innovate and communicate our messages better.

DR. LEDERER:

Yes, and if you look at a journal like *Science*, to me it's amazing because their articles are three pages long. That's it. I suspect *Science* articles do not include a lot of the nitty-gritty details of the methods. So when you look at a *Science* article, it's pretty easy to scan two or three pages as opposed to something longer in another type of journal.

JASN has relegated methods to the end of the article in a smaller font so that you can read what most people would consider the "gee whiz, this is the heart of the matter" if you are not interested or savvy in methodology.

Speaking of methodology, one of the biggest challenges, even for me, not being a clinical researcher, is that it's very difficult to evaluate the types of statistics used today. So I wonder, do general nephrologists simply have to take for granted that journals have done a superb job of vetting the statistics used and then verifying their validity when a paper is written?

DR. MEHROTRA:

You bring up another extremely important point with regard to the various methods used in clinical research. Various organizations and groups put together checklists for what should be included, say, when you're publishing results of a clinical trial or what should be included when you're publishing the results of a meta-analysis.

CJASN has taken it a step forward and has endorsed and adapted those checklists. Every time an article is expected to move forward to revision, *CJASN* associate editors complete the checklist for the article type that is involved. For a clinical trial, we would use the CONSORT checklist. For an observational cohort study, we would use a STROBE checklist. For a meta-analysis, we would use a PRISMA checklist. These are the three we started with and now include with our first assessment of the article we send back to the author. Checklists allow us to tell authors additional information they need to include so we can standardize our way of reporting clinical research.

DR. LEDERER:

Articles from journals like *CJASN* are frequently used for journal clubs and training programs.

One of the questions that we always ask our fellows to address when they're reviewing an article is: "Will this finding change your practice, and, if so, how?" I find it interesting that this specific question is never really addressed in an article. Why do you think that is? Why would authors be reluctant to step out and say "this is how we think you should change your practice"?

DR. MEHROTRA:

That's actually the first thing we look at when we assess a paper, and I would call it "significance." There are two ways an article could be significant. First, it could change clinical practice. I have to admit that most of the articles published do not use the research methods necessary for us to be certain that this is how clinical practice should be changed. But most papers should meet the threshold for how the finding advances our knowledge of this or that aspect of kidney disease and whether it allows us to clarify something we didn't understand in terms of what the next clinical trial should be: Now that this study is done, how we can design a clinical trial?

DR. LEDERER:

Shifting gears, from a clinical knowledge standpoint, is there any area of general nephrology in which you feel you have really picked up some knowledge even in the relatively brief period of time that you have been Editor-in-Chief?

DR. MEHROTRA:

You know, the answer goes back to the point you raised earlier when you mentioned how there are things we love and things we don't spend much time thinking about on a day-to-day basis. For me, that's been glomerular diseases and transplantation.

With regard to the rare glomerular diseases, it has been amazing to see how collaborative networks have been established and how people are doing the difficult work of understanding the pathophysiology and/or treatment of rare diseases. That has been absolutely amazing.

Similarly with regard to transplantation, since the time of my fellowship I have only taken care of people after the acute phase of receiving a kidney transplant. The second area I have learned more about includes the partnerships with sophisticated transplant programs and the advances and work people are doing there, and I'm gratified to learn about that.

DR. LEDERER:

I think another thing you are pointing out is that not only do each of us have an area or a few areas where we tend to focus our attention while we ignore others, but also that everything changes so quickly. Even though we talk about nephrology sometimes as if "it's kind of the same as it was 50 years ago…" it isn't.

DR. MEHROTRA:

I agree. It is easy to say there hasn't been much progress, but looking at the work people are doing and the effort they're putting in to solve some of the problems we face is actually very humbling.

Even Patients Whose Kidney Function Returns to Normal after AKI Have High Risk of Renal Progression

For patients who have had acute kidney injury (AKI), the long-term risk of renal progression remains high even if their kidney function ultimately returns to normal, suggests a new study in *Kidney International*.

Using data from one UK health region, the researchers identified 14,651 patients who survived to hospital discharge in 2003. Of these 1966 patients had stage 1 to 3 AKI, based on KDIGO criteria. Follow-up data to 2013 were used to assess rates of subsequent renal decline, defined as a sustained 30% decline in eGFR or de novo stage 4 chronic kidney disease. These outcomes were compared for patients with versus without AKI, and for AKI patients at differing levels of postdischarge kidney function.

During follow-up, 37.5% of patients died, 11.3% had sustained decline in eGFR, and 4.5% developed stage 4 CKD. Kidney function declined by at least 30% from the prehospital to posthospital period in 25.7% of AKI patients (nonrecovery), compared to 2.3% of patients without AKI.

Rates of subsequent renal decline were 14.8% in AKI survivors and 11.3% in those without AKI. This risk was greatest for AKI patients with a postdischarge eGFR of 60 mL/min/1.73 m^2 or higher: multivariate hazard ratio 2.29. The excess risk associated with AKI persisted throughout the 10-year follow-up period, regardless of AKI severity or post-episode proteinuria.

It has been unclear whether the risk of renal progression after AKI is different for patients who do and do not have "recovery" of kidney function. The new study suggests that AKI survivors are at increased risk of renal progression up to 10 years after discharge, even if they regain normal kidney function. The researchers conclude, "Follow-up plans should avoid false reassurance when eGFR after AKI returns to normal."

Sawhney S, et al. Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. *Kidney Int* 2017; doi: 10.1016/j.kint.2017.02.019.

New Risk Tool Helps Predict Short-Term Mortality in Elderly who Start Dialysis

A clinical risk prediction tool based on readily available data performs well in identifying older adults at high risk of death within 6 months after dialysis initiation, reports a study in the *American Journal of Kidney Diseases*.

It is generally accepted that older adults are at increased risk of death and other adverse outcomes in the months after starting dialysis. The investigators wanted to investigate whether a clinical risk prediction tool that takes into account the characteristics of older adults with kidney failure might help to inform the decision to initiate maintenance dialysis.

Using renal registry data from Alberta, Canada, the investigators identified 2199 patients aged 65 or older who initiated maintenance dialysis therapy between 2003 and 2012. Patients with acute kidney injury were excluded. A wide range of clinical and laboratory factors were evaluated as potential predictors of all-cause mortality within 6 months after the start of dialysis. The model was derived using data from the full cohort of patients. Internal validation was performed using the tenfold cross-validation sample use-reuse method.

The mean age for patients in the study was 75.2 years, and about 61% of those were men. Six months after dialysis initiation, all-cause mortality was 17.1%.

Seven predictors were included in the final model and incorporated into a 19-point scoring system: age 80 or older (2 points), estimated glomerular filtration rate of 10 to 14.9 mL/min/1.73 m^2 (1 point) or 15 mL/min/1.73 m^2 or higher (3 points), atrial fibrillation (2 points), lymphoma (5 points), congestive heart failure (2 points), hospitalization within 6 months (2 points), and metastatic cancer (3 points).

Patients who had higher scores on these predictors were generally at higher risk of death. The six-month mortality was less than 25% for patients with scores of less than 5, but more than 50% for those with scores of greater than 12.

The researchers concluded that the 19-point clinical decision tool evaluated in their study may predict early mortality after initiation of dialysis in older adults, but that the tool has yet to be externally validated.

An editorial that accompanied the research raised some questions to consider when deciding whether to incorporate this clinical decision tool or previously developed risk scores into clinical practice—including "whether the score accurately predicts outcomes in people like their patients."

