ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN 50 years

Kidney News

July 2016 | Vol. 8, Number 7

Kidney Circadian Clock Affects Metabolic Processes, Drug Pharmacokinetics

Many of the body's processes follow a natural daily rhythm, or circadian clock, that is based on regular light-dark cycles that correspond to day and night. A circadian clock in the kidneys plays an important role in maintaining balance throughout the body, and alterations to the clock can influence metabolism in both health and disease. For example, in individuals who take medications, the kidney's circadian clock may control the process of drug elimination and therefore influence the duration of a drug's action and the effectiveness of the therapy. The findings are published in the *Journal of the American Society of Nephrology* (Nikolaeva S et al. *J Am Soc Nephrol*. 2016 Apr 7. pii: ASN.2015091055).

The body's circadian clock can have a range of influences, from determining when a person experiences peak cognitive performance to the timing of acute medical events such as strokes and heart attacks. The clock even enables maximum expression of genes at appropriate times of the day, allowing individuals to adapt to the earth's rotation. Research has also shown that it can change as people age, so, for example, the brain signals the body to sleep earlier in the evening and to awaken earlier in the morning.

In the kidneys, physiologic processes such as sodium reabsorption, renal blood flow, and glomerular filtration follow a daily rhythm, and coordination of the timing of these processes allows the kidney to anticipate changes in metabolic and physiological demands throughout a 24-hour cycle. Results from animal and human studies indicate that circadian disruption and sleep deprivation can have detrimental effects on the kidneys.

In the *JASN* study, a team led by Dmitri Firsov, PhD, and Natsuko Tokonami, PhD, of the Department of Pharmacology and Toxicology at the University of Lausanne in Switzerland, blocked kidney cells' expression of Bmal1, a gene critically involved in the circadian clock system, and found that the clock is responsible for the temporal adaptation of kidney function to the light and dark phases of the day that correspond to activity and rest.

"Since urine formation and excretion by the kidney is one of the most easily detectable rhythmic processes—we are forming and excreting much more urine during the day—we had hypothesized

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ASN, KHI Announce New Initiatives at White House Organ Summit

By Rachel Meyer

On June 13, 2016, ASN and the Kidney Health Initiative (KHI)—the society's public-private partnership with the US Food and Drug Administration—participated in a summit the White House convened to address the shortage of organs available for transplantation. The White House Organ Summit brought together a wide variety of stakeholders committed to building on the Obama administration's efforts to improve outcomes for individuals waiting for organ transplants and support for living organ donors.

Approximately 100,000 Americans are on the waitlist for a kidney transplant alone, and 13 die every day waiting for their name to be called. ASN engaged in dialogue with the White House regarding challenges to transplantation and new kidney therapeutics prior to the summit for several months, and was invited to unveil initiatives in support of the summit's goals.

ASN announced three initiatives at the summit: the first $7 million toward a kidney disease XPRIZE, commitment to

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Inside

Kidney Circadian Clock

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that at least a part of this rhythmicity is dependent on the circadian clock mechanism," Tokonami said.

The researchers also performed experiments that combined functional, transcriptomic, and metabolomic analyses in mice with inducible conditional knockout of *BMAL1* (the mouse version of *Bmal1*) in renal tubular cells. Blocking *BMAL1* in adult mice did not produce obvious abnormalities in sodium, potassium, or water handling in the kidneys, but there were significant changes in the expression of genes related to metabolic pathways. Furthermore, kidneys from knockout mice exhibited changes indicative of altered mitochondrial function, an effect that could have a range of impacts on diverse functions within cells. The animals' blood also contained altered levels of various amino acids, lipids, and other components, with significant increases in plasma urea and creatinine. The investigators' partial analysis covered less than 5% of the total number of metabolites found in plasma, but even this restricted approach identified more than 50 metabolites that are differentially represented in the plasma of knockout mice.

The investigators noted that the animals' kidneys had a reduced capacity to secrete the diuretic furosemide, paralleled by an approximate 80% decrease in expression of SLC22a8, a member of the organic anion transporter family of proteins that is known to mediate the excretion of many drugs.

"We've shown that the circadian clock in the kidney plays an important role in different metabolic and homeostatic processes at both the intrarenal and systemic levels and is involved in drug disposition," Firsov said. The findings related to SLC22a8 suggest that by controlling the process of drug elimination, the kidney's circadian clock may control how long a drug remains active, and therefore its effectiveness.

"In normal light-dark conditions and on a normal diet, these kidney-specific conditional *Bmal1* knockout mice exhibit an intriguing phenotype that includes dramatic changes in gene expression affecting, among other things, pharmacokinetic pathways," said Michelle Gumz, PhD, who was not involved with the research and is an Assistant Professor in the Division of Nephrology, Hypertension and Renal Transplantation within the University of Florida's Department of Medicine. Her laboratory is investigating the role of the circadian clock in the kidney, with a focus on sodium transport regulation. "These findings have important implications for our understanding of how chronotherapy may affect renal function and drug efficacy. It will be very interesting to determine the effect of a modified diet or light cycle on fluid and electrolyte handling in this novel knockout mouse model."

New Initiatives

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developing a roadmap to achieve the goal of creating a bio-artificial or bioengineered alternative to dialysis, and a partnership with the US Department of Veterans Affairs called the Kidney Innovation Initiative.

Onstage at the White House, ASN announced its commitment of the first $7 million toward a kidney disease prize completion, in partnership with the XPRIZE Foundation.

"With more than 450,000 Americans and millions of people around the world suffering from kidney failure who depend on dialysis to live, ASN is committed to finding a superior alternative that improves their lives and today announced its pledge of the first $7 million toward a possible XPRIZE competition to achieve that goal," said ASN President Raymond C. Harris, MD, FASN.

Developed in partnership with the XPRIZE Foundation, the kidney disease prize competition would incentivize the development of a novel wearable or implantable device that replaces kidney function and improves patient quality of life.

The Medicare program entitles every American suffering from kidney failure—regardless of age— to lifesaving dialysis at a cost of nearly $35 billion annually, more than the National Institutes of Health's total budget. Despite this commitment to care for patients with kidney diseases, little innovation in the field of kidney treatment has occurred for decades.

"ASN believes a prize competition has the power to catalyze the radical degree of change patients deserve and to ignite the science that is poised to develop life-changing solutions," Harris said.

Michelle A. Josephson, MD, FASN, former chair of the ASN Transplant Advisory Group, made the kidney disease XPRIZE announcement on behalf of ASN.

"It was wonderful to see the White House recognize the problem of kidney failure, the large number of people affected by kidney failure, and that treatments need innovation and improvement," Josephson said. "As excellent as our interventions are, they are not good enough; we really need improvements in the dialysis field."

Following a morning of panel discussions and other announcements of commitments to advance the goals of increasing access to transplantation, participants divided into breakout groups—including one group focused on innovation opportunities. In that discussion, XPRIZE emerged as "really the subject of the roundtable with members of the FDA, CMS, and some of the other scientific agencies there, talking about the best way to get this implemented and to move things forward," recounted ASN Public Policy Board Chair John R. Sedor, MD, FASN.

"We also focused on kidney diseases under-recognized, as research in kidney diseases has been underinvested, and we asked the White House to help us raise awareness about the problem kidney disease is for patients across the country and in fact, worldwide," Sedor said.

In addition to pledging the first $7 million for the kidney disease XPRIZE, ASN announced the Kidney Innovation Initiative—a partnership with the US Department of Veterans Affairs (VA) that challenges innovators worldwide to compete in developing technology resources that improve quality of life and outcomes for people with kidney diseases and those anticipating a kidney transplant.

Also at the summit, KHI committed to initiate the development of a roadmap that will describe scientific, technical, and regulatory milestones needed to achieve the goal of creating a bio-artificial or bioengineered alternative to dialysis as renal replacement therapy. The roadmap will consider challenges to development, provide "state of the art" expectations for entrepreneurs and other technology developers, and spur innovation in producing functioning kidney replacements by engaging stakeholders, identifying research priorities to alleviate critical knowledge gaps, and advancing the science of alternatives to dialysis.

The White House asked participating organizations, companies, and other stakeholders to report back on progress concerning the goals and announcements set at the summit in 6 months.

"We think this is a very positive step that the White House has identified kidney disease broadly as an issue which is very important for the country's health. We are delighted that they took the time and energy to put together this conference, and we're hoping this is just the beginning of a much larger initiative," Sedor said.

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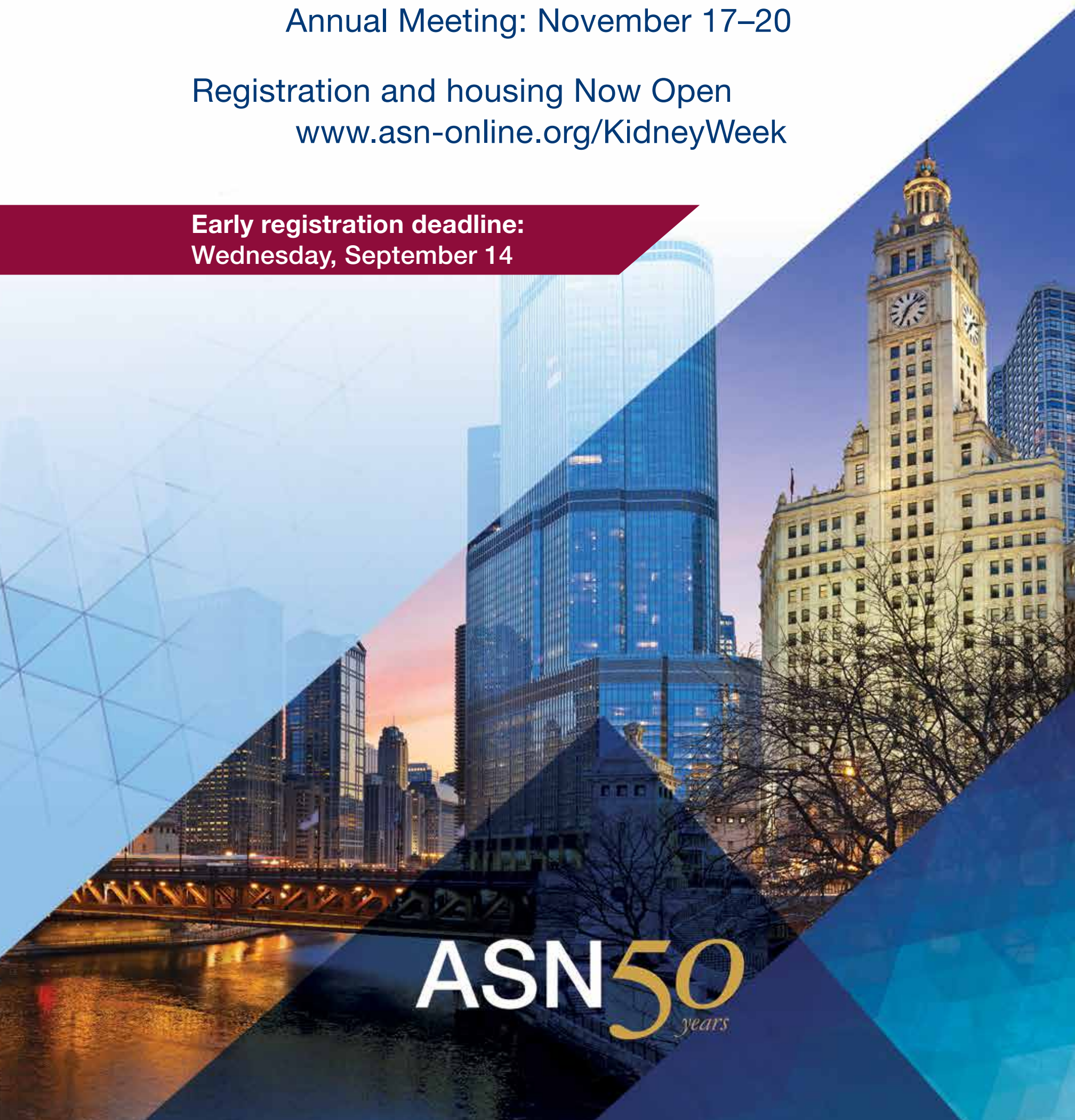

