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ASN 50 years

Kidney News

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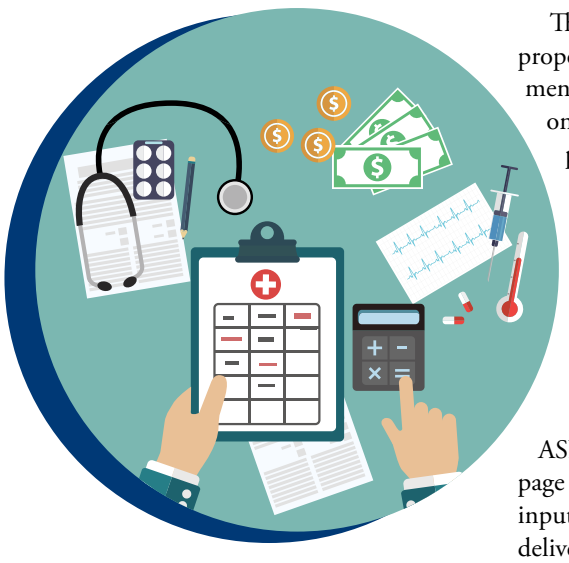
Innovative ESRD Care and Payment Models: CMS Seeks Input

By Eric Seaborg



A request from the Centers for Medicare & Medicaid Services (CMS) for input on new care and payment models has ASN gearing up to weigh in on what could be significant changes in the way that Medicare treats kidney disease.

The CMS request came in its annual proposed updates of policies and payments related to renal disease. Published on June 24, 2016, other noteworthy parts of the updates include permitting acute kidney injury (AKI) patients to be treated in end stage renal disease (ESRD) clinics, introducing equivalency payments for more frequent dialysis treatment, and offering higher payment for home dialysis training.

The provision that has many in ASN excited is on page 204 of the 260-page proposed rule, where CMS "seeks input on innovative approaches to care delivery and financing for [Medicare] beneficiaries with end stage renal disease. This input could include ideas related to innovations that would go above and beyond the Comprehensive ESRD Care (CEC) Model with regard to financial incentives, population or providers engaged, or the scale of changes, among other topics."

CMS requests responses to 10 questions covering a broad range of issues, including how providers who participate in alternative payment models could:

- coordinate care for beneficiaries with chronic kidney disease (CKD) and improve their transition to dialysis;
- target key interventions for beneficiaries at different stages of CKD;
- promote increased rates of renal transplantation;
- help reduce disparities in rates of serious kidney disease and adverse outcomes among minority groups; and
- facilitate changes in care delivery to improve patient quality of life.

"ASN is thrilled that CMS is seeking input to develop and refine innovative payment models in the kidney space," said ASN President Raymond C. Har-

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Ultrafiltration Rate Reporting Could Lead to Longer Dialysis Times

The Centers for Medicare & Medicaid Services (CMS) has proposed introducing an ultrafiltration rate quality measure into its End-Stage Renal Disease Quality Incentive Program (QIP). A study of competing models of this quality measure found that meeting the standard is likely to require lengthening dialysis treatment times by durations that could prove challenging to dialysis unit operations.

CMS has been considering adding this measure for some time because fast ultrafiltration rates are associated with adverse outcomes, although data on direct links is far from definitive.

After CMS first proposed its model for the standard, the Kidney Quality Care Alliance (KQCA) responded with a proposal of its own. Both proposals use a benchmark of 13 milliliters per hour per kilogram of body weight as the upper acceptable limit, but there are two major differences in the plans. First, the CMS model relies on data from a single treatment, whereas KQCA uses the mean of three treatments in a week. Second, the KQCA proposal gives a facility credit for dialysis sessions that last four hours or more, regardless of the actual ultrafiltration rate.

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Inside

CMS Requests Input

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ris. "We are particularly enthused about the possibility of expanding beyond the focus on dialysis to potentially include CKD and transplant care. The society strongly supports more integrated care for kidney patients across the spectrum of kidney disease, and looks forward to providing input to CMS and encouraging the agency to explore truly comprehensive models ranging from CKD through transplant and end of life."

Rachel Meyer, associate director of policy and government affairs, said that ASN is already promoting the need for these kinds of innovations. ASN included the outline of a comprehensive model for care of CKD in a letter it sent to CMS on June 27, 2016, detailing its comments on the agency's proposals for implementing the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). That law ended the Sustainable Growth Rate formula for determining Medicare payments to providers and was designed to create a framework for rewarding providers for supplying better care rather than more care.