The editorial authors noted the need for prospective studies of factors affecting outcomes in older adults with chronic kidney failure. Such studies should include patients who choose a "supportive pathway," rather than just those who initiate dialysis, they said.

Wick JP, et al. A clinical risk prediction tool for 6-month mortality after dialysis initiation among older adults. *Am J Kidney Dis* 2017; 69:568–575; Foote C, et al. Scoring risk scores: considerations before incorporating clinical risk prediction tools into your practice. *Am J Kidney Dis* 2017; 69:555–557].

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End Stage Renal Disease Risk

Continued from page 1

as hypertension and age).

"There are over 120,000 living kidney donors in the United States, and more than 5000 donations every year. Both people who already donated and people considering donation want to understand their long-term risk of kidney failure," said Dorry Segev, MD, PhD, of the Johns Hopkins University School of Medicine and the Johns Hopkins School of Public Health.

To provide insights, Segev and his team set out to construct a prediction model of ESRD after living kidney donation and to create an easy-to-use web-based risk calculator, where a user could provide characteristics of a potential donor and receive estimates of ESRD risk over time.

The investigators first studied information on 133,824 living kidney donors from 1987 to 2015, as reported to the Organ Procurement and Transplantation Network. The median age at donation was 40 years. Among these donors, 40.8% were men, 12.5% were black, and 59.4% had a first-degree biologic relationship to their recipient.

The investigators identified 331 donors who experienced incident ESRD. These donors who experienced incident ESRD were more likely to be men (60.4% vs. 40.7%), black (34.4% vs. 12.5%), and first-degree biologically related to the recipient (85.6% vs. 59.4%).

Overall risk for developing ESRD was quite low: the investigators predicted that the median risk was only 1 case per 10,000 donors at 5 years after donation, 6 cases per 10,000 donors at 10 years, 16 cases per 10,000 donors at 15 years, and 34 cases per 10,000 donors at 20 years. One percent of donors had a predicted risk exceeding 256 cases per 10,000 donors, however. Black race and male sex were associated with 3.0- and 3.9-times increased risks of developing kidney failure, respectively. Among nonblack donors, older age was linked with greater risk, but this was not seen in black donors. Higher body mass index was also associated with an increased risk of kidney failure.

"We were able to produce a calculator that estimates donors' risk based on age, race, gender, body mass index, and whether or not they have a first-degree biological relationship to their recipient," said lead author Allan Massie, PhD, MHS. The findings suggest that greater permissiveness may be warranted in older black candidate donors, and that young black candidates should be evaluated carefully.

"Because living kidney donors voluntarily undergo surgery for no direct medical benefit to themselves, it is incumbent upon the transplant community to provide them with accurate estimates of long-term risk," Segev said.

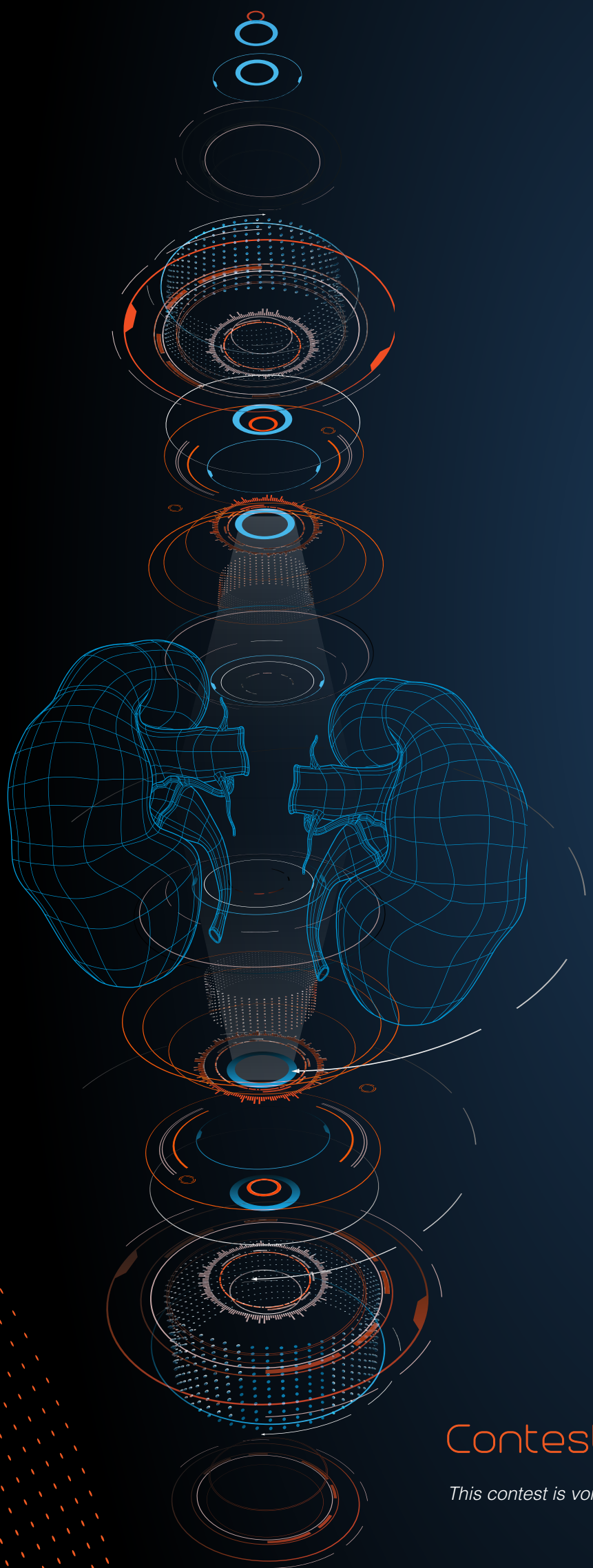
The authors noted that because ESRD is very rare in living kidney donors and takes many years to develop, they were unable to study other important potential risk factors like pre-donation kidney function, smoking, and blood pressure. Information on these risk factors was not collected in the early years of living donor registration.

Geir Mjøen, MD, who was not involved with the study but has published many articles on outcomes after kidney donation, stressed that additional long-term research is needed. "The study is important because it describes large differences in the risk of ESRD after donation; however, because of limited follow-up time, risks faced by younger donors could be under-communicated," he said.

Mjøen, who conducts research at Oslo University Hospital in Norway, and his colleagues have noted that many analyses of donor risks have included control groups that are less healthy than the living donor population and have had relatively short follow-up periods. Also, it can be difficult to compare these analyses owing to variations in design.

One of Mjøen's recent studies notes that living kidney donation has increased by approximately 50% globally but that there has been stagnation and even a decline in some countries, which may reflect ambiguity concerning the use of living donors. To safely increase living kidney donations, ensure proper informed consent, and provide guidance for follow-up care, it is imperative to provide accurate information concerning the long-term effects of donor nephrectomy, Mjøen said.

Help ASN Build the Future of Kidney Care



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Kidney Transplantation 2017
Development of the UNOS Kidney Transplant Learning Center

By Amy D. Waterman, Dianne LaPointe Rudow, Catina O'Leary, Rachel Patzer, Mike Pressendo, and David Serur

The Rogosin Institute's roundtable event

In December 2016, 25 people, including researchers, nurses, doctors, business professionals, nonprofit leaders, health literacy and media specialists, legislators, and individuals affected by kidney disease and kidney failure, gathered in New York City for The Rogosin Institute's Transplant Roundtable. The focus was on organ donation and access to transplantation, and the goal was the generation of new ideas and action plans to increase the number of registered organ donors, increase kidney transplants, and improve health outcomes and quality of life for individuals with kidney disease.