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ASN President's Column

By Raymond C. Harris, MD, FASN

Raymond C. Harris, MD, FASN

When I think back over the time that I have been in nephrology, I am struck by how many advances we have made in our understanding of kidney function and the pathogenesis of kidney disease. In no particular order, a (very) incomplete list includes: the enormous new insights into the biology of the podocyte and its importance as a target of kidney disease; the regulation of the renin-angiotensin system, its role in kidney diseases, and the effectiveness of its targeting in slowing progression; the role of inflammatory cells in kidney diseases; insights into the underlying pathophysiology of numerous genetic kidney diseases (e.g., PKD, Alport's syndrome, cystinosis, Bartter's syndrome, Liddle's syndrome, Gordon's syndrome); elucidation of underlying causes of glomerular diseases (e.g., IgA nephropathy, membranous nephropathy); the discovery of a genetic predisposition of certain populations to glomerular disease (ApoL1); spectacular success in developing more effective immunosuppression so that both patient and transplanted kidney survival have significantly improved; and immunotherapy for a variety of glomerular diseases.

Still, there remain concerns about the relative lack of success at developing new therapies for our patients, and the paucity of randomized controlled trials. We lag behind other specialties in implementation of new trials.

There are certain obvious reasons for this discrepancy:

First, designing trials for interventions in kidney diseases can be difficult because of the variability of individual patient rates of GFR decline and the necessity to use significant loss of renal function as a hard outcome. Everyone recognizes that to design and implement more effective clinical trials, we need better biomarkers and better understanding of how to stratify patients into "fast" and "slow" progressors. More generally, in order to identify the most effective targets, we need to better understand the underlying pathogenesis of human kidney diseases.

Second, there is insufficient funding for both preclinical and clinical research for kidney disease. While NIH has committed $2978 per patient with AIDS and $568 per patient with cancer, it commits only $29 per patient for kidney disease, even though there are more patients living with kidney disease in the US than with cancer and AIDS combined. This disparity is even starker when one considers that the amount spent by the government on the Medicare ESRD program is more than the entire NIH budget. Think how much more could be accomplished if we had the sort of funding that is lavished on these other diseases.

Recently, there have been two exciting developments that we hope will spur further successful research into approaches to prevent and treat kidney diseases.

The NIDDK Kidney Precision Medicine Initiative aims to obtain human kidney tissue for molecular interrogation. Many of the recent advances in understanding cancer biology and development of targeted therapies have arisen from similar direct analysis of the human tissue, so this NIH initiative may provide similar insights for our field and aid in identification of new targets for therapy, development of more effective biomarkers, and provide a fuller understanding of the natural history and variability of human kidney diseases.

In addition, it is especially encouraging for our discipline that the White House recently convened a summit to discuss the shortage of organs for transplantation and the need for innovative alternatives to traditional dialytic therapies for ESRD patients. There has been an unfortunate lack of innovation in therapeutic options for renal replacement in patients with ESRD and an inadequate number of donor kidneys available for what is still the best option for our ESRD patients. Representatives from ASN, along with representatives from FDA representing KHI, the public-private partnership of ASN with FDA, attended and announced new commitments to further research to improve treatment options for patients with ESRD. Specifically, ASN has pledged the first $7 million toward a possible XPRIZE competition to achieve that goal. We hope that this White House Initiative will spur exciting new research and innovative approaches and will lead to better options for our patients.

ASN applauds the foresightedness that led to the development of these two initiatives. We are very optimistic that they will result in new and exciting approaches for nephrologists to continue to provide the best care for patients with kidney diseases.

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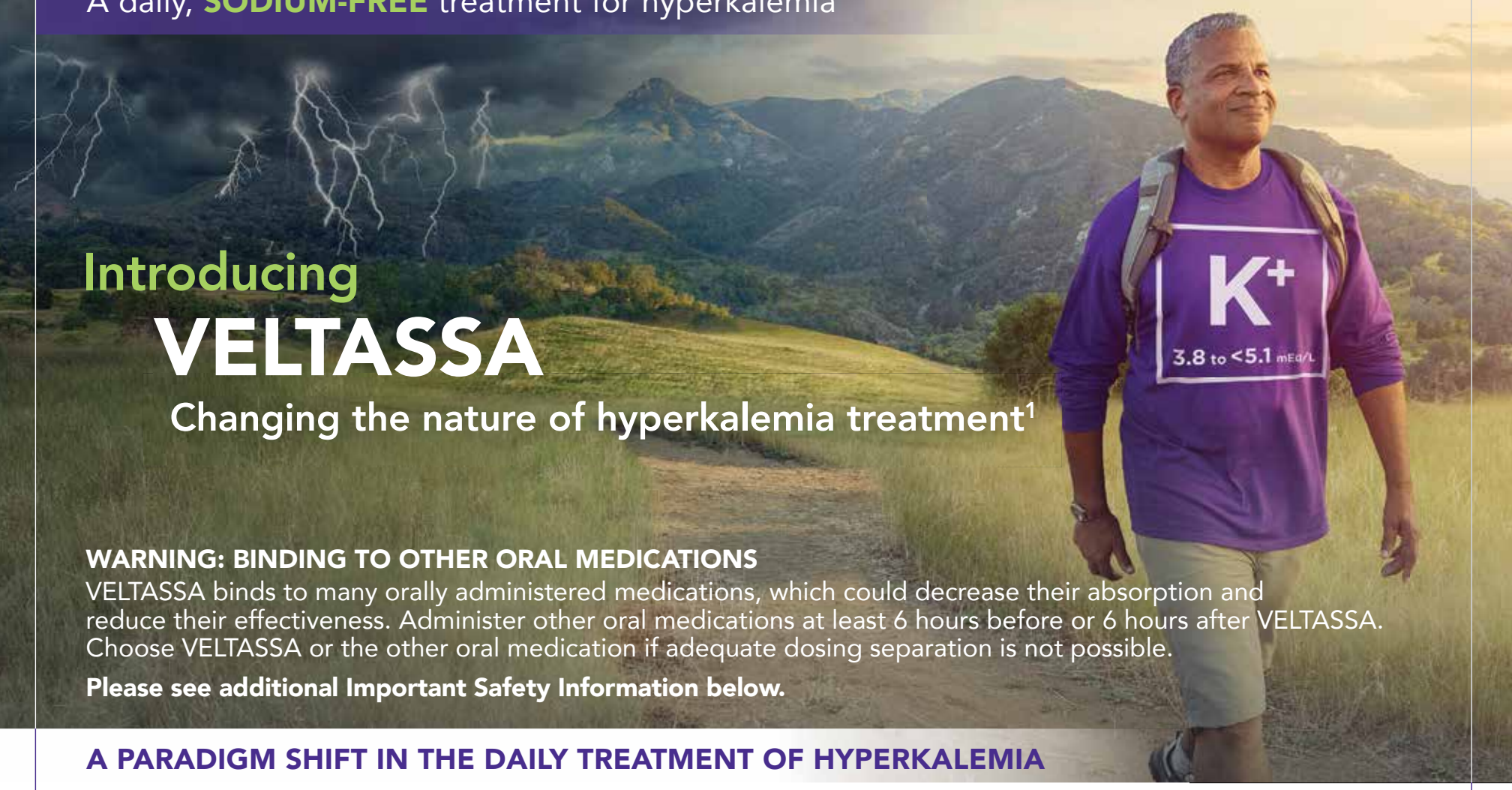

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*Across 4 studies up to 1 year.

†Approximately 69% of all patients studied completed treatment at 52 weeks.

Reference: 1. Bakris GL, Pitt B, Weir MR, et al; for AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-161.

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Findings

Prediabetes linked to increased risk of hyperfiltration and albuminuria

Middle-aged adults with prediabetes are at increased risk of developing glomerular hyperfiltration and albuminuria, reports a study in *The American Journal of Kidney Diseases*.

The researchers analyzed prospective data on a general population sample of 1261 Norwegian adults drawn from the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) Study and the RENIS Follow-Up Study. At baseline, subjects were 50 to 62 years old and free of diabetes. On the basis of fasting glucose and hemoglobin A1c levels, 595 participants had prediabetes according to American Diabetes Association criteria, and 169 participants had prediabetes according to International Expert Committee of 2009 (IEC) criteria.

At a median follow-up of 5.6 years, change in measured GFR (mGFR) was compared between groups; hyperfiltration was defined as mGFR above the 90th percentile adjusted for age, sex, height, and weight. Rates of high-normal urinary albumin-to-creatinine ratio (ACR; greater than 10 mg/g) were assessed as well.

On multivariable analysis, both sets of prediabetes criteria predicted an increased mGFR at follow-up and a lower annual rate of decline in mGFR. Baseline fasting glucose and HbA1c were also significant predictors. In the smaller group of patients meeting IEC criteria, odds ratios were 1.92 for hyperfiltration and 1.83 for high-normal ACR. The associations remained significant after adjustment for baseline BP, use of antihypertensive medications, and other cardiovascular risk factors [Melsom T, et al. Prediabetes and risk of glomerular hyperfiltration and albuminuria in the general nondiabetic population: A prospective cohort study. *Am J Kidney Dis* 2016; 67:841–850].