AKI treatment in ESRD facilities

Another potentially significant change proposed in the rules is that Medicare and Medicaid patients with AKI will be able to receive dialysis services in ESRD facilities beginning next year. CMS will provide payment based on the ESRD prospective payment rate, as adjusted by the wage index. However, CMS said in a press release that "drugs, biologicals, laboratory services, and supplies furnished to beneficiaries with AKI that are not considered to be renal dialysis services but that are related to the dialysis as a result of their AKI would be separately payable."

ASN will certainly seek to influence the shape of this new program, said John R. Sedor, chair of the ASN Public Policy Board: "As CMS begins to implement this new law, it will be tremendously important for them to take into account the many ways in which patients with AKI are unique from patients with ESRD. Their care will need to reflect those differences, and be reimbursed accordingly. On the quality front, what constitutes optimal care for patients with ESRD is often not even appropriate care for patients with AKI, so keeping the new AKI patients out of quality reporting systems such as the Quality Incentive Program is vital. At the same time, we need better data to inform what exactly optimal AKI care looks like."

This change in coverage of AKI was mandated by a provision tucked into the Trade Preference Extension Act of 2015. Although AKI care would seem to have nothing to do with international trade, the provision was probably included as a budget offset to save money and keep the trade bill budget neutral.

Change in payments for more treatments

CMS is also proposing a change in the payment system when an ESRD facility provides a patient with more than three hemodialysis treatments per week, which is often the case for hemodialysis patients who are dialyzing in their homes. Payment is generally capped at three dialysis sessions per week, with more sessions reimbursable if they are deemed medically necessary by a physician, such as in the case of congestive heart failure or pregnancy.

The proposed rule's intent is to "provide a mechanism for payment for evolving technologies that provide for a different schedule of treatments that accommodate a patient's preference and thereby improve that patient's quality of life," and it notes that more frequent dialysis allows for shorter treatments, affording patients greater flexibility in managing their illness. CMS seems to justify the capped payment proposal by noting that the same level of toxin clearance can be achieved in three treatments, and "there is a lack of objective data to justify additional payment for HD treatments beyond three treatments per week."

However, CMS notes that ESRD facilities have expressed concern that because of the limit, they are not able to report additional treatments on their monthly claim forms and are not paid for each treatment. To encourage facilities to report all treatments, CMS is proposing a payment equivalency formula for these treatments similar to the one used in peritoneal home dialysis, in which patients receive more than thrice weekly treatment sessions, but the total payment is capped.

CMS proposes to "calculate a per treatment payment amount that would be based upon the amount of treatments prescribed by the physician" regardless of how many actual treatments the patient receives. Thus, the equivalency payment would be based on three treatments a week. Because allowing more bills would represent "a substantial change for the ESRD facility's billing systems and for the Medicare Administrative Contractor," the change would not be fully implemented until July 1, 2017.

Home dialysis training increase

The proposed rule also contains a provision that could improve the climate for home dialysis by paying more for training. CMS proposes to increase the number of reimbursable hours for training for a registered nurse for home dialysis and self-dialysis teaching from 1.5 hours or $50.16, to 2.7 hours, to $95.57. (CMS assumes that the hourly wage for a nurse providing dialysis training in 2017 will be $35.93.)

Little change in prospective payment

Although the updates contain some big changes in other areas, it's pretty much the status quo when it comes to the base bundled payment rate for renal dialysis services to treat ESRD in Medicare beneficiaries. CMS proposes increasing it by 65 cents, from this year's $230.39 to $231.04 in calendar year 2017.

Quality Incentive Program

Under the ESRD Quality Incentive Program (QIP), facilities that fail to achieve a minimum score on quality measures face a reduction in their payment rates of up to 2%. The new rule does not propose any changes in quality measures for next year, but does propose changes for 2018, 2019, and 2020.

For 2018, for example, CMS proposes two changes to the hypercalcemia clinical measure. The changes involve including plasma as an acceptable substrate in addition to serum for calcium and a technical change to the denominator definition to account for periods during which a facility reports no calcium values.