Roundtable participants coalesced around paradigm-shifting ideas and strategies to increase the number of people benefiting from kidney transplants. The group agreed that achieving this goal requires improving transplant advocacy and education outside of transplant centers, developing a responsible public message about kidney disease and living donation, implementing public policy initiatives to reduce barriers to organ donation, and including patient and donor voices in all of these efforts.

Building on the White House Organ Summit and call to action

The roundtable also provided an opportunity to continue to address the call to action issued by the Obama administration in the spring of 2016 (i.e., to improve outcomes for individuals waiting for organ transplants and enhance support for living donors). The announced actions are "aimed to increase the number of people who register to become organ donors, increase the number of transplants and improve outcomes for patients, and change what might be possible for future patients by facilitating breakthrough research and development." In addition to generating new ideas, the roundtable attendees were invited to join the existing initiatives developed through the White House Organ Summit.

For the more than 100,000 patients who are currently on the waiting list to receive a kidney transplant in the US, depending on the generosity of strangers is not a choice; it is a necessity. As a leader in the field of transplant and living donation education and research, Amy D. Waterman, an Associate Professor in Residence at the David Geffen School of Medicine at the University of California, Los Angeles, understands this better than most. "Every day I witness the gratitude that kidney patients feel when they realize that someone will donate an organ to them so that they can have a longer and better-quality life," Waterman commented. "And, although there are not enough kidneys for everyone in need, there is certainly enough education to go around, to make people aware of their options. We must disseminate this education as widely as possible."

Partners from eight universities and hospitals (Beth Israel Deaconess Medical Center, Duke University School of Medicine, Emory University, Johns Hopkins University, Mount Sinai Hospital, Northwestern University, Temple University, and the University of California, Los Angeles) have responded to the White House call to action and the education challenge by forming a Blue Ribbon Education Advisory Panel with the aim to disseminate organ donation education more broadly across the US through a national online clearinghouse of public educational resources.

Significant progess has been made in this effort. The United Network for Organ Sharing (UNOS) Kidney Transplant Learning Center, to launch at the end of 2017, is a product of their work. Through this effort, leaders from these institutions have agreed to share their own clinical expertise and educational content with the public, ensuring that patients, donors, and their social networks will have the educational tools they need to make informed decisions about transplantation and organ donation.

The UNOS Kidney Transplant Learning Center content will be hosted within www.TransplantLiving.org in partnership with the UNOS—a trusted nonprofit organization that manages the nation's organ transplant system under contract with the federal government. The expertise of the UNOS in bringing hundreds of transplant and organ procurement professionals together with thousands of volunteers has made them an ideal partner for this project. This learning center, designed in partnership with the UNOS, Health Literacy Media, and 501creative (a graphic design group), will address the shortage of reliable organ donation and transplant education currently available outside of transplant centers, providing more consistent and readily usable resources about kidney transplantation and living donation to the 670,000 Americans living with end stage kidney disease as well as their families, social networks, and the general public.

The Kidney Transplant Learning Center's development has been in progress since 2016, when a team of Health Literacy Media experts first began to curate educational content for the site from each of the panel members' institutions. Their process included thoroughly reviewing and sorting the multimedia topical content of each available education program to create a master collaborative document, which was then subjected to a rigorous health literacy review to develop a user-friendly, understandable, and actionable resource and learning experience.

In an ever-changing field, creating a unified and reliable hub for transplant and living donation information and education for patients, living donors, and the interested public is essential. In addition to this audience, it is anticipated that educational partners, transplant societies, and clinicians will use this information, each disseminating it to their constituents. Transplant programs, nephrology practices, and dialysis centers will be invited to endorse and use the educational site.

"I am especially excited to see that so many leading kidney organizations and education leaders are teaming up and working cohesively toward one common goal: to educate as many kidney recipients and living donors as we can," Waterman commented.

"As a team, we're really passionate about ensuring equal access to transplant education for all patients and working as a community to solve the kidney-donor shortage," added Dianne LaPointe Rudow, Panel Cochair.

Development of the Kidney Transplant Learning Center is supported by Sanofi Genzyme and has engaged several strategic nationally active partners, including the UNOS, the American Society of Transplantation, the American Society of Transplant Surgeons, DaVita, Donate Life America, the National Association of Transplant Coordinators, the National Kidney Foundation, ORGANIZE, and The Rogosin Institute. With cross-collaboration and patient and donor voices at the forefront, this initiative will lead to the development of a critically important and relevant resource for those with kidney disease and the whole kidney community.

Amy Waterman, PhD, is affiliated with the University of California, Los Angeles, Dianne LaPointe Rudow, DNP, with the Mount Sinai Medical Center, and Catina O'Leary, PhD, LMSW, with Health Literacy Media. Rachel Patzer, PhD, MPH, is affiliated with Emory University School of Medicine, Mike Pressendo, with the United Network for Organ Sharing (UNOS), and David Serur, MD, with The Rogosin Institute.

Practice Pointers

Advancing Our Understanding of Glomerular Disease Through Omics

By Krzysztof Kiryluk and Jan Novak

The word omics or multiomics refers to high-throughput agnostic methods commonly used in systems biology and systems genetics. Systems genetics is a relatively new approach that combines a range of experimental and computational methods to quantify and integrate genetic effects across intermediate phenotypes, such as transcript, protein, or metabolite levels, in order to better understand the flow of genetic information through cellular regulatory networks. This approach studies the effects of DNA variants (genome) on RNA transcription (transcriptome), protein synthesis (proteome), metabolic functions (metabolome), and ultimately, disease phenotype (phenome). These approaches are ideally suited to study multifactorial traits with complex genetic architecture. Notably, most types of kidney and glomerular disorders fall in this category.

In light of recent progress in the genomics of complex traits, where do we stand with glomerular disease?

The progress in the genetics of complex traits has been remarkable due to the declining cost of genotyping, sequencing, and computation combined with unprecedented multicenter collaborations and open data sharing models widely adopted in genomic sciences. These advances allowed for discovery of thousands of susceptibility alleles for complex traits in large-scale population-based genetic studies. From the time of the first genome-wide association study (GWAS), there have been over 2500 GWASs published, reporting over 20,000 unique single-nucleotide polymorphism trait associations.

In addition to GWAS, next generation sequencing technology, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), is now being used to investigate the role of rare genetic variants in complex traits. Unfortunately, glomerular disease has not been at the forefront of this genomic revolution. Nevertheless, several notable success stories in our field are worth mentioning. One of the landmark successes was the identification of *APOL1* risk alleles with large effect on the risk of focal segmental glomerulosclerosis (FSGS) in African Americans (1). Another success involved membranous nephropathy, where a small GWAS identified impressively strong associations of the class II major histocompatibility region and at the M-type *phospholipase A2 receptor (PLA2R)* gene locus (2).

In the field of IgA nephropathy, several large GWASs have been conducted and identified nearly 20 independent risk alleles, shedding new light on the underlying pathogenic pathways and refocusing mechanistic research toward better understanding of the role of intestinal immunity in this disease (3). Although these success stories are extremely encouraging, the GWAS approach has not been systematically applied to the entire spectrum of glomerular diseases. Adequately powered genetic studies are still missing for many common disorders, such as minimal change disease, mesangioproliferative glomerulonephritis (MPGN), lupus nephritis, or Henoch–Schönlein purpura nephritis, to name a few. The lack of systematic genetic work in this area is particularly alarming, because many glomerular disorders are in dire need of effective treatments, but potential drug targets remain largely undefined owing to poorly understood pathogenesis.