What happens to kidney donors who develop ESRD?

A high proportion of living kidney donors who have developed ESRD are never waitlisted for kidney transplantation, reports a study in *Transplantation* that was part of a special issue on living organ donation.

Using data from the Scientific Registry of Transplant Recipients, the researchers identified 96,127 individuals who donated kidneys between 1994 and 2011. Of these, 99 developed ESRD. Median age at diagnosis of ESRD was 50 years old; 56 percent of patients were men, and 34 percent were black. Causes of ESRD were GN in 29.3 percent of donors, hypertension in 24.2 percent, diabetes in 5.1 percent, and other causes in 41.4 percent. Median times to developing ESRD in these groups were 7.4, 12.0, 9.9, and 9.6 years, respectively.

Initial treatment for ESRD was dialysis in 78 patients. Thirty-seven patients were waitlisted for kidney transplantation, and two received a live donor transplant without being listed. Twenty patients were listed pre-emptively, 19 of whom received a transplant. The remaining 39 patients were never listed and never received a transplant.

The donors were waitlisted earlier than a matched group of nondonors with ESRD (median of 14 versus 120 months) and transplanted earlier (2.8 versus 21.5 months). Donors were less likely than controls to receive a live donor kidney (13 versus 39 percent) and more likely to receive a standard criteria deceased donor kidney (87 versus 50 percent). The two groups had similar posttransplant graft and patient outcomes.

Living kidney donors have a "demonstrated, albeit low" risk of ESRD. This national study finds that living donors who develop ESRD are waitlisted and transplanted faster than matched nondonor controls. However, about 40 percent of donors with ESRD are never waitlisted, leading to very high mortality. This finding "warrants further study to ascertain why these donors with ESRD never gained access to the waiting list," the researchers write [Muzaale AD, et al. Outcomes of live kidney donors who develop end-stage renal disease. *Transplantation* 2016; 100:1306–1312].

Does low sodium increase cardiovascular disease risk?

In individuals with or without hypertension, low urinary sodium excretion is associated with an increased risk of death and cardiovascular death, according to a controversial meta-analysis published in *The Lancet*.

The researchers analyzed pooled data on more than 133,000 individuals from 49 countries drawn from four large prospective studies. About 64,000 participants were classified as having hypertension defined as untreated BP of 140/90 mm Hg or greater or prescribed antihypertensive medications at baseline. The relationship between estimated 24-hour urinary sodium excretion and a composite outcome of death and major cardiovascular disease events was assessed for the groups with versus without hypertension.

At a median 4.2 years of follow-up, there were 6835 events in individuals with hypertension and 3021 in those without hypertension. Per gram of increased sodium, systolic BP increased by 2.08 mm Hg in the hypertensive group versus 1.22 mm Hg in the nonhypertensive group. In the hypertensive group, risk of death or cardiovascular events was increased at sodium excretion of 7 g/d or greater and at less than 3 g/d (hazard ratios of 1.23 and 1.34, respectively).

In individuals without hypertension, higher sodium excretion was not significantly associated with risk of death or cardiovascular disease events. However, risk was elevated for nonhypertensive subjects with sodium excretion of less than 3 g/d (hazard ratio of 1.26). In both groups, 11 percent of participants had sodium excretion less than 3 g/d.

The results suggest that, in individuals with hypertension, both high and low sodium intakes are associated with an increased risk of cardiovascular disease and death. Among those without hypertension, risk is increased only for those with low sodium intake. The investigators conclude that "[t]hese data suggest that lowering sodium intake is best targeted at populations with hypertension who consume high sodium diets" [Mente A, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: A pooled analysis of data from four studies. *Lancet* 2016, DOI: http://dx.doi.org/10.1016/S0140-6736(16)30467-6].

High sodium linked to increased cardiovascular risk in chronic kidney disease

In patients with chronic kidney disease (CKD), high urinary sodium excretion is associated with an increased risk of cardiovascular events, concludes a study in *The Journal of the American Medical Association*.

The prospective cohort study included 3757 patients with CKD enrolled at seven sites in the Chronic Renal Insufficiency Cohort Study. Urinary sodium excretion was estimated from the mean of three 24-hour urinary samples and calibrated to the sex-specific mean of 24-hour urinary creatinine excretion in the study population. Urinary sodium was evaluated for association with a composite of cardiovascular disease events.

Fifty-five percent of patients were men; the mean age was 58 years old (2). At a median follow-up of 6.8 years, there were 575 patients with heart failure, 305 with myocardial infarction (MI), and 148 with stroke.

Quartiles of calibrated sodium excretion ranged from less than 2894 to greater than 4548 mg/24 hours. From the lowest to the highest quartile, cumulative incidence rates of cardiovascular events were 18.4 percent, 16.5 percent, 20.6 percent, and 29.8 percent. In the highest compared with the lowest quartile, rates of specific events were 23.2 versus 13.3 percent for heart failure, 10.9 versus 7.8 percent for MI, and 6.4 versus 2.7 percent for stroke. On multivariable analysis, hazard ratios were 1.36 for overall events, 1.34 for heart failure, and 1.81 for stroke; the association with MI was no longer significant.

Among patients with CKD, those with the highest level of sodium excretion were at increased risk of cardiovascular disease independent of other risk factors. The associations are similar across patient subgroups and independent of total caloric intake and systolic BP. "These findings, if confirmed by clinical trials, suggest that moderate sodium reduction among patients with CKD and high sodium intake may lower CVD risk," the researchers conclude [Mills KT, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA* 2016; 315:2200–2210].

Early or late renal replacement therapy for severe acute kidney injury? The Artificial Kidney Initiation in Kidney Injury Trial finds similar outcomes

For patients with stage 3 acute kidney injury (AKI), early and delayed strategies for renal replacement therapy (RRT) yield similar mortality rates, concludes a randomized trial in *The New England Journal of Medicine*.

The Artificial Kidney Initiation in Kidney Injury (AKIKI) Trial included 620 patients with severe AKI enrolled at 31 French intensive care units (ICUs). All patients had Kidney Disease Improving Global Outcomes (KDIGO) stage 3 AKI requiring mechanical ventilation and/or catecholamine infusion, with no potentially life-threatening complications directly related to kidney failure.

In open label fashion, patients were assigned to early (immediate) or delayed RRT. In the delayed group, RRT was started if the patient developed severe hyperkalemia, metabolic acidosis, pulmonary edema, BUN level greater than 112 mg/dL, or oliguria lasting longer than 72 hours.

The primary outcome of 60-day overall survival was not significantly different between groups. Mortality was 48.5 percent in patients assigned to the early strategy and 49.7 percent in those with the delayed strategy. In the delayed group, 49 percent of patients received no RRT.

Catheter-related bloodstream infections developed in 10 percent of patients with the early strategy versus 5 percent with the delayed strategy (3). Most other complications were similar between groups. Time to adequate diuresis was shorter with the delayed strategy.

There is ongoing debate over the optimal timing of RRT for severe AKI. The AKIKI Trial shows similar mortality in patients with stage 3 AKI assigned to an early versus delayed strategy. The authors point out that their delayed strategy avoids the need for any RRT in about one-half of patients [Gaudry S, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016, DOI: 10.1056/NEJMoa1603017].

The ELAIN Trial shows advantages of early RRT

In critically ill patients with stage 2 AKI, early RRT leads to lower mortality compared with delayed RRT, reports a trial in *The Journal of the American Medical Association*.

The randomized ELAIN Trial included 231 patients with KDIGO stage 2 AKI and plasma neutrophil gelatinase-associated lipocalin levels greater than 150 ng/mL. All patients were treated at a single German center. One group received early RRT that was initiated within 8 hours of diagnosis of stage 2 AKI. The other group received delayed AKI that was initiated within 3 hours of developing stage 3 AKI.

Nearly two-thirds of patients were men; the mean age was 67 years old. All patients in the early group received RRT along with 90.8 percent in the delayed group. Median times for eligibility for RRT initiation were 6.0 and 25.5 hours, respectively.

Ninety-day mortality was 39.3 percent with early RRT versus 54.7 percent with delayed RRT (hazard ratio of 0.66) (4). Patients assigned to early RRT had a higher rate of recovery of renal function by 90 days (53.6 versus 38.7 days), shorter duration of RRT (9 versus 25 days), and shorter hospital stay (51 versus 82 days). There were no significant differences in RRT after 90 days, organ dysfunction, or length of ICU stay.

The optimal timing of RRT for severe AKI without life-threatening indications remains unclear, although evidence suggests benefits of early RRT. The ELAIN Trial results show reduced 90-day mortality of an early RRT strategy for stage 2 AKI. The investigators conclude, "[o]ur study provides important feasibility data for an AKI stage-based biomarker-guided interventional trial in AKI" [Zarbock A, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN Randomized Clinical Trial. *JAMA* 2016; 315:2190–2199].

The Glomerulus: The Parts That Form a Greater Whole

In this issue of *Kidney News*, we build upon a new series of articles providing insight into the nature and care of patients with glomerular disease. The first article, "Complement-Mediated Glomerular Diseases," was published in the May, 2016, issue. Future issues will include a spectrum of general conversations about glomerular disease and focused pointers on individual diseases. This effort acknowledges the complexity of glomerular disease and our incomplete but improving understanding of disease mechanism and approaches to care. The series will offer answers to questions on how to best identify glomerular disease patients, and to categorize and treat these patients.

This effort originated in the ASN Glomerular Disease Advisory Group, expertly spearheaded by Carla Nester, MD. It is meant to accompany a *CJASN* series, "Glomerular Disease," that will run concurrently.

These articles should offer important viewpoints into this critical and fascinating area of nephrology research, education, and practice. We hope you will find the articles valuable to your clinical practice.

Lawrence Holzman, MD, Chair, ASN Glomerular Disease Advisory Group, Professor of Medicine (Nephrology), Perelman School of Medicine at the University of Pennsylvania.

By James F. Dylewski and Judith Blaine

What is a glomerulus, and what does it do?

The glomerulus in its strictest form refers to the collection of specialized capillaries lined by a thin, fenestrated endothelium located at the initial portion of the nephron. These capillaries and endothelium, or glomeruli, are interconnected by mesangial cells and their matrix and lined by a basement membrane that is surrounded by visceral epithelial cells or podocytes. The cell bodies of the podocytes extend into a small cavity referred to as Bowman's space or the urinary space. A layer of parietal epithelial cells and its basement membrane are just outside of the space and referred to as Bowman's capsule (Figure 1). Anatomically, the collection of the glomeruli, mesangial cells and matrix, the two epithelial layers, the two basement membranes, and Bowman's space are called the renal corpuscle. The terms renal corpuscle and glomerulus are often used interchangeably, although in strict anatomic terms, they are different (1).