The proposed QIP for 2019 adds a new Safety Measure Domain, so it includes seven clinical/outcome measures and five to six reporting measures, a large increase from the two to three measures in the early years of the QIP, according to Daniel E. Weiner, chair of the ASN Quality Metrics Task Force. "The struggle for CMS and the community is trying to find reliable measures that evaluate truly important aspects of dialysis patient care," Weiner said. "This is very difficult when clinical trials lack dialysis data to support any of the currently existing measures, not to mention any measures that may be proposed in the future. Ironically, this lack of evidence seems to have led to more measures being applied to the QIP, a trend that runs the risk of diluting the impact of high performance on measures that may be more important and better supported, such as the vascular access measures. Ultimately, the ideal QIP is both more parsimonious, containing fewer measures, as well as more important, containing the measures that, if achieved, are most likely to make meaningful differences in patients' lives."

Ultrafiltration Rate Reporting

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A study in the August *Clinical Journal of the American Society of Nephrology* drew on the database of a large dialysis organization to analyze how some 150,000 patients would have fared against each measure. It found that 21–23% of patients would have exceeded the 13 mL benchmark under the CMS rules, and about 16% would have exceeded it under the KQCA rules. Although limiting fluid gain through diet is in many ways the better option, the most likely way facilities will lower ultrafiltration rates is by extending treatment times—and the researchers calculated that a 100-patient facility would need to add 33 treatment hours per week to get all its patients below 13 mL—and that's using a treatment duration cap of 4 hours (per the KQCA measure).

"That number tripled—up to 98 hours per week—when we removed the 4-hour treatment cap," said lead study author Jennifer Flythe, MD, MPH, assistant professor of medicine at the University of North Carolina. "So there are some very interesting patient and facility implications that need to be thought through to ensure that there are no unintended consequences from implementation of the ultrafiltration rate measure."

The study identified some other pitfalls of applying a uniform standard to all patient groups. For example, ultrafiltration rates rose in winter and fell in summer, probably because patients' hydration levels vary during colder and hotter seasons.

"Certain patient groups tended to have had higher ultrafiltration rates, including patients that were younger, women, nonblack, of Hispanic ethnicity, and smaller in body weight," Flythe said. Higher rates for smaller patients are not surprising, considering that the measure is by definition indexed to body weight, but the implication of higher rates among these patients is an open question.

Why an ultrafiltration standard?

Flythe said that the physiological underpinnings for the desirability of lower ultrafiltration rates are sound: "The thought is that the faster you pull the fluid off during dialysis, the more cardiac and other organ stress you may be causing." And the negative consequences are backed up by observational data, but the evidence base is not strong.

"We have an absolute lack of clinical trial data looking at the effects of ultrafiltration rates," said Daniel Weiner, MD, MS, a nephrologist and associate professor of medicine at Tufts University School of Medicine, and chair of the ASN Quality Metrics Task Force. "Just like pretty much every other metric in dialysis, there are not good randomized trial data comparing different interventions and looking at important clinical outcomes"

Just the same, Weiner believes that

volume control "is the next big thing" in dialysis management: "It is much more important in my opinion than anemia management and hypercalcemia."

He said that when KCQA surveyed the dialysis community about developing new quality measures, fluid management was the top priority.

But he acknowledges the uncertainty of any standard at this point. The 13 mL threshold was endorsed by the National Quality Foundation, but "for some people, 8 mL may be too high, and for some people, an ultrafiltration rate of 18 mL may be OK. But you had to start somewhere. Importantly though, we need a continuing iterative process by which we reassess what may be the optimal filtration rate."

Eduardo Lacson Jr., MD, MPH, also from Tufts, is not as enthusiastic about the prospect of an ultrafiltration rate measuring standard. He noted that the most direct evidence has come from studies using technologies to prevent intravascular volume depletion—and these studies found that the avoidance of depletion had no effect on outcomes.

Weiner and Lacson co-wrote an editorial that accompanied Flythe's study and concluded that proposals like this one epitomize the balancing act between the two aphorisms, "the perfect should not be the enemy of the good" and "first do no harm." But they also note that the QIP already exists, so the kidney community must be ready for new measures being added regularly.

CMS says it is coming

And CMS' latest draft updates to policies and payment rates for end stage renal disease make it clear that this one is coming. Released on June 24, 2016, the updates propose incorporating an ultrafiltration rate reporting measure into the QIP in payment year 2020. That timing is actually a year's postponement—the 2015 updates proposed beginning the program in 2019.