What are the main challenges in functional genomics of glomerular disease?

Presently, the key challenges in the field are to elucidate dysregulated pathways downstream of known genetic susceptibility loci, to understand the nature of their pleiotropic effects and interactions, and to place their functional consequences within a coherent biologic network. Such insights may then be translated into clinical benefits, including reliable biomarkers, effective strategies for screening and prevention, and rational selection of new therapeutic targets.

For follow-up of GWAS findings, the key challenges are that many of the causal alleles reside in the noncoding regions of the genome and that the target genes for these regions are frequently unknown. Because many regulatory regions are tissue specific, another challenge is to correctly identify the causal cell type for each disease. The structural complexity of kidney tissue and the relative inaccessibility of relevant cell types represent major challenges for functional genomics in nephrology. The National Institute of Diabetes and Digestive and Kidney Diseases recognized this problem and announced the new Kidney Precision Medicine Project (KPMP) that aims to build a kidney tissue resource for the purpose of such studies. This new initiative, although not specifically targeting glomerular disease, offers prospects to enhance our ability to implement disease- and cell type–specific functional genomics.

Can proteomics help with identification of pathogenic targets in glomerular disease?

Proteomics, the large-scale study of proteins, their structures, and their functions, has been successfully applied to kidney tissue and body fluids, including serum and urine. One of many examples in the field of glomerular diseases is the discovery of the cause of primary membranous nephropathy. Targeted proteomic analyses identified a major antigen recognized by circulatory autoantibodies as PLA2R (4) and a minor antigen as thrombospondin type 1 domain-containing 7A protein (5). Both antigens are membrane glycoproteins present in normal podocytes and immune deposits in idiopathic membranous nephropathy. Independently, GWAS for membranous nephropathy discovered risk alleles in the region encoding the *PLA2R* gene. The convergence of proteomic and genetic results solidified the evidence for the pathogenic role of antibodies against PLA2R in membranous nephropathy and exemplified the power of these approaches in the field of glomerular disease.

Can urine peptidomics enhance discovery of disease-specific biomarkers?

Urine is thought to contain molecules reflecting the health status of the kidney. Consequently, urine from patients with glomerular diseases may contain disease-specific molecules, including naturally occurring peptide fragments of protein originating from the circulation and/or the kidney. Analyses of peptides—peptidomics—in the urine have identified >5000 different peptide fragments that can be used for disease stratification. A recent article outlined approaches that characterized association of urinary peptides with kidney disease, with the goal to further our understanding of the pathophysiology of kidney disease and the related extracellular matrix remodeling (6).

What is glycomics, and what can it do for studies of glomerular disease?

Most human proteins are glycosylated by N- and/or O-linked glycans. Glycomic workflows are being developed to characterize glycosylation of proteins and better understand changes of glycosylation in organ development and disease pathogenesis (7, 8).

The kidney filtration system depends on proper glycosylation of proteins produced by the resident glomerular cells; several genetic studies revealed key roles of specific glycoproteins in normal kidney function. Moreover, changes in glycosylation of immunoglobulins (Igs) are related to glomerular diseases. For example, in IgA nephropathy, an elevated proportion of IgA1 has some of the clustered *O*-glycans without their normal complement of galactose; these galactose-deficient glycoforms are recognized by autoantibodies, resulting in the formation of nephritogenic complexes (9). Interestingly, IgA1 glycosylation profiles in IgA nephropathy have a strong genetic determination and recent GWAS demonstrated that *O*-glycosylation defects were influenced by functional genetic variants in key glycosylation enzymes (10).

As another application of glycomics to kidney disease, a recent study of monozygotic twin pairs discordant for renal function revealed that galactosylation, sialylation, and level of bisecting *N*-acetylglucosamine of the IgG glycans associate with GFR (11). Thus, glycomics can provide new information that is highly relevant to pathogenesis of kidney disease, and specifically glomerular disorders.

What is the role of the microbiome in the pathogenesis of glomerular disease?

At this time, we do not know. Next generation sequencing technology has the ability to accurately quantify commensal microbial communities, including their transcriptional activity and diversity across multiple body sites, such as skin, intestine, urine, and mucosal surfaces. Our recent genetic data indicate that host–pathogen interactions might have shaped the genetic susceptibility to IgA nephropathy (3), raising questions about the role of the microbiome in the pathogenesis of this disease. However, well-designed and adequately powered microbiome studies are presently missing for IgA nephropathy and other forms of glomerular disorders. The interaction between human genome, microbiome, and disease susceptibility remains one of the most exciting areas of research, and we are certain to see more glomerular nephritis-related microbiome studies in the near future.

How are Electronic Health Record data being used to enhance omics approaches?

As the number of patients undergoing GWAS, WES, and WGS continues to increase, DNA sequence information will inevitably become part of our Electronic Health Record (EHR). There are already thousands of patients with genetic data linked to EHR information for research studies. EHRs represent a rich source of phenotypic data for genetic studies, allowing us to define an electronic phenome or disease-trait signature of an individual. This allows for a completely new class of genetic studies, such as phenome-wide association studies, in which individual genetic variants are tested for associations with thousands of disease-related traits. This specific approach may be particularly helpful to establish new pleiotropic effects of genetic susceptibility variants. Other active research in this area involves the development of novel computational algorithms to refine electronic kidney phenotypes using natural language processing of clinical notes or to predict disease course and prognosis in real time on the basis of longitudinal information contained in health records. This relatively young field is evolving rapidly as our electronic health systems continue to improve in terms of accuracy and interoperability. Without a doubt, these developments will have a large effect on the future studies of glomerular diseases.

Krzysztof Kiryluk, MD, is affiliated with the College of Physicians and Surgeons, Columbia University, Department of Medicine, Division of Nephrology, and Jan Novak, PhD, is affiliated with the University of Alabama at Birmingham, Department of Microbiology.

Suggested Reading

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Some Pediatric Transplant Patients May Have a Markedly Increased Cancer Risk

Children who have received solid organ transplants are at high risk of cancer, particularly non-Hodgkin's lymphoma, according to a study in *Pediatrics*.

In the US Transplant Cancer Match study, data from the Scientific Registry of Transplant Recipients were linked to 16 state and regional cancer registries. Of approximately 40,500 solid organ transplants performed between 1987 and 2011 in patients younger than 18 years, 45% were in a region covered by one of the linked cancer registries.

Counts of registry-observed cancers were divided by the counts that were to be expected from general population rates in order to calculate standardized incidence ratios (SIRs). The researchers than assessed patient characteristics associated with cancer risk. Because most of the observed cancers were non-Hodgkin's lymphomas, risk factors for this cancer and combined cancers that did involve non-Hodgkin's lymphoma were assessed separately.

The analysis included 17,958 transplants performed in 17,732 children and adolescents. About 44% of transplants were kidney transplants. A total of 392 cancers were diagnosed, and the median time from transplantation to diagnosis was 2.5 years. Non-Hodgkin's lymphomas accounted for 71% of posttransplant cancers, with a median time to diagnosis of 1.6 years.

The incidence of non-Hodgkin's lymphoma was greatly elevated among transplant recipients, compared to the general population, with a SIR of 212. Risk was also increased for Hodgkin's lymphoma, which had a SIR of 19, and for leukemia, which had a SIR of 4. There was also a very large increase in myeloma risk, which showed a SIR of 229, although this was based on only 3 observed cases.