The function of the renal corpuscle or the glomerulus is to filter the plasma to keep the cellular components and large proteins in the intravascular space while forming the ultrafiltrate containing water, electrolytes, and various other substances. This task is accomplished mainly by the structures located between the blood and Bowman's space that are collectively referred to as the filtration barrier. The filtration barrier is made up of the endothelium, the glomerular basement membrane (GBM), and a slit diaphragm formed between the foot processes of the podocytes.

How do the glomerular endothelial cells select what goes into the ultrafiltrate?

The endothelial cells have a cell body with fenestrated cytoplasmic sheets encircling the capillary. The fenestrations allow ions and other substrates to pass through this layer and into the underlying basement membrane. The permeability of the endothelium is affected by vascular endothelial growth factor (VEGF). When VEGF is bound to the VEGF receptor of the glomerular endothelial cells, it induces the formation of fenestrations and increases the permeability of the endothelial cells (2).

How the endothelial cells selectively filter the plasma is controversial. The traditional theory (two pore or heteroporous model) suggests that the endothelial cells have many small pores and a few larger pores that allow for different-sized molecules to pass through to the GBM (3). The difficulty with this theory is that it cannot explain how albumin, with a diameter of approximately 70 Å, does not pass through the larger pores or clog the small pores. It has also been suggested that the luminal side endothelium is also negatively charged because of a glycocalyx (made of glycoproteins and glycosaminoglycans), which repels negatively charged substances like albumin (4). However, in recent years, an alternative explanation has been offered to account for how the filtration barrier prevents small proteins from entering or clogging the pores. This theory is referred to as the electrokinetic model (5). This model suggests that an electrical field is created by the convection and diffusion of differently charged ions across the filtration barrier. The electrical field prevents negatively charged proteins from crossing into the filtration barrier and will effectively move albumin away from the basement membrane by electrical current like an electrophoresis gel (5, 6).

What does the GBM do, and how can it lead to kidney disease?

The role the GBM plays in filtration is currently being debated. Although in vivo tracer studies suggest the GBM provides a charge- and size-selective barrier, in vitro models failed to show charge selectivity in isolated GBM, and size selectivity seems to be more the result of the cellular structures.

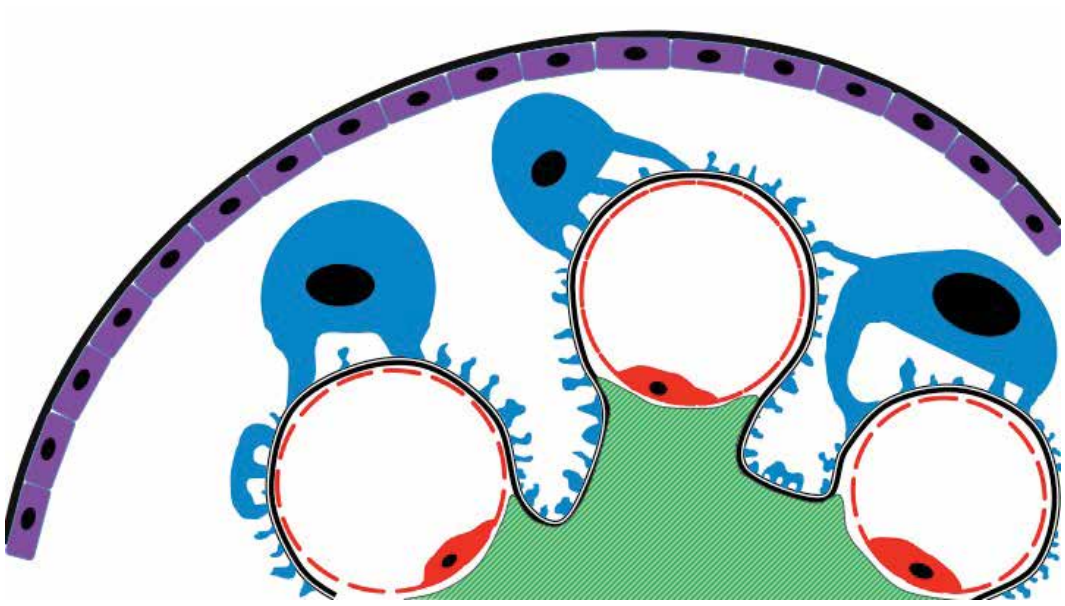
The GBM is made up of primarily type IV collagen, laminin, and sulfonated proteoglycans, with nidogen/entactin and types V and VI collagen also being present (1, 4). These materials are typically present in all other basement membranes in the body, but the GBM has unique type IV collagen α-chains (namely α3, α4, and α5) and laminin 11. These components unique to the GBM can lead to diseases such as Alport syndrome and Goodpasture disease if they are mutated or targeted by the immune system, respectively (1, 4).

What is the mesangium, and what does it do?

The endothelial cells line the entire 360° circumference of the capillary. Underneath the endothelial cell layer is the GBM. However, the GBM only forms an incomplete pouch-like covering. An analogy would be like laying a towel over a cardboard tube; the towel covers the tube but does not wrap all of the way around. The portion of the endothelium that is not covered by the GBM is actually covered by the mesangium. The mesangium is a collection of mesangial cells and their surrounding matrix that anchor the glomerular tuft. Each mesangial region can interact with a few different glomeruli for stability. The mesangial cells have cytoplasmic extensions with microfilaments that extend into the GBM to form the complete enclosure around the endothe-

Figure 1. Schematic diagram of the renal corpuscle

Mesangium, green; fenestrated endothelial cells, red; podocytes, blue; and parietal epithelial cells, purple.



lium. By having the mesangium complete the enclosure around the endothelium, it allows the GBM to be pulled tight or relax as a compensatory mechanism for intracapillary hydraulic pressure (1). The mesangial cells also have receptors for vasopressin, angiotensin II, prostaglandin, TGF-β, and other vasoactive factors that can induce relaxation or contraction of the cell and thus apply tension to the GBM, leading to an alteration in glomerular filtration (7).

The mesangial cells make the mesangial matrix, a fibrillary substance composed of material similar to that of the GBM, which surrounds the cells and links to their cytoskeleton to provide stability and assistance during contraction. When exposed to stress, the mesangial cells also make various growth factors, including VEGF, NO, and other soluble factors, that can alter hemodynamic flow (8).

What is the role of the podocyte?

Outside of the GBM is the visceral epithelium (better known as podocytes). The podocytes are highly differentiated cells with cell bodies suspended above the basement membrane. Podocytes have cytoplasmic processes that subdivide numerous times to form finger-like projections called foot processes or pedicels, which encompass and attach to the lamina rara externa of the GBM. Each podocyte's foot processes interdigitate with the neighboring cell, such that small filtration slits are formed. Between each slit are extracellular structures that interconnect each podocyte to its neighbor. These structures form what is termed the slit diaphragm (Figure 2).

Podocytes are crucial to filtration, and it is well established that a fully functional slit diaphragm is necessary for preventing proteinuria. One means by which podocytes regulate filtration is by producing VEGF, which will then regulate the permeability of the glomerular endothelium. Podocytes have also been shown to actively endocytose proteins and other components from the ultrafiltrate (4).

In healthy animals, podocytes generally appear stationary, but when under stress or in vitro, podocytes become very dynamic and will cluster together or migrate in response to the stress (9). Movement is accomplished by the many and complex networks of microtubules, microfilaments, and actin filaments that are present throughout the cell but particularly concentrated in the foot processes. To move in response to stress may be adaptive, because podocytes lack the ability to replicate in vivo (4).

Why are parietal epithelial cells important?

At the vascular pole, where the afferent arteriole enters and divides into the capillaries and the efferent arteriole exits, the podocytes and parietal epithelial cells are in contact with each other. The parietal epithelium, however, looks more like squamous cells with the broad cytoplasm, few organelles, and lack of foot processes. The parietal cells line the basement membrane of Bowman's capsule, function as a final barrier for filtration, and funnel the ultrafiltrate into the proximal tubule. In animal models, when the parietal layer is compromised, molecules will spill out into the periglomerular space. Another important feature of the parietal epithelium is that parietal cells can differentiate into podocytes and repopulate the glomerular tuft after podocyte loss (10). The repopulation of the glomerular tuft by parietal epithelial cells may be the reason behind the adhesions formed between the glomerular tuft and Bowman's capsule during focal segmental glomerular sclerosis (FSGS) or the formation of glomerular crescents in rapidly progressive glomerulonephritis (1).

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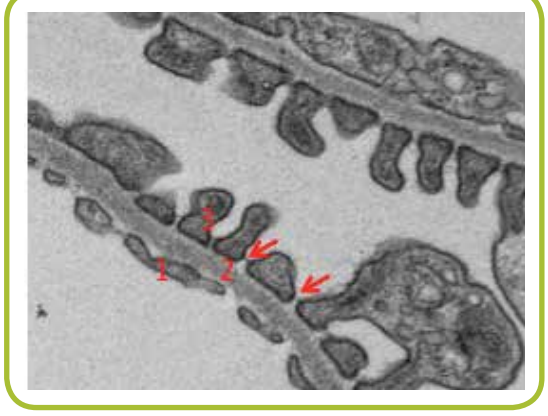
Figure 2. Transmission electron microscopy image of a podocyte

(1) Fenestrated endothelial cell; (2) glomerular basement membrane; (3) podocyte foot process. Arrows indicate the slit diaphragm.



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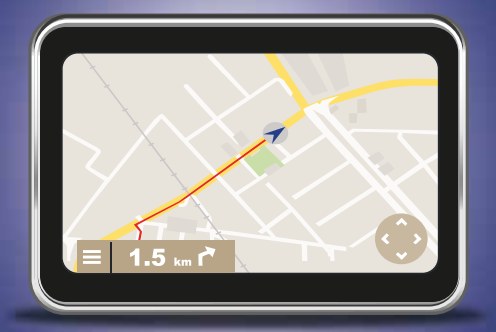

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Distinguished Conversations

In this installment of "Distinguished Conversations," we are delighted to feature two outstanding leaders in American nephrology: Bill Bennett, MD, FASN, interviewing William Couser, MD. The two leaders beautifully share their thoughts on what made Dr. Couser's career so special and what it takes to emulate that kind of success in today's world of academic nephrology.