The 2016 CMS proposal moves toward parts of the KCQA model, including reliance on a week of testing instead of a single measure. Although this requirement actually increases a facility's data reporting requirements, Weiner and Lacson said that one reason the KCQA included it was not only to get a more accurate picture of a patient's status, but also to prevent dialysis facilities from gaming the system. As long as patients are scheduled for three sessions in a seven-day week, there are going to be shorter and longer periods between dialysis sessions, with more fluid building up during the longer breaks. "Patients who come in after the 72-hour gap are probably going to have more fluid taken off than those who come in after the 48-hour gap," Weiner said. "So if you are a dialysis facility that draws its labs on a Wednesday or Thursday, you are going to look better under the [original] CMS measure than if you draw your labs on a Monday or Tuesday." In addition, Lacson said that a facility could tailor a single treatment to meet the reporting requirement, temporarily leave the patient slightly fluid overloaded, and remove excess fluid at the next session.

Flythe's study did in fact find that ultrafiltration rates varied according to the time between treatments, "with greater ultrafiltration rates occurring after the long interdialytic break."

The updated CMS version did not include an exemption for dialysis sessions of four hours or more. This exemption in the KCQA model was part of the reason more facilities met the guideline compared with the CMS proposal. Weiner said that a session of this duration shows that "the dialysis facility is doing what they can to minimize the ultrafiltration rate. You don't want dialysis units to limit the amount of fluid they take off someone, leaving them fluid overloaded, just to hit a measure."

Lacson noted that not only would longer treatment times pose challenges for the operation of a dialysis facility—such as longer hours and juggling patient schedules when treatment durations are unknown—but many patients will not happily greet the prospect of longer treatment.

Implementation plan

CMS plans to score facilities on whether they successfully report the required data in a timely fashion, not on the values reported. Weiner said that CMS often phases in a measuring standard in this fashion to make sure that the data capture is feasible and reliable. He said the ASN Quality Metrics Task Force will be submitting comments on the latest CMS proposal.

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ASN President's Column

By Raymond C. Harris, MD, FASN

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We are all aware that the landscape for the practice of medicine in the United States is rapidly changing. For Nephrology in particular, how we practice currently will be very different from practice patterns 20, 10, or even 5 years from now. Three recent developments may have significant effects upon the practice of Nephrology:

1. **MACRA.** MACRA (legislation approved in 2015) repealed the Medicare SGR physician payment system and replaced it with two tracks for Medicare physician payments, MIPS (Merit-based Incentive Payment System) and APMs (Alternative Payment Models).

The SGR model was unsustainable, and ASN joined the rest of organized medicine to support its repeal. ASN also supports the goals of the new payment system: to reward better care rather than more care, and to consolidate the existing quality reporting programs into a single program. In this regard, the society has provided thoughtful comments to CMS about modifications to MACRA that will make the system more reflective of high-quality clinical practice and fully supportive of the latitude clinicians require to deliver the best care to individual patients. ASN's letter to CMS represents hard work by members of the Public Policy Board, led by John Sedor, and by the Quality Metrics Task Force, led by Dan Weiner, and especially through the efforts of ASN staff, Rachel Meyer and David White.

While the legislation is specific to Medicare payments, these changes will impact commercial health plans as well. ASN will help educate its members about these changes in practice, the timelines that will affect each of us, and how the Final Rule differs from the Proposed Rule.

2. **Changes to AKI coverage.** The 2017 ESRD Prospective Payment System provides changes to coverage of patients with AKI in outpatient ESRD facilities. This change represents a potential benefit to our patients with AKI, who will no longer be required to remain hospitalized or return to acute dialysis facilities for treatment. At the same time, these changes require careful attention by physicians and dialysis facilities to tailor the dialysis prescription and provide close follow-up so that patients will be provided an optimal chance for recovery from AKI. ASN has met with CMS to share preliminary observations and will work with CMS and others to achieve these goals.