Other significant associations based on 8 or fewer cases included cancers of the kidney, thyroid, liver, testis, soft tissue, brain, bone and joint, ovary, skin (melanoma), bladder, breast, and vulva.

The risk of non-Hodgkin's lymphoma was particularly high for children younger than age 5 at the time of their transplant; the associated SIR was 313. It was also high for those who were seronegative for Epstein-Barr virus (EBV) at transplant, SIR 446; and for those who underwent intestinal transplantation, SIR 1280. Among the independent predictors of non-Hodgkin's lymphoma incidence were first year posttransplant, hazard ratio (HR) 4.04; seronegative EBV status, HR 2.71; and induction immunosuppression, HR 1.31.

"Pediatric recipients have a markedly increased risk for many cancers," the researchers write. They

note that their study population is more than 20 times larger than in a previous Swedish study, which reported more than a 100-fold increase in cancer risk among pediatric transplant recipients.

Most posttransplant cancers are non-Hodgkin's lymphomas, with the risk being highest in the first posttransplant year. The authors suggest that strong associations with immunosuppression and EBV infection suggest a cancer prevention opportunity, if EBV infection can be prevented or controlled.

Yanik EL, et al. Cancer risk after pediatric solid organ transplantation. *Pediatrics* 2017; 139: e20163893.

Fellows Corner

We hope you, the reader, have been pleased with the reintroduction of the Fellows Corner column of *Kidney News*. Thanks to wonderful leadership from Robert Rope, MD, who has been serving as feature editor, we enjoyed broad participation and believe we have delivered some very informative, poignant, and reflective content. Rob will be stepping down as he completes his third year of fellowship at Stanford and joins the nephrology faculty at Oregon Health & Science University, where he started his medical training. He looks forward to continuing his work with fellows and to bolstering interest in nephrology and education.

We are excited to announce that two terrific contributors will be stepping in as co-editors of Fellows Corner. Please welcome Devika Nair, MD, a fellow at Vanderbilt University, and Daniel Edmonston, MD, a fellow at Duke University. I am confident they will do a terrific job, and together with the rest of the team at *Kidney News*, look forward to ongoing reader contributions to Fellows Corner in the future.

—*ASN Kidney News* Editor Richard Lafayette, MD

Time-Limited Trials of Dialysis in the Intensive Care Unit: Are We Timing Dialysis Initiation Appropriately?

By Arjun Sekar, MD

Arjun Sekar, MD

Nephrologists are often consulted for renal replacement therapy (RRT) in critically ill patients in whom the overall prognosis is poor and the benefit of RRT is questionable (mortality in these scenarios is 50% or higher) (1). Initiating RRT can lead to worsened morbidity, extra suffering, and increased health care costs. Time-limited trials (TLTs) in these scenarios offer a potential bridge between conflicted providers or family members.

The "technological imperative" is an imperative of possibility in health care: If it is possible, it has to be done. With the availability of continuous RRT, dialysis can be done more safely, even in critically ill patients. As a consultant in the intensive care unit, the nephrologist often rounds separately, which can lead to fragmented messages delivered to patients and families. Alternatively, the primary team might have already discussed dialysis as a "life-saving" intervention, creating expectations from patients and families. The intensive care unit is a highly stressful environment for families and staff, and fragmented communication can augment difficulties. Within this environment, the technological imperative and cultures of care can mean that starting a patient on dialysis might be easier than withholding it, even when nephrologists might disagree (2).

These scenarios can lead to interprofessional conflict among staff and to clinician unease. Providers' unexamined emotional responses can lead to burnout, cynicism, frustration, and ultimately, poor patient care (3). I describe some scenarios below where TLTs of dialysis can set clear treatment goals for the primary team and the nephrologist.

When the overall prognosis or clinical benefit of RRT is uncertain, TLTs of dialysis must be considered. TLTs are goal-directed trials of RRT limited by predetermined outcomes evaluated at planned intervals. The emphasis must be on clearly defining and documenting the goals of care with an understanding that the intervention must be stopped if goals are not achieved (4).

There are potential benefits of a TLT of dialysis (5). It allows the nephrologist to assess the reversibility of acute kidney injury, the response to RRT, and changes in the patient's overall prognosis. TLTs can allow families to come to terms with the guarded prognosis without a sense of abandonment (Tables 1 and 2).

The guidelines of the Renal Physicians Association on shared decision-making are a useful tool for nephrologists in these ethical situations. There are guidelines specific to the acute setting as well, with step-by-step details on sharing prognosis, communication tools, and TLTs. One very specific recommendation is to offer RRT in critically ill patients when there is ongoing conflict between medical staff and the patient. Dialysis can be provided while pursuing conflict resolution, provided that the patient or legal agent requests it. Physicians familiar with these tools were more comfortable applying these guidelines clinically than those who were not (6).

The decision to initiate RRT in a critically ill patient is tough when the overall prognosis is unclear. Nephrologists in practice and training should familiarize themselves with the Renal Physicians Association guidelines to assist with realistic decision-making and communication with patient surrogates. Establishing clear indications for TLTs in dialysis and studies that assess outcomes, including morbidity, can help us be better at predicting prognosis and communicating with families in these scenarios.

From a personal perspective as a fellow, having these conversations with families and explaining the prognosis helped develop a relationship of trust with the families, which has been very rewarding.

Information in the *Clinical Journal of the American Society of Nephrology* ethics series (5) can help guide us regarding TLTs in dialysis.

Arjun Sekar, MD, is a fellow at the Cleveland Clinic.

Table 1: Examples of potential clinical scenarios in which time-limited trials may be of use

- In advanced heart failure with hypervolemia where transplant or LVAD therapies are not available, a TLT could allow assessment of patient response to inotropes and medical management
- Medical optimization before a potentially life-saving high-risk procedure
- Relief of dyspnea in a hypervolemic patient being transferred to hospice care
- Continuing RRT until the arrival of a family member

Abbreviations: LVAD, left ventricular assist device; RRT = renal replacement therapy; TLT = time-limited trial.

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Table 2: Steps in the process of a time-limited trial of dialysis

Preparation	• Gather information regarding context of overall prognosis, severity, and prognosis of AKI, and discussions with other providers to obtain consensus • Identify short- and long-term clinical milestones to assess for progress (or decline) • Consider palliative care consult for assistance
Communication	• Explore patient/family values and goals of care • Share prognosis with family • Discuss the milestones to be achieved with RRT in accordance with a patient's values and goals • Share the anticipated timeframe of the trial (this can be variable) • Document all discussions and goals clearly
After initiating a TLT	• Meet with family and providers regularly • Communicate with providers before and after meetings to maintain a unified message • Consider available choices, including hospice, at the predetermined end of the TLT if the patient has not met the goals

Abbreviations: AKI = acute kidney injury; RRT = renal replacement therapy; TLT = time-limited trial. Adapted with permission of Scherer and Holley (5).

Policy Update

Health Care Legislation Moves to Senate

By David L. White

Efforts to dismantle the Affordable Care Act (ACA) continue in Washington on several fronts. On March 7, 2017, Health and Human Services Secretary Tom Price, MD, explained the three phases of ACA repeal: repeal legislation; regulatory review; and subsequent legislation that cannot be included in the first repeal effort due to Senate rules on the budget reconciliation process (see box). Action is occurring on all three phases.