Dr. Couser, originally a Northeasterner, graduated from Harvard College, moving on to Dartmouth and then to Harvard Medical School for his MD. He traveled for residency and special renal training between UCSF, the University of Chicago, and Boston City Hospital, with an interval during which he served as Captain in the US Medical Corps during the Vietnam War. He started his academic career at the University of Chicago, moving to Boston University for some time, and then spent more than 20 years as Chief of the Division of Nephrology at the University of Washington, where he also directed the George O'Brien Kidney Research Center. His service to the field of nephrology includes stints as President of ASN and the International Society of Nephrology, Editor-in-Chief of *JASN*, board member of KDIGO, and Vice President of the American Society for Clinical Investigation. He has authored more than 150 original papers, and more than 150 book chapters, editorials, and reviews focusing on seminal contributions to the immunology of glomerular disease. He has been honored with the David M. Hume Award of the National Kidney Foundation and the Joel D. Kopple Award of the International Federation of Kidney Foundations.

Dr. Bennett traveled in similar circles as Dr. Couser, training in Chicago at Northwestern, moving to Boston as a fellow at Massachusetts General Hospital, and then on to Oregon where he spent many years at Oregon Health & Science University. He is currently Medical Director of Transplantation and Director of Renal Research at Legacy Health in Portland, OR. Dr. Bennett has more than 460 peer-reviewed papers to his name. He also served as President of ASN, is Editor-in-Chief Emeritus of *CJASN*, and has been awarded the Polycystic Kidney Disease Foundation's Jared J. Grantham Distinguished Achievement Award and the ASN Belding H. Scribner Award. He founded the William and Sandra Bennett Clinical Scholars Program of the ASN, with the aim of advancing nephrology education and teaching.

Richard Lafayette, MD, editor-in-chief, ASN *Kidney News*

Bill Bennett, MD, FASN

William Couser, MD

Dr. Bennett: Dr. Couser, would you introduce yourself briefly and describe a little bit about your current activities?

Dr. Couser: I am a nephrologist who was president of ASN 20 years ago and was Head of the Division of Nephrology at the University of Washington for 22 years, before retiring from clinical practice in 2004.

My life since then has been quite busy. I was Editor-in-Chief of *JASN* for 6 years from 2001 to 2007. I also held leadership positions with ISN from 2001 to 2013, which involved a great deal of time and travel. I'm still busy writing book chapters and review articles, and reviewing manuscripts for journals. I also continue to teach some fellows at the University of Washington and in courses elsewhere.

Dr. Bennett: How did you end up becoming a nephrologist?

Dr. Couser: It all began with a young man with Goodpasture's syndrome I saw as an intern at UCSF in 1966, 50 years ago. The patient rapidly developed severe renal failure and was not considered eligible for a transplant because of his pulmonary disease. Dialysis in those days was only available to patients waiting for transplants, so I was instructed to inform the patient and his family there was nothing further we could do and to send him home to die.

I went to the library, looked up glomerulonephritis (GN) (there was no PubMed then!) and found a paper about a study from NYU in the 1950s in which several patients with severe GN were treated with infusions of nitrogen mustard and some responded. We treated this patient with nitrogen mustard, he had a dramatic response and was discharged free of pulmonary disease with a serum creatinine that had fallen from about 4 to 1.8 mg/dL, and he did well over the 2 years that I followed him. However, I formed a very negative opinion of nephrologists at the time because they seemed to know and care mostly about how normal kidneys worked and had little knowledge of, or interest in, kidney diseases.

Two years later as a senior resident on the Harvard Medical Service at Boston City Hospital (now Boston Medical Center), I met Ed Lewis, the new Chief of Nephrology, who had a particular interest in immunologically mediated renal diseases like Goodpasture's. That reignited my interest in what caused Goodpasture's syndrome in my patient at UCSF. So I entered nephrology training as a research fellow with Ed, funded by the National Kidney Foundation (NKF), started working on animal models of GN, and continued that work in my own laboratory with NIH funding for the next 3 decades.

Dr. Bennett: Dr. Couser, it is well known that during that time you contributed a great deal to the nephrology literature in the areas of immune-mediated kidney diseases. Looking ahead 25–30 years, how would you say the results of your work will translate into modern research? Where do you think it will all end up?

Dr. Couser: I am already gratified to see that happening. The experimental work I did around 1980, with David Salant as my fellow, on *in situ* immune deposit formation and the role of complement C5b-9 in membranous nephropathy, has now

been brought to fruition in human disease by David with his recent discovery of anti-PLA2R antibody as the pathogenic antibody in human membranous nephropathy. That is a beautiful bench-to-bedside story and a major advance that already has an impact on the care of patients with this disease.

Clinically, it has also been rewarding to see the entity of crescentic GN without immune deposits that we first described in 1979 evolve into the whole ANCA-associated vasculitis story, and steroid pulse therapy for GN, which we first described in 1976, remains (somewhat to my embarrassment!) standard of care for crescentic, rapidly progressive GN. In a broader sense, that early work on membranous nephropathy helped change the prevailing thinking about immune complex nephritis from the older concept, that these diseases were like serum sickness induced by foreign antigens and circulating immune complex trapping, to a new view that most were autoimmune and involved in situ deposit formation due to antibody binding locally to antigens fixed or planted in the glomerulus. I think the ultimate significance of that work will come as advances in autoimmunity lead to identification of more nephritogenic antigens, clarification of the genetics of autoimmune responses, and then to ways of restoring tolerance to immunogenic proteins in autoimmune diseases like GN.

But research is like building a pyramid where each of us adds a few bricks to what has been laid down before and others then build on our work to eventually create a pyramid of knowledge that allows prevention or successful treatment of a disease.

Dr. Bennett: Well said. Having led a division and served as president of the two largest renal societies (ASN and ISN), what are your thoughts about the way we're training people for the future? Are we doing it correctly? Also, why do you think nephrology is less popular with residents than it used to be, and how would you get it back on track if it is indeed off track?

Dr. Couser: The era you and I grew up in, the era of the physician-scientist, is coming to an end. During that era, those who went into academic medicine were expected to do research, take care of patients, and teach all at the same time and at the same level of excellence. It is still possible, but now much more difficult, to be that kind of physician. To successfully run a productive lab, secure research funding, and train research fellows is a full time job. The same is true of clinical care. If you want to be on top of the latest in clinical medicine and develop and maintain the necessary skill set to provide the services your patients expect and deserve, you have to do that almost full-time. So there likely will be increasing separation of physicians who are actively involved in research and those who are primarily involved in clinical practice. That requires the best training programs to offer a diversity of faculty and well developed options and pathways that can accommodate the different career goals of trainees.

Dr. Bennett: You were president of ASN in 1996–1997 and served on, or near, the Council for 13 years including your term as Editor-in-Chief of *JASN*. What do you consider your most important contributions to the society?

Dr. Couser: One of the accomplishments I am most proud of was leading the discussions with the NKF that led to NKF discontinuing its fall meeting, which took place for many years in the same venues in the three days preceding the ASN meeting. That agreement allowed ASN to control the venues, program events before the main meeting, and expand into "Renal Week," a format that continues today as Kidney Week and has been essential to ASN's meeting its overall goals.

Second, I emphasized public policy as a new priority for ASN. As president, I helped recruit the first full-time ASN public policy staff person (Jill Rathbun, a former House staffer). ASN public policy efforts have continued and become much more robust since then and have contributed to many legislative initiatives that have greatly benefited both research and patient care.

Finally, I had the good fortune to work with particularly visionary presidents of NKF (Alan Hull) and RPA (Rick Latos) to create the Council of American Kidney Societies (CAKS) to coordinate and streamline policy initiatives on behalf of kidney patients, and to serve as the first president of CAKS. Prior to CAKS, congressional testimony from the 3 major kidney societies on behalf of kidney patients was separately delivered, disjointed, overlapping, often in conflict, and consequently often counterproductive. Although CAKS itself has undergone several iterations since then and never totally fulfilled its initial promise, ASN does continue to work closely with the other sister renal societies in the US on issues of common interest.

It is very gratifying to me to see outgrowths of all three of my major initiatives as president still apparent in ASN policies and programs now 20 years later.

Dr. Bennett: How has the career and field of nephrology changed during your professional life?

Dr. Couser: Dramatically! Nephrology as a clinical discipline did not exist until the advent of hemodialysis in the 1960s, which gave nephrologists a real clinical tool for treating patients and thus created a whole new patient population with some of the most complex clinical problems in medicine. Thus the discipline was new, exciting, and had unlimited opportunity when I first entered it in the 1970s.

The research enterprise has changed dramatically too with the advent of cell and molecular biology tools, molecular immunology and genetics, and the capacity to generate big data and probe very large databases for new clues to etiology and pathogenesis of renal diseases. When I began attending ASN meetings in the 1970s, my own research area of pathogenesis of GN was allocated only one 2-hour session called "Immunology and Pathology." Today that topic is covered in an entire theme with many sessions held on every day of the meeting. This change reflects in part the growth of research on renal diseases like GN in departments of medicine whereas it was previously done mostly by pathologists. I hope my own career choice as a clinical nephrologist to pursue basic research on mechanisms of GN played some role in stimulating that type of research within divisions of nephrology where research previously was almost entirely devoted to renal physiology.

Dr. Bennett: If a young resident came to you and said, "I'm interested in nephrology," what would you tell them in 2016?

Dr. Couser: First, I would applaud and encourage them for selecting a field with the uniquely interesting and challenging clinical problems that nephrology presents. We are often told on consult services that nephrologists are the best clinicians and teachers in the hospital, and I think that has generally been true, although the current decrease in interest in nephrology as a career may imperil that status.

If you are interested in nephrology and want to become a clinician, you have to enjoy the challenges sick patients present and appreciate the rewards of being able to deliver long-term primary care to those patients. The training path is clear and can be provided by many programs.

If you want to pursue an academic career with a research component trying to understand and better treat kidney disease and be involved with clinical care primarily in a teaching and training capacity, you're facing a longer path. You have to be willing to put in the extra research training time, which may be years, and maintain a focus on long-term goals before your work actually pays off in terms of discoveries that make a difference to patients. Most residents or fellows tell me: "Well, I love clinical care, but I think research is very interesting and I want to try it out for a while." I can honestly say I don't think I've seen anyone who just "tried it out" in the 30 years I've trained people in the laboratory who ultimately decided research was what they wanted to do and were successful at it. Most who excelled in research had prior experience with research as a college or medical student and already knew it was what they wanted to do before they began basic research training. I cannot over-emphasize the importance of early exposure to nephrology and research at the medical student level in influencing subsequent career choices. That is something we need to get much better at.