3. **The White House Organ Summit.** As I noted briefly in my June column, this Summit provided a unique opportunity to highlight the importance of kidney transplantation for our patients. Specific to practice, the Summit addressed the need for increasing the rate of transplantation, including discarding fewer organs, increasing organ donation after circulatory death, increasing the ability of all transplant centers to provide the best outcomes, being open to new payment plans through ESCOs, and using social media as a means to increase organ donations. In addition, at the Summit the Department of Defense announced a plan to partner with industry to provide up to $160 million for innovative biomanufacturing and regenerative medicine approaches that transform care. ASN's pledge to provide the initial $7 million to fund an XPRIZE for development of novel alternative approaches to existing methods of dialysis will further this push to innovate care of kidney patients.

As clinicians, we pride ourselves on our ability to balance a wide range of complex health issues to improve quality of life for people with kidney diseases. I am excited about the growing number of initiatives that will prove catalysts to incorporating transformative change into kidney care.

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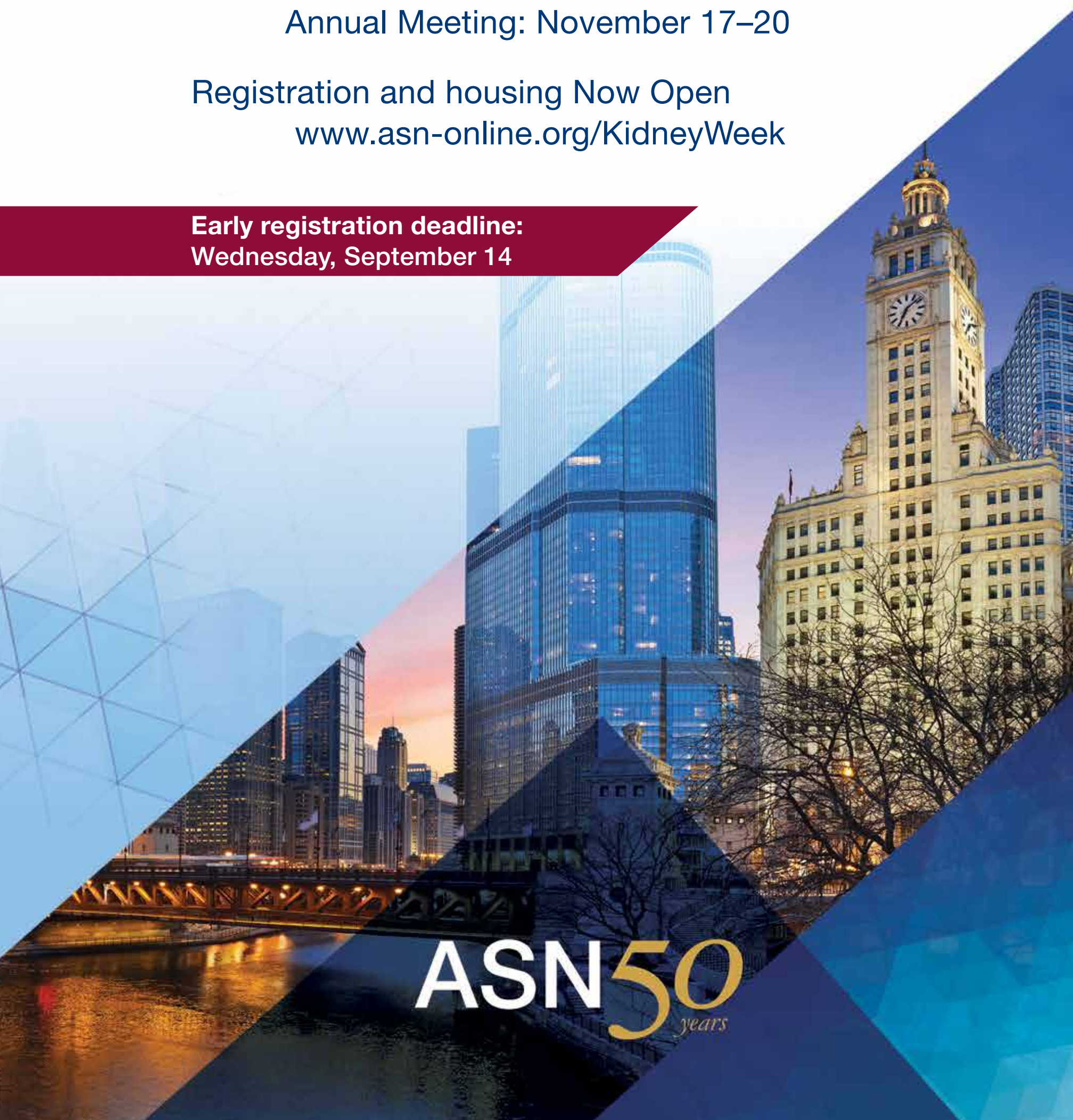

Findings

Empagliflozin improves renal outcomes in type 2 diabetes

The sodium-glucose cotransporter 2 inhibitor empagliflozin slows kidney disease progression in patients with type 2 diabetes at high cardiovascular risk, reports a study in *The New England Journal of Medicine*.