> "There are three phases of this plan," HHS Secretary Price said. "One is the bill that was introduced [March 7, 2017] in the House of Representatives… Second are all the regulatory modifications and changes that can be put into place… [t]here were 192 specific rules that were put out as they relate to Obamacare, over 5,000 letters of guidance and the like."
>
> "And we are going to go through every single one of those and make certain that they—if they help patients, then we need to continue them. If they harm patients or—or increase costs, then obviously they need to be addressed," he said about phase two.
>
> "And then there's other legislation that will need to be addressed that can't be done through the reconciliation process," he said, moving on to phase three. "So, the goal of all of this is patient-centered health care, where patients and families and doctors are making medical decisions and not the federal government."

Phase One

The American Health Care Act (AHCA), legislation to repeal the ACA, narrowly passed the House last month after the bill was amended to address concerns raised by the first Congressional Budget Office (CBO) score of the bill that estimated AHCA would leave 14 million more people uninsured next year than under President Obama's health law—and 24 million more in 2026. However, on May 25, the CBO released the updated CBO score for the House-passed version of AHCA. This second estimate was required by Senate rules before the chamber could take up the bill.

The second estimate projects that the bill will save $119 billion over 10 years, $32 billion less than the previous scored version of the bill, and approximately $220 billion less in savings than the initial bill, and was projected to erode coverage by 23 million by 2026.

Here are some highlights from the new CBO score. CBO stressed the uncertainty of its estimates, given that it is hard to know which states would take up the chance to opt out of certain key parts of the ACA. All figures are for the decade spanning 2017 to 2026 unless otherwise specified.

- 14 million fewer people will be insured one year after passage.
- 23 million fewer will be insured in 10 years.
- AHCA would cut spending on Medicaid, the joint federal-state health program for low-income people, by $834 billion. The program would cover 14 million fewer people.
- Premiums will go up in 2018 and 2019. After that, there will be significant variation depending on whether someone lives in a state that opts out of key ACA insurance rules.
- One out of 6 Americans will live in an area with an unstable insurance market in 2020 where sick people could have trouble finding coverage.
- Poor, older Americans would be hit especially hard. The average 64-year-old earning just above the poverty line would have to pay about 9 times more in premiums.
- In 2026, 51 million people under age 65 would be uninsured—almost twice as many as the 28 million who would have lacked coverage under the ACA.
- The bill will save $119 billion, which is $32 billion less than a previous version of AHCA.
- It repeals $664 billion worth of taxes and fees that had financed the ACA.

The path forward for the bill in the Senate is unclear. The next step is for the Senate parliamentarian to determine which provisions of the bill can pass through reconciliation, which is important even if the Senate plans to largely start from scratch.

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Policy Update

Affordable Care Act

Continued from page 17

Phase Two

The second phase began in earnest on May 17, 2017, when the Trump administration and the Centers for Medicare & Medicaid Services (CMS) announced that starting with coverage in 2018, consumers can buy an ACA-approved plan directly from a broker or an insurer's website instead of having to go through HealthCare.gov. It is unclear how many people could be eligible for this new path, but brokers historically sign up at least 50% of exchange enrollees.

The Obama administration had raised the idea for a direct enrollment in proposed rulemaking, but it was never finalized. Serious concerns had been raised about consumers having to provide personal financial information to third parties, which some critics said creates more opportunities for that information to be vulnerable.

The news came on the heels of an announcement by CMS allowing small businesses to skip the federal marketplace to sign their employees up for Small Business Health Options Program (SHOP) coverage. SHOP had been criticized for underperforming when out of the nearly 30 million small businesses in the country, fewer than 8000—less than 0.1% of small businesses—currently participate.

Phase Three

At the same time the second CBO estimate was being released on May 24, 2017, the House Ways and Means Committee was passing three health care bills that make up a part of Phase Three to repeal the ACA. The bills were written to work in conjunction with the AHCA.

The first bill, approved with no Democratic support, allows veterans to retain eligibility for ACA subsidies should the AHCA become law. Critics blasted the legislation, saying it would not protect veterans with preexisting medical conditions under AHCA, which allows states to opt out of certain coverage protections.

Another bill would allow tax credits available under the AHCA to be applied to COBRA plans. The panel approved that measure with one Democrat voting with Republicans.

The final bill, approved with no Democratic support, would require individuals to verify their income eligibility and citizenship or legal immigration status with the Social Security Administration before accessing premium tax credits.

NIH, Medicaid Hit Hard in Federal Budget

By Zachary D. Kribs

On May 23, 2017, the Trump administration released its full budget request to Congress. The budget provides for a $1.7 trillion cut to domestic programs over the next 10 years, while drastically increasing defense spending. The budget, titled "A Foundation for American Greatness" by the White House, provides recommendations to Congress regarding both mandatory spending (entitlements like Medicaid) and discretionary spending (budgets funded yearly by Congress such as the Department of Defense and the National Institutes of Health. Relying on predictions of economic growth of nearly twice the level projected by the non-partisan Congressional Budget Office (CBO), the budget would significantly decrease the federal deficit from current levels by slashing domestic programs, despite a massive increase in military spending and a reduction in revenue from tax breaks to high-income earners.

The American Society of Nephrology (ASN) and peer societies expressed grave concern for the more than $7 billion proposed cuts to the NIH budget. Distributed nearly evenly over all the institutes, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) would receive an allocation of $1.45 billion, a cut of over $429 million from enacted FY 2017 levels and far short of the $2 billion increase ASN is currently advocating for.

Other major changes to the NIH budget include the elimination of the John E. Fogarty International Center, which studies the global impact of climate change on health outcomes, and the creation of a $272 million National Institute of Research on Safety and Quality, which would replace the $324 million Agency for Healthcare Research and Quality (AHRQ) eliminated by the budget.

Altogether, the budget proposal cuts of $12.4 billion from the Department of Health and Human Services (HHS), which, if enacted, would severely inhibit the operation of all affiliated agencies. A number of these cuts are of particular concern to ASN, including a $1.3 billion cut to the Centers for Disease Control (CDC), and a one-third reduction of the HHS General Departmental Management Fund, a cut that could potentially affect key ASN initiatives.

In a first for any presidential budget proposal, the Trump administration also proposes a massive $610 billion cut to Medicaid over the next 10 years. It is unclear if these cuts stand in addition to or replacement of the $839 billion in cuts proposed by the House Affordable Care Act replacement bill, but if enacted would leave the program only able to offer a fraction of its current services.

In response to the budget release, ASN President Eleanor Lederer, MD, FASN, issued a statement "denouncing" the drastic cuts. ASN has also coordinated responses regarding the budget with numerous peer societies, and continues to advocate for a $2 billion increase in funding for the NIH.

High School Student Discusses Research, Interest in Nephrology

Kidney News *Editorial Board member Edgar V. Lerma, MD, FASN, interviewed Uma Alappan, a rising high school senior in Columbus, GA, about her interest in nephrology and the poster she presented at ASN Kidney Week 2016, titled "Analysis of Acidity and Phosphorus Levels in Commonly Consumed Sodas."*

Tell us something about yourself and how you developed an interest in nephrology.

Both of my parents are doctors—my mother a pediatrician, my father a nephrologist—so I have always been interested in the medical field. As a child I joined my parents while they made rounds at the hospital or saw patients at their private practices. It was not until my sophomore year of high school that I realized I had an interest in nephrology. For my annual science fair project, I decided to analyze the acidity and phosphorus levels of several sodas and conduct a survey around my hometown, Columbus, GA, to identify a general pattern of soda consumption and use this information to help prevent future health issues. Through research I discovered that excess phosphorus consumption can lead to several fatal renal diseases—for example, calciphylaxis. During this research, I learned more about the general processes and functions of the kidney, and thus began my budding interest in nephrology.