Dr. Bennett: What would you like to tell readers of *Kidney News* about ASN or your experience as an academic leader, research contributor, and physician-scientist regarding the future?

Dr. Couser: The top challenge ASN and the kidney community face today is addressing why nephrology is becoming less popular as a subspecialty.

Continued on page 14

Continued from page 13

Multiple committees and learned bodies have examined this question, written papers about it, and made suggestions for changes, and all of them make important points. I think the bottom line is that nephrology is not as appealing a career as it once was because of perceptions that 1) the work is too hard because the patients are very sick, complex, and usually don't get better, and increased government regulation (like G codes) make additional work without improving patient care, and 2) the job opportunities, especially locally, and income potential are too low. These two things play a big role in most peoples' career choices today. They played less of a role when you and I were starting because career paths were chosen then based more on role models, people you respected and whose skills and careers you wanted to emulate.

Students today, and I doubt this is unique to medicine, have a much more personal perspective about life choices and look much more carefully than we did at the income they will make and the impact of their careers on their personal lives, their families, and the time they have available to do other things. Nephrology, when viewed in light of those priorities, does not look as attractive as some other less clinically intense options.

Salvaging nephrology is likely to involve more dramatic changes than just tinkering around the edges. ASN and other kidney organizations work hard to mitigate the clinical challenges and reimbursement issues for nephrologists, and a strong public policy effort is essential to keep these issues alive and under discussion. The workload problem can probably be improved if nephrologists become leaders in new care models where Advanced Practitioners take on a larger share of daily patient management, if reimbursement policies support that model. More telemedicine may also help. But because of ASN's strong connection to training programs and research, it can play a major role in structuring the discipline in other ways. For example, it is possible we are trying to train too many nephrologists and thereby compromising job opportunities for graduates. ASN can certainly play an important role in defining the optimal size and structure of the nephrology workforce to meet current needs. I applaud ASN for its many committees and taskforces working on issues like the Match, better exposure of students and residents to nephrology, and other workforce-related issues.

Enhancing the attractiveness of an academic research career will require making successful physician-scientists more visible to students and house staff as role models, as the ASN Kidney TREKS program is starting to do. Then we need to increase the security of a research career by improving overall research funding and providing some bridge support by which people who successfully complete good research training programs are guaranteed initial research funding for the start-up phase of their careers. Recent increases in NIH funding are encouraging, but by providing inadequate funding for many years, we have been bleeding the physician-scientist workforce in the US for a long time, so there is a long way to go to rebuild it. And saving the renal physician-scientist from extinction will require that the earning potential of successful researchers compete better with the income earned by most clinicians than it does today.

I think the current status of nephrology as an "endangered subspecialty," reflected by the low level of interest of US residents and difficulty in the past few years filling training program slots, justifies developing an "affirmative action" plan that addresses the major issues. For example, residents might be offered special incentives to enter nephrology training such as "sign-up" bonuses, loan forgiveness programs, help with visa waivers, guaranteed start-up research grants for good research fellows, and compensation packages that narrow the gap between those doing the research and training and those only providing patient care. When considered in light of the overall healthcare expenditures for kidney patients, the cost of steps like those would be trivial. And we have good data showing that care provided by well-trained nephrologists is both better and cheaper than care provided by non-nephrologists. It is not fair to assign ASN all of the responsibility for making nephrology more attractive to residents because there are many larger forces at play in the healthcare world, but ASN, both directly and through its public policy efforts, can have a significant impact in several of these areas. A giant step forward, which is unlikely to ever happen, would be if the US had the wisdom to initiate a national service requirement that physicians could satisfy by undertaking research training or entering endangered subspecialties like nephrology.

My message to readers would be the same as the major message of my ASN Presidential Address in 1997: If you want to see change, and we need it more now than we did then, get involved and contribute your time and voice to making things happen. And that is true not only at the national level where ASN operates, but particularly at the local level where nephrologists need to be much better organized and more active to prevent the discipline from being marginalized by forces constantly focused on the bottom line rather than improving care of sick patients.

Dr. Bennett: Dr. Couser, I'd like to officially congratulate you on a wonderful career, significant contributions to the discipline of nephrology, and very significant contributions to the workforce of nephrology by your many trainees, who are now following in your footsteps and leading many university nephrology programs all over the world.

Policy Update

MACRA: New Incentive-Based Physician Pay Program
ASN Responds to CMS

By Rachel Meyer

In the coming months, the Centers for Medicare & Medicaid Services (CMS) will begin implementing a 2015 law that changes how doctors who provide care to Medicare beneficiaries are paid. ASN is working with CMS to help the Agency get the new system—which aims to reward value over volume—right for nephrology clinicians and the patients with kidney disease they serve.

Last year, Congress repealed and replaced the Sustainable Growth Rate (SGR), the outdated physician payment system that called for substantial annual cuts to physician reimbursement, by passing the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA).

"One thing everyone agrees upon in Washington was that the old payment system was broken, and ASN advocated for its repeal and replacement. The new payment system aims to move healthcare in the right direction, emphasizing quality of care instead of quantity of care and reducing administrative burdens so physicians can focus their efforts on providing the highest quality of care to patients," said ASN President Raymond C. Harris, MD, FASN. "ASN delivered nearly 20 pages of recommendations concerning how to improve and successfully implement the new system and achieve the goals Congress outlined when it enacted MACRA."

The new payment system—termed the Quality Payment Program—will offer two tracks for Medicare physician payments: MIPS (Merit-based Incentive Payment System) and APMs (Alternative Payment Models) (Table 1).

On June 27, 2016, ASN submitted extensive recommendations to CMS regarding its 962-page proposal for putting in place the significant changes called for by MACRA. CMS is expected to issue a final rule on MACRA implementation in the fall of 2016, taking into account input from ASN and other stakeholders. The society emphasized several key themes, described here:

Delay the start of data collection

MACRA requires that the new Quality Payment Program take effect starting January 1, 2019. Although CMS proposed to start collecting data on physicians' quality of care, resource use, and other aspects of care starting January 1, 2017, ASN believes that an additional six-month period is needed to educate clinicians. The society recommended that CMS delay the start of the performance period until July 1, 2017.

ASN believes that clinicians will need this time period to familiarize themselves with the final rule and prepare their practices to deliver the best patient care possible in the new payment system. The society urged CMS to develop a robust educational program to help clinicians—especially nephrologists, given that they treat patients with varying degrees of sickness and complexity in multiple types of facilities—approach the pathways available in the Quality Payment Program. ASN also intends to complement and amplify educational programs developed by CMS with its own educational tools.

The delay ASN proposed (to July 1, 2017) would allow clinicians time to come up to speed and to review their data before their payments start to be adjusted on January 1, 2019.

Factor in how patients with kidney disease are unique

Throughout its 19-page commentary to CMS, ASN emphasized the complex needs of kidney patients and their status as among the most vulnerable in the entire Medicare program. Kidney disease disproportionally affects underrepresented minorities, and patients with advanced kidney diseases suffer from multiple other serious chronic co-morbidities, including diabetes, hypertension, peripheral vascular disease, and heart failure. More than 50% of patients with CKD have 5 or more other co-morbid conditions, and CKD care for patients age 65 and older exceeded $50 billion in 2013—representing 20% of all Medicare spending in this age group.

ASN also emphasized the heterogeneous nature of nephrology care: nephrologists typically provide medical care in multiple settings with variations in patient population characteristics and health status and differential access to electronic health records (EHRs)—variations that may influence their ability to be successful in the MIPS program and should be considered by CMS.

The society recommended a number of modifications to CMS' proposals based on these two factors of unique patient status and practice structure. In particular, ASN recommended that CMS require that reporting mechanisms include the ability to stratify the data by demographic characteristics such as race, ethnicity, and gender—and ASN urged CMS to use its resources in an active effort to continually improve the risk adjustment methodology employed within MACRA implementation. The need for appropriate quality measures that reflect the value of care nephrologists provide is also paramount.

Modify MIPS reporting requirements

In large part reflecting the unique patient and practice issues in nephrology, ASN also recommended a number of changes to the MIPS program. Specifically, the society promoted:

- Reducing the number of patients on whom clinicians must report quality data to lower than that proposed by CMS in the "Quality" category.
- Adjusting the "Resource Use" component of MIPS downward so that it makes up less of the total performance score; CMS proposed that Resource Use account for 10% of the total.
- Increasing the number of proposed "Clinical Practice Improvement Activity" categories that qualify as "high value," more accurately reflecting the effort clinicians put into improving their practices.
- Implementing less stringent standards for use of EHRs (which CMS has branded "the Advancing Care Information" category of MIPS).

ASN collaborated with a number of other organizations in developing comments—including the American College of Physicians and the Council of Medical Subspecialty Societies—which echoed similar comments regarding making the MIPS program less onerous.

Create greater flexibility for APMs to form

APMs will provide new ways to pay health care providers for the care they give Medicare beneficiaries. APMs aim to deliver more coordinated, comprehensive care that focuses on population health and value, and they also take on an element of financial risk if the care that they deliver does not, in fact, provide good value. For the time being, every APM is a demonstration project currently being tested by the Centers for Medicare and Medicaid Innovation (CMMI). CMS proposed that clinicians who participate in APMs will get certain bonuses in the MIPS program—and ASN has urged the agency to give as much credit as possible to these clinicians, reflecting the challenges of practice transformation necessary to become an APM.

However, only clinicians who participate in Advanced APMs will be exempted from the MIPS program—and, these clinicians will receive a 5% bonus in the first few years of the Quality Payment Program. ASN is concerned that CMS proposed a very stringent defini-

Table 1. MIPS vs. APMs

Merit-Based Incentive Program (MIPS)

- MIPS consolidates three existing Medicare programs—the Physician Quality Reporting System, the Value-Based Modifier, and the Electronic Health Record (EHR) Meaningful Use program
- The program will assess physicians' EHR use, quality of care, use of resources, and "Clinical Practice Improvement Activities," to calculate a total performance score that will impact how much they are reimbursed by Medicare.
- Physicians will see their payments adjusted up or down depending on their performance in these four areas. Starting in year one (2019) the maximum adjustment will be 4%, but that percent will grow over time with more latitude for risk or reward based on performance.

Alternative Payment Models (APMs)

- APMs are currently demonstration projects being tested by the Centers for Medicare and Medicaid Innovation.
- Participating physicians will receive certain benefits under MIPS.

Advanced Alternative Payment Models

- Physicians participating in APMs that meet CMS's criteria as Advanced APMs would be exempt from the MIPS reporting requirements.
- Advanced APMs must accept "more than nominal" financial risk under value-based payment systems
- The majority of physicians must use certified EHRs.
- Physicians in Advanced APMs may earn bonus payments and avoid potential Medicare reimbursement cuts. They will also receive an annual 5 percent lump sum bonus between 2019 and 2024.