The study included 6185 patients with type 2 diabetes and eGFR of 30 mL/min per 1.73 m^2 or higher enrolled in the EMPA-REG OUTCOME Trial. In that study, patients were randomly assigned to once daily treatment with empagliflozin (10 or 25 mg) or placebo. Previous results showed a significant reduction in major adverse cardiovascular events with empagliflozin.

The analysis focused on prespecified microvascular outcomes, particularly kidney disease progression. At a median of 3 years, rates of incident or worsening nephropathy were 12.7% for patients assigned to empagliflozin versus 18.8% in the placebo group (hazard ratio [HR], 0.61).

Doubling of serum creatinine occurred in 1.5% of patients receiving empagliflozin versus 2.6% with placebo (HR, 0.54). Rates of renal replacement therapy were 0.3 and 0.6%, respectively (HR, 0.45). Incident albuminuria was similar between groups. Adverse events were also similar between treatment groups in patients with or without impaired kidney function at baseline.

Added to standard treatment, empagliflozin reduces kidney disease progres-

sion and clinically relevant renal events in patients with type 2 diabetes at high cardiovascular risk. The researchers note that these outcomes were achieved in a patient sample with well controlled BP, including high use of renin-angiotensin-aldosterone system blockers [Wanner C, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016, in press].

New model predicts acute kidney injury risk after cardiac surgery

A bedside prediction model provides a simple approach to identifying patients at high risk of developing acute kidney injury (AKI) requiring renal replacement therapy after cardiac surgery, reports a study in the *Canadian Medical Association Journal*.

The model was developed using prospectively collected data on 6061 patients undergoing cardiac surgery (other than transplantation) in Alberta between 2004 and 2009. Of these, 2.5% developed AKI requiring renal replacement therapy within 14 days after cardiac surgery.

Multivariable logistic regression identified eight independent predictors of AKI: congestive heart failure (adjusted odds ratio [OR] of 3.03), Canadian Cardiovascular Society angina class 3 or higher (OR of 1.66), diabetes (OR of 1.61), baseline eGFR (OR of 0.96 per 1-mL/min per 1.73 m^2 increase), preoperative hemoglobin level (OR of 0.85 per 10-

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Findings

New Model

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g/L increase), proteinuria (OR of 1.65), coronary artery bypass graft (CABG) plus valve surgery (OR of 1.25 versus CABG only), cardiac procedures other than CABG (OR of 3.11), and emergent surgery (OR of 4.63).

A model comprising these eight variables had excellent performance, with c statistics of 0.87 in the derivation cohort and 0.83 in a validation cohort of 4467 patients. Net reclassification improvement was 13.9% compared with the best existing prediction model (Cleveland Clinic Score).

On the basis of readily available clinical and laboratory data, the new model provides a practical and accurate tool for predicting the risk of AKI requiring renal replacement therapy after cardiac surgery. Although additional validation is needed, this simple score could be a useful aid in talking to patients about AKI risk before heart surgery [Pannu N, et al. A new model to predict acute kidney injury requiring renal replacement therapy after cardiac surgery. *CMAJ* 2016, in press].

Healthy lifestyle lowers chronic kidney disease and mortality in type 2 diabetes

In the population with type 2 diabetes, even modest changes in lifestyle and dietary risk factors could have a substantial effect on chronic kidney disease (CKD) cases and deaths, suggests a study in *The American Journal of Kidney Diseases*.

The researchers analyzed the population-attributable fraction (PAF) of diabetes-related CKD and mortality associated with lifestyle factors and diet. The study included 6916 middle-aged adults with type 2 diabetes but without severe albuminuria drawn from the international Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial Study. Median baseline urinary albumin-to-creatinine ratio was 6.6, and eGFR was 71.5 mL/