For my junior year of high school, I realized that nephrology has a lot to do with both biology and chemistry, so I signed up for AP Biology and AP Chemistry—advanced placement college classes offered at the high school level. Upon returning from ASN Kidney Week 2016 in Chicago, I instantly felt a difference in my knowledge that helped me tremendously with these classes. For example, in AP Biology, I was able to easily learn the anatomy of the nephron and the absorption/secretion processes involved in it, including the filtration process in the glomerulus of the Bowman's capsule and the facilitated diffusion/osmosis and active transport that occurs in the proximal tubule, loop of Henle, distal tubule, and collecting duct. Being able to confidently explain the process of the nephron to my teacher, Mrs. Lingo, and explore the exciting concept of the kidney, inspired me to pursue a career as a nephrologist.

As for my other interests, I am a rising high school senior at Brookstone School in Columbus. I sing in the school's chorus, take piano and voice lessons after school, and compete in musical competitions. I am the captain of the Varsity Girls Golf Team at Brookstone and play in several golf matches/tournaments throughout the season.

Tell us about your experience attending Kidney Week 2016 in Chicago.

When I first submitted my study abstract, I did not expect it to be accepted by such a prestigious society, especially as I was competing with highly trained medical professionals. At the most I hoped ASN would publish my abstract online in *JASN*. I was completely shocked when I received an email not only congratulating me on my abstract's acceptance to *JASN*, but also inviting me to Chicago for a poster presentation.

Because I am a high school student, my father called ASN to ensure my abstract was not accepted by mistake. It was not: ASN recognized that I was a high school student and generously granted me a free student membership and registration. I was going to Chicago.

From the moment I walked into the convention center, an academic vibe radiated from the well dressed, focused,

sophisticated nephrology professionals. My father—an ASN member himself—said he could attend all the lectures while I stayed in the hotel room, but I insisted that I make the most out of the experience and joined him. During several lectures—including presentations by Mona Calvo, MS, PhD, on the changes in the FDA's representation of phosphorus content in food labels; by Charles O'Neill, MD, on observation of the progression of medial arterial calcification in ESRD patients; and by Mariano Rodriguez, MD, PhD, on his study finding that calcimimetics maintain bone turnover in a PTH-independent manner in uremic rats—I had to look up key vocabulary terms, but once I deciphered the refined medical lexicon, I was able to fully grasp the concepts.

I was also intrigued by the various products displayed on the exhibit floor, as well as the study posters of nephrologists from many different countries, including Spain, Germany, Japan, Italy, Portugal, Argentina, Qatar, and Egypt. As for my own poster, presenting it was the most rewarding experience I have ever had. Because I was a high school student presenting to medical professionals, I was not sure if I would be able to accurately respond to every question; however, I prepared well beforehand and ended up answering questions without a problem. The feeling I had when I could finally share my knowledge was exhilarating. Over 250 people came to visit my poster—so many that I lost count—and it was a satisfying moment to realize that as a high school student from small Columbus, GA, all my hard work was being appreciated by medical professionals across the globe.

Tell us about your paper, how you developed the idea for doing the research, and what you learned.

When I was a child, my parents always told me not to drink sodas. As I grew older, my curiosity increased: *What do sodas contain that makes them so unhealthy*? I knew my parents were aware of the health issues caused by overconsumption of sodas, but I decided to investigate further on my own. For my annual science fair project, I decided to test the pH and phosphorus levels of various commonly consumed sodas, such as Coke, Pepsi, and Sprite, because this information is not readily available on product labels. I would also conduct a random survey in and around Columbus to determine survey participants' general soda consumption pattern and knowledge of its long-term health impact. Questions included each participant's favorite soda, their soda-consumption frequency, and their knowledge of soda contents. The nationally recognized Cott Beverages manufacturing company, located in Columbus, allowed me to estimate the pH and phosphorus content of various sodas using their precise instruments.

After analyzing the data collected, I came to the conclusion that many popular sodas contain a significant amount of phosphorus and have high acidity levels that may pose a great health risk if overconsumed. The survey results revealed that people are not aware of these adverse contents of soda, so they continue to overconsume it.

I felt it was crucial that my findings be released so I entered the Columbus Science & Engineering Fair. I won first place and the title "Best Overall Project," allowing me to advance to the state level, where I won second place for my category and received the prestigious United States Metric Association (USMA) SI Metric System Award, which is presented to three students in Georgia with the most accurate experimental data, collected using precise metric system instruments.

These fairs still were not enough to inform the public of my findings, so I took it one step further. I spoke with my nephrologist father about other methods to convey my findings, and he suggested submitting an abstract to ASN, because the topic is important in dealing with fatal conditions such as calciphylaxis, a form of calcific uremic arteriolopathy resulting from calcium phosphate salt formed when there is excess phosphorus in the body. I worked to perfect my abstract and showcase my information at its best in hopes of acceptance. After receiving the email detailing my abstract publication in *JASN* and an invitation to Chicago for a poster presentation, I was ecstatic. I would finally be able to share my knowledge at the prestigious ASN annual meeting.

Uma Alappan at her Kidney Week 2016 poster.

Are there any individuals you would like to emulate in your career, such as family members, teachers, or mentors?

My parents, Drs. Raj and Devica Alappan, are two of the most motivated, hard-working individuals I know. They are always focused on their careers, yet still find time for their families and those they love. In the future I want to not only be a successful nephrologist, but also a successful mother and wife. Both my mother and father have always made time for my brother and me. Nevertheless, they have reached extraordinary levels in their medical careers, having received numerous accolades for their work, publication in several reputable journals, and expansion of their own medical practices over the years. If I become a nephrologist, I hope to not only attain their level of prestige as doctors but also to be as good a parent to my children as they have been to me.

I have always admired my older brother Harish. We are about as close as two siblings can get. Harish has long had a passion for soccer, and as a child I had to play along with him so he could practice his skills on an opponent. Harish has achieved much not only as a soccer player, but also as a student, maintaining "high A" averages while still pushing himself to new heights in soccer. Very few people can balance both academics and sports as well as he can, and I hope to emulate my brother and, like him, manage both my hobbies and my career as a future nephrologist.

Without my mentor, Mr. Prem Virmani, my statistical data analyst, Mr. Madhusudan Bhandary, and my teachers, Dr. Dorothy Cheruiyot and Mrs. Cynthia Lingo, I would not have reached ASN Kidney Week in Chicago.

Mr. Virmani generously allowed me to conduct my research in his Cott Beverages Laboratory in Columbus and was my mentor throughout the study. Mr. Bhandary assisted me in analyzing the statistical significance of my data. Without the guidance of my teachers, I would not have had the encouragement needed to pursue the research. In my future career I hope to be as generous, encouraging, and supportive as these four individuals have been to me throughout this experience.

Attending Kidney Week 2016 allowed me to make connections with several extraordinary people I would like to emulate in the future.