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Policy Update

Future Physician Payment

Continued from page 15

tion of Advanced APMs, one that requires a significant amount of financial risk. Indeed, just six CMMI models currently being tested would meet the proposed financial risk criteria. As currently proposed, the substantial financial risk for losses for Advanced APMs will likely limit physician-driven participation and slow achievement of the goals of MACRA.

ASN believes the principle of comprehensive, integrated care inherent in APMs is a vitally important concept to advance to improve patients' outcomes. The society urged CMS to create as many mechanisms as possible for interested physicians to establish and participate in APMs and Advanced APMs. In particular, the society encouraged CMS to consider alternate—still appropriately rigorous, but alternate—definitions of financial risk for "physician-focused payment models." Physician-Focused Payment Models are an important aspect of MACRA that call for the creation of APMs centered on physician leadership—a concept that ASN strongly supports.

Set the stage for a comprehensive physician-led CKD model

At this time, CMS was not seeking recommendations for new APMs or Physician-Focused Payment Models. However, ASN indicated that it anticipates putting forward a "comprehensive CKD," Physician-Focused Payment Model for consideration in the future.

A potential comprehensive CKD Physician-Focused Payment Model would put nephrologists at the helm of helping patients navigate the entire course of their advanced CKD. Encompassing all patients with advanced CKD, including kidney transplant recipients, such a model could focus on slowing the progression of kidney disease and other complex chronic conditions that are common in patients with advanced kidney disease. Inclusion of transplant patients for the duration of their lives within the scope of this model would create inherent incentives to promote transplantation for the greatest number of patients possible who are candidates, in addition to dialysis. Similarly, ASN envisions that a potential comprehensive CKD model would include palliative and/or conservative care options as those become appropriate considerations.

"I would like to commend the members of the Public Policy Board, led by John R. Sedor, MD, FASN, and by the ASN Quality Metrics Task Force, led by Daniel E. Weiner, MD, FASN, for their hard work in assessing and commenting on this proposed rule," Harris said. Moving forward over the coming weeks and months, "ASN will be providing resources and insights to help our members understand how to prepare for and succeed in the Quality Payment Program, and will continue to engage with CMS to ensure a smooth transition going into 2019."

Home Dialysis: Advocates Urge Better Telehealth Access, Education about Dialysis Options

Highlighting successful strategies to increase patient access to home dialysis and reduce racial disparities in home modalities, ASN Councilor Susan Quaggin, MD, FASN, of Northwestern University in Chicago, addressed a packed briefing room on Capitol Hill in May 2016.

The US has one of the lowest utilization rates of home dialysis in the world, with just around 10% of patients dialyzing at home via peritoneal dialysis (PD) or home hemodialysis (HHD). Furthermore, there are significant disparities in home dialysis: African-Americans and other minority populations are considerably less likely to use a home modality compared to Caucasians.

The congressional briefing, "Alliance for Home Dialysis Hill Briefing: Improving Access through Policy Innovation," addressed the equitability of home dialysis, care partner requirements for home patients, telehealth, and kidney disease education. The briefing was convened by the Alliance for Home Dialysis, a Washington, DC-based coalition—of which ASN is a member—dedicated to advancing policies that support appropriate utilization of home dialysis.

Quaggin and other speakers called attention to policy changes that may eliminate barriers to home dialysis for some patients. Having recently moved to the US from Canada—where "home first" is the standard approach in many dialysis clinics—she shared an international perspective and illustrated, through her more recent efforts at Northwestern University, that significant advances in home dialysis utilization are achievable. But in addition to demonstrating the potential to grow home dialysis, Quaggin also called for congressional support for several key policy changes supported by ASN, the Alliance for Home Dialysis, and other stakeholders in the kidney community.

Designating a patient's home as an "originating site" under Medicare would allow home dialysis patients to interact with their nephrologist via telehealth technology (such as videoconferencing on an iPad) from home instead of going into an office. The bipartisan Medicare Telehealth Parity Act of 2015 proposes giving patients this option, and the Senate Finance Committee has also considered including designating the patient's home as an originating site in its forthcoming Chronic Care bill. Also under consideration is a proposal that would designate the dialysis facility as an originating site (meaning patients can interact with their doctor via telehealth technology from the dialysis facility when the doctor is offsite). This policy change is currently proposed in the bipartisan, bicameral CONNECT Act. ASN and the Alliance for Home Dialysis support both policy changes.

Ensuring more people get access to education about their dialysis treatment options is crucial to increasing appropriate home dialysis use. Larry Weisberg, MD, nephrology division chief at Cooper University Hospital near Philadelphia, presented compelling data demonstrating that patients who receive education about home dialysis choose it over in-center dialysis significantly more often than patients who do not.

In 2008, Congress enacted the Medicare Kidney Disease Education Benefit, which was designed to help people learn about options and manage their disease before starting dialysis. But the Government Accountability Office recently reported that fewer than 2% of eligible beneficiaries have utilized this benefit, in part because only a few types of providers can offer it. ASN and the Alliance are urging Congress to identify mechanisms to enable more patients to access this benefit.

Building support on Capitol Hill for these and other policy changes that would support home dialysis remain a top advocacy priority for ASN and the Alliance for Home Dialysis. Continuing engagement with congressional champions on the Senate Finance Committee, securing more bipartisan co-sponsors for the CONNECT Act and the Medicare Telehealth Parity Act of 2015, and raising awareness about home dialysis among policymakers are among the activities still in store for the final months of the 114th Congress.

Industry Spotlight

New Drug for SHPT in CKD Stages 3–4

The US Food and Drug Administration (FDA) approved Rayaldee (calcifediol) (OPKO Health, Miami, FL) extended-release capsules for treatment of secondary hyperparathyroidism (SHPT). The approval applies only to treating adults with SHPT who have CKD stage 3 or 4 and serum total 25-hydroxyvitamin D <30 ng/mL.

Rayaldee has a patented design intended to increase serum total 25-hydroxyvitamin D (prohormone) levels to targeted levels and also to decrease elevated intact parathyroid hormone (iPTH). It is the first drug approved for this specific purpose.

"Rayaldee is an important new option for treating SHPT in patients with stage 3 or 4 CKD and vitamin D insufficiency," Kevin J. Martin, Director of Research, Division of Nephrology, at Saint Louis University School of Medicine, stated in the company media release. "The great majority of SHPT cases in this patient population are associated with vitamin D insufficiency, a problem that Rayaldee can correct."

The FDA approval was based on data from two 26-week placebo-controlled, double-blind phase 3 trials that showed a greater proportion of CKD stage 3 or 4 patients with SHPT and vitamin D insufficiency achieved reductions of >30% in plasma iPTH after treatment with Rayaldee vs. placebo. More than 80% of patients receiving Rayaldee were able to correct their vitamin D insufficiency compared with <7% of patients receiving placebo.

Over-administration of calcifediol can cause hypercalciuria, hypercalcemia, hyperphosphatemia, or oversuppression of intact PTH, the company noted.

Rayaldee extended-release capsules will be available in the second half of 2016.

New Combo Drug for Hypertension

A combination therapy called Byvalson has been approved by the FDA to treat high blood pressure.

Taken together once a day in a fixed dose pill from Allergan (Parsippany, NJ; Dublin, Ireland), the two drugs—Nebivolol and Valsartan—work by using different mechanisms to lower blood pressure.

Nebivolol (marketed in the US as Bystolic) is a beta-adrenergic receptor blocking agent. While the drug's mechanism of action "has not been definitively established," the company suggested that its actions might include vasodilation and decreased peripheral vascular resistance (PVR), reduced heart rate, and myocardial contractility and renin suppression.

Valsartan (brand name Diovan) is an angiotensin II receptor blocker that blocks the binding of angiotensin II to the AT1 receptor in many tissues.

Allergan noted that Byvalson is the first and only fixed-dose combination of a beta blocker and angiotensin II receptor blocker available in the US.

FDA approval was based on a phase 3, double-blind, placebo-controlled, dose-escalating, 8-week efficacy and safety study, published in *The Lancet*.

The study randomized approximately 4100 patients with stage 1 or 2 hypertension to the drug. In an efficacy and safety study, treatment with the combination of Nebivolol and Valsartan for 4 weeks was associated with statistically significant reductions from baseline in diastolic and systolic blood pressure versus either Nebivolol or Valsartan alone. The overall rate of adverse events was similar across treatment groups and placebo.

Allergan said it expects Byvalson to be available in the second half of 2016.

Fresenius Enters Regenerative Medicine Field

The world's largest provider of dialysis services now has a new business: a regenerative medicine company. Frensenius Medical Care (Bad Homburg, Germany) has opened the doors of Unicyte AG, a subsidiary that will undertake research into kidney and liver diseases, diabetes, and cancer.

Fresenius' primary partner in Unicyte is the Molecular Biology Center at the University of Turin in Italy. The center specifically focuses on the study of the molecular mechanisms underlying the physiopathological processes that result in cardiovascular diseases, inflammation, and cancer, as well as on the intricacies of stem cell biology. The research efforts are aimed at developing advanced molecular imaging technology and bioinformatic analysis, and generating mouse and zebrafish models.

Fresenius, which has collaborated with the University of Turin since 2003, says it will work with additional partners as needed to advance these projects. One of the first successes between the partners was the isolation and characterization of a human stem cell population from an adult liver.

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Certification Concerns Persist

The ongoing debate about maintenance of certification (MOC) among internists, nephrologists, and other subspecialists continued unabated after the American Board of Internal Medicine (ABIM) announced on May 5, 2016, that it would provide more details about the changes it is considering to its MOC program or "alternative assessment options" by the end of the year.

In the meantime, an alternative certifying body, the San Diego-based National Board of Physicians and Surgeons (NBPAS), has issued board certifications to more than 3300 practitioners in 39 states. A nonprofit launched in early 2015, NBPAS requires initial certification by an American Board of Medical Specialties (ABMS) board and 50 hours of continuing medical education every 2 years. The cost? $169 for two years at NBPAS, compared with thousands of dollars for ABIM initial and continuing certification.

Also, Oklahoma became the first state to enact legislation that aims to remove MOC as a requirement for physicians to obtain a license or secure hospital admitting privileges. Passed with bipartisan support, the law frees physicians to certify through alternative boards like NBPAS or not at all. Other states may follow suit: 19 state medical societies have passed resolutions opposing compulsory MOC, and some are working to turn those resolutions into legislation.

The Oklahoma move may be a big deal if other states follow suit because now "insurance companies [in Oklahoma] cannot use MOC as a criterion for payment," said NBPAS President Paul Teirstein, MD. "Insurance companies often have contracts that require providers be ABMS-certified," and that has been one of the biggest impediments to more institutions accepting NBPAS certification.

Several nephrologists took their concerns about the need for recertification every 10 years—or at all—to a recent thread on the ASN Communities website.

"Whereas there is unison in the opinion of the entire medical field that an initial Board Certification upon completion of a residency/fellowship training program is a must (although not required to practice medicine in the US), whether or not we as physicians need to take a "recertification exam" every 10 years is highly debatable," noted Mukesh Sharma, MD, of the Arkansas Renal Group on the ASN Communities discussion, "MOC Debate and Where Do We Stand?"

In a follow-up interview, Sharma stated: "NBPAS is trying not to mitigate ABIM regarding initial certification. Instead, many physicians are against having to take an exam every 10 years and with having to pay so much for an exam that's out of touch with practice. I am all for initial certification, but I want choice when it comes to recertification—exam, CME, MOC, open book.

"There are so many resources a physician uses today," Sharma said. "If they come across something they don't understand in a publication, they may use UptoDate—doing so makes them a better physician. With [recertification] exams, you should have similar resources."

The medical knowledge tested on the recertification exams continues to be a sticking point with practitioners.

"The aim should be to keep up with fresh medical knowledge, not a punishment-like system that threatens livelihood, because at 50-plus age, some people might not be in the habit of taking hourlong tests but are excellent physicians and provide good care, but may lose their board status and have trouble in jobs," said Farhan Ali MD, MBBS, of the University of Maryland. "Board questions are mostly research-based and add to knowledge, not treatment paradigms per se, so they do not impart much to clinical practice on a large scale. In addition, my argument always is . . . that if recertification is such a good thing, it should be for all physicians. Why are some physicians (who graduated before 1991) exempt?"

Search for Agents to Prevent Contrast Nephropathy Continues

The recent finding that the experimental drug CMX-2043—developed to prevent ischemic-reperfusion injury (IRI)—does not reduce the risk of contrast-induced kidney injury compared to placebo dealt a setback to the search for agents to prevent the condition. The negative clinical trial results were presented at the American College of Cardiology (ACC) meeting, held this spring in Chicago.

Other products have been or are being tested for acute kidney injury (AKI)—including recombinant alkaline phosphatase, THR-184, and Bendavia—all targeting different pathways. Most recently, a trial in The *New England Journal of Medicine* found an increased risk of AKI, as a secondary outcome, in patients receiving rosuvastatin before cardiac surgery.

"There is a huge unmet need, but therefore a great opportunity for novel therapies to be evaluated, and hopefully, validated," said lead investigator Deepak L. Bhatt, MD, MPH, Professor of Medicine, Harvard Medical School and Executive Director of Interventional Cardiovascular Programs, Brigham and Women's Hospital Heart and Vascular Center. "In patients undergoing cardiac catheterization and especially percutaneous coronary intervention, there is a high rate of renal complications in those patients at elevated baseline risk for contrast-induced kidney injury."

The CARIN trial (NCT02103959) included 361 patients undergoing angiography at 31 North American medical centers. All enrollees were considered at high risk of angioplasty due to acute coronary syndrome or poor stress test results. They also had mild-to-moderate or severe loss of kidney function, together with at least one additional risk factor such as diabetes, hypotension, or age over 75. Patients with heart attack, life-threatening arrhythmias, or total kidney failure were excluded.

Before angiography, patients were randomly assigned to receive placebo or CMX-2043—a derivative of α-lipoic acid analog developed to reduce cellular injury and organ damage due to IRI. "The thought was [CMX-2043] would be safe and potent, that it has multiple mechanisms of action, and that it's active in multiple tissues, including the kidneys and the heart," Bhatt said.

CMX-2043 was given at one of three fixed doses: a single dose of 2.4 or 3.6 mg/kg or two doses of 2.4 mg/kg. The primary outcome was reduction in the incidence of AKI, based on KDIGO criteria. Biomarkers of renal and cardiac injury and 90-day clinical outcomes and adverse events were evaluated as well.

At four days, the incidence of AKI was not significantly different across the four study groups: 25.6 percent for the single low dose of CMX-2043, 25.3 percent for the single low dose, 18.9 percent for two low doses, and 18.6 percent for placebo.

There were also no differences in adverse cardiac and kidney events, and no evidence of major side effects related to the CMX-2043 doses used. The study did not confirm the previously reported reduction in myocardial damage during stent placement.

The final results of the phase 2 CARIN trial showed no reduction in the primary outcome of contrast-induced acute kidney injury, as it had done in pre-clinical models. "Contrast-induced acute kidney injury remains a really significant problem in the population," Bhatt said. "It remains an unmet clinical need to find drugs or devices or strategies to help reduce the risk."

"The thought was that this drug had antioxidant and cell membrane stabilizing effects and that these benefits would translate into less kidney cell damage and heart muscle damage," Bhatt commented. "But as is often the case in this field, drugs that seem to be good based on preclinical work, when used in humans don't always have an effect."

A previous randomized trial (SUPPORT-1) found that patients receiving the 2.4 mg/kg dose of CMX-2043 had a significant reduction in cardiac injury after percutaneous coronary intervention, based on standard cardiac biomarkers.

The negative clinical results with CMX-2043 don't necessarily close off the possibility of some effective intervention targeting the α-lipoic acid pathway, according to Bhatt. "But the specific drug we tested, at least at the doses we tested, does not work."

The study was funded by Ischemix LLC, the manufacturer of CMX-2043. In a statement, the company said it was performing further preclinical studies to understand the results observed in the CARIN trial.

One bright spot was that the study showed it is possible to recruit a sufficiently large group of patients at risk of renal and cardiac injury during percutaneous coronary intervention. "The design of this trial might serve as a useful template for future trials to efficiently determine whether novel agents that appear promising in animal studies are worth actually taking into larger, more expensive phase 3 evaluations," Bhatt said. "Because in this case, we did actually prevent a large, 10,000-patient study that would have likely been negative from happening by efficiently studying this in about 300 patients."

The CARIN results are a setback in the search to develop some effective means of preventing contrast-induced nephropathy in the large group of patients at high risk for this complication. Currently, the most effective approach to prevention is intravenous hydration—and even this isn't always possible, especially in emergencies.

"There have been so many trials over the last 15 years, trying to find an agent that helps us in the cath lab to prevent kidney damage," commented ACC Vice President C. Michael Valentine, MD. "It's a huge problem, because there are so many patients who have concomitant kidney and heart disease. When patients come in with heart attacks or acute coronary syndromes and need catheterization, we're in a double bind trying to protect their kidneys while saving their hearts."

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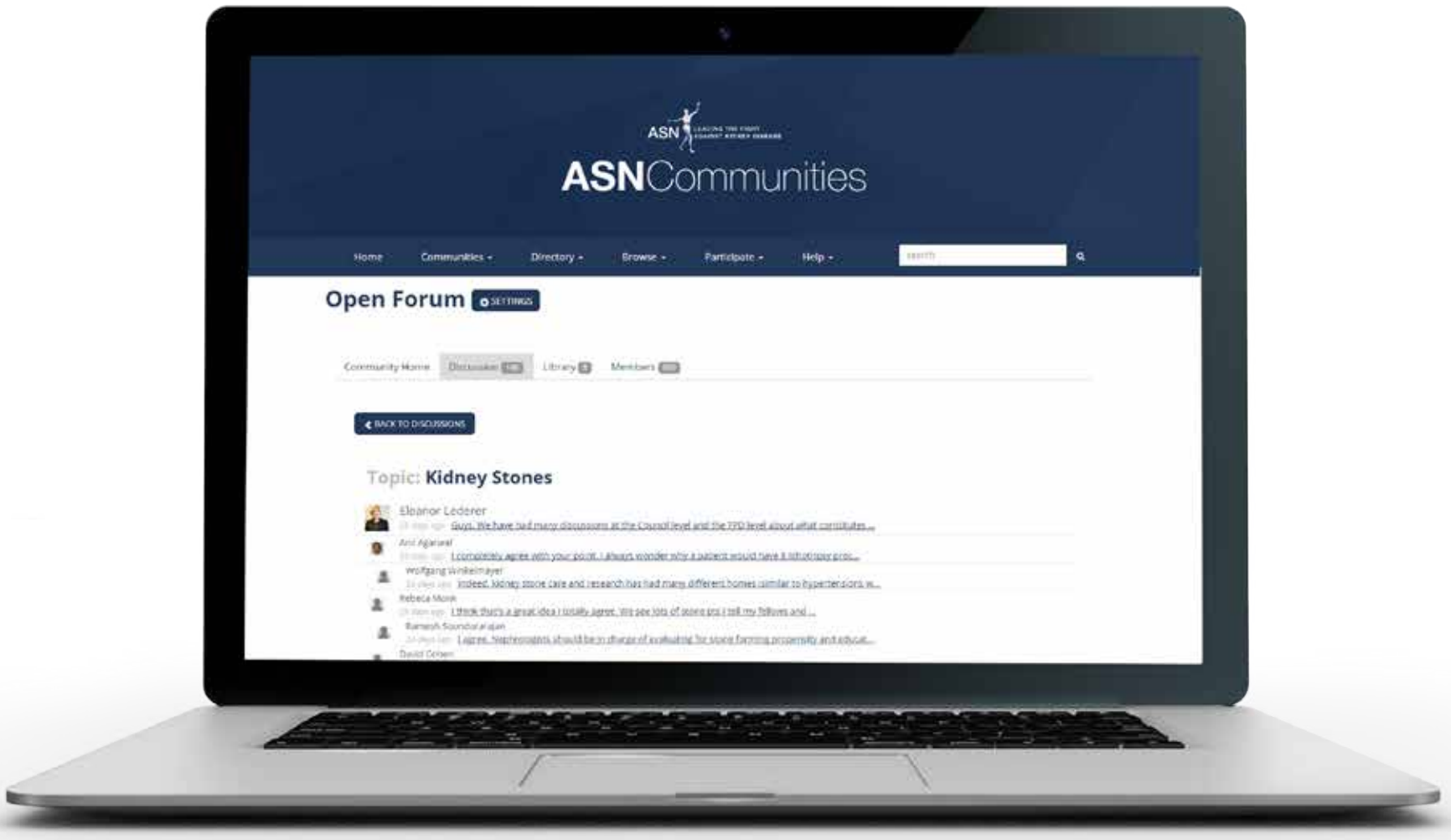

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