Everyone had conducted such complex research, offered valuable structural criticism of my own study and poster presentation, and generously offered connections for future research. They included Randy Hennigar, MD, PhD, Arkana Laboratories nephropathologist, who connected me with people who could help in future research; Mark Perazella, MD, FASN, Professor of Nephrology at Yale, who instilled confidence in me by eagerly listening to my poster presentation; Matt Sparks, MD, FASN, Duke Assistant Professor of Medicine, who tweeted a picture of my father and me posing in front of my poster board that went viral; Mona Calvo, MS, PhD, retired FDA Expert Regulatory Review Scientist, who offered me an FDA summer internship; Mariano Rodriguez, MD, PhD, Professor of Medicine at the Hospital Universitario Reina Sofia in Córdoba, Spain, who offered several ideas for future research and provided helpful criticism for my poster presentation; and Edgar V. Lerma, MD, FASN, Clinical Professor of Medicine at the University of Illinois at Chicago/Advocate Christ Medical, who generously connected me with *ASN Kidney News* to share my ASN experience. In my career as a nephrologist, I hope to be as successful, generous, and motivated as these individuals are.

I am building on the connections I made at ASN Kidney Week, and am trying to conduct future research with those I met in Chicago. I recently submitted both an abstract and research paper for the Kidney Week study to the Georgia Junior Science and Humanities Symposium (GJSHS) hosted at the University of Georgia in February. I was one of 50 students from the entire state of Georgia selected to give an oral presentation at this all-expense-paid, 3-day symposium.

After the ASN meeting, I was interviewed on the local NBC affiliate's TV news segment "Straight Forward with Gloria Strode" to discuss my experience in Chicago and spread awareness and interest in the field of nephrology.

Where do you see yourself in the next 10 years?

In 10 years, I hope to have attended a prestigious undergraduate university that will have given me the opportunity to expand my knowledge, gain experience, and attend a well-respected medical school. I hope to have conducted advanced research and to be a resident physician with the intention of specializing in nephrology. I also hope to have settled down with a husband to start a family, while still balancing my professional career responsibilities. I also aim to have served as an inspiration to students like myself willing to work hard to expand their knowledge base and attain a successful career.

What advice would you give ASN leaders about how to reach out to young people and expose them to nephrology?

ASN might create a forum for high school students where they can present their studies to trained experts, develop presentation skills, and foster an interest in nephrology. Another possibility is a separate section at Kidney Week for high school students to give either oral or poster presentations. If ASN were the first to offer students this experience, it might start a trend, encouraging other medical organizations such as the American Heart Association or the American Academy of Neurology to help students develop their interest for other aspects of medicine as well.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Industry Spotlight

First Quarter 2017 Results for US Dialysis Providers

For the first quarter of 2017, the dialysis business for Fresenius Medical Care North America (FMCNA) grew by 14% (10% at constant currency). Quarterly growth was influenced by the positive effect of an agreement with the US Departments of Veterans Affairs (VA) and Justice for a settlement for underpayment, a favorable impact from commercial payers, and an increased number of treatments. Dialysis care revenue for the quarter rose to $2.65 billion from $2.32 billion from the first quarter of 2017 to the first quarter of 2016.

DaVita had overall patient service revenues of $2.6 billion in the first quarter of 2017, compared with first quarter 2016 revenues of $2.48 billion, a 5% increase. DaVita also noted a favorable impact from the VA settlement in its quarterly announcement.

According to their respective web sites, FMCNA delivered care to 188,987 patients in 2016 and DaVita to 188,000 patients by December 31, 2016. However, at the end of the first quarter of 2017, DaVita reported providing services to "approximately 205,900 patients at 2544 dialysis centers (2382 in the US, or 94% of DaVita centers)."

In the first quarter of 2017, DaVita opened 24 new dialysis centers and acquired 12 dialysis centers in the US, as well as opening five new dialysis centers and acquiring three centers outside the US.

The third largest US dialysis service provider is US Renal, based in Plano, Texas, which serves more than 23,000 patients across 31 states and the Territory of Guam.

Pfizer's Biosimilar to Epogen Nears Final FDA Approval

The US Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee in a 14–1 vote recommended approval of a Pfizer drug that is a biosimilar compound to epoetin alfa (Amgen's brand name anemia drug Epogen). The committee voted to support the biosimilar drug for approval of all four of Epogen's clinical indications, making it the first biosimilar of an erythropoiesis-stimulating agent in the US recommended for approval by an FDA advisory committee.

Analytical similarity data between the biosimilar and the FDA-licensed reference product is the basis for biosimilar development. The new biosimilar product must be demonstrated to be "highly similar" to an FDA-licensed biological product under FDA rules. The licensure pathway of a biosimilar means it can be licensed based on "less than a full complement of product-specific preclinical and clinical data," known as an abbreviated licensure pathway, the FDA states.

In this case, the biosimilar drug, developed by Pfizer's subsidiary Hospira, was designed to be similar to the reference drug for all of its clinical indications. Epogen is a man-made protein that stimulates red-blood cell production for anemia owing to chronic kidney disease (CKD) and other conditions.

One member of the FDA committee voted against approving the biosimilar for two of four indications, reported Regulatory Focus website. "I have residual concerns about lack of immunogenicity and basic safety data in patients with HIV and cancer, and for that reason I voted 'no' for the broader indication," said Thomas Uldrick, MD, clinical director for the HIV & AIDS Malignancy Branch at the National Cancer Institute. Uldrick did vote to approve the biosimilar drug to treat anemia due to CKD and to reduce allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

Other panelists agreed with Uldrick regarding the uncertainty due to immunogenicity, but at least one stated that clarity was likely to emerge during postmarket surveillance.

According to the Pink Sheet, a publication that follows biopharma regulations, laws, and business news, only four biosimilar products had been approved by January 2016, although five are slated for review in 2017 to date in first-cycle review. The new epoetin alfa biosimilar drug returned for FDA review after an earlier application failed to pass at the committee approval phase.

Dialysis Chair Market Growth

A quietly flourishing sector of the hemodialysis products market is dialysis chairs. According to a new draft report from Persistence Market Research, the market for hemodialysis chairs in India is growing quickly as the number of people with chronic kidney disease worldwide increases.

The rate of growth in the hemodialysis chair market in India is 31% per year, the highest noted in the draft report, which will be published in July 2017. Overall, the number of patients with diabetes in India will more than double by 2040. Online lists of dialysis chair manufacturers and suppliers in India and China are lengthy.

The market report, "Hemodialysis Chairs Consumption Market: Global Industry Analysis and Forecast 2016–2024," states that the growth rate for the dialysis chair market in the US is 6% and 8% on average in the rest of the world. The market can be generally divided into electric chairs and manual hemodialysis chairs.

The Elkhart, IN, medical chair manufacturer Champion recently celebrated 25 years in the medical chair business. The company began by producing chairs for dialysis patient comfort, and its product line now includes other types of medical chairs.

Although the company's focus is on US sales, Champion also sells chairs in Saudi Arabia, Singapore, India, Mexico, and Canada. Champion attracted investment from Levine Leichtman Capital Partners (LLCP), which noted in 2013 that "with its leading position in the dialysis center market and growing position in similar healthcare markets, the company is ideally positioned to benefit from the continued strong growth within these market segments. On May 9, 2017, LLCP sold Champion to an undisclosed buyer.

Index to Advertisers

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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 [^{14}C]-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 [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-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]*.

AMGEN®

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/

USA-416-035346 02-17

Introducing Parsabiv™
The first and only IV calcimimetic

You control delivery.
Parsabiv™ lowers 3 key sHPT lab values.

A new era in the delivery of calcimimetic treatment has begun. Lower PTH, phosphate, and corrected calcium with the only calcimimetic you administer at the end of hemodialysis. With Parsabiv™, control of calcimimetic delivery is now in your hands.

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

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.

Parsabiv™
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Visit **ParsabivHCP.com** for more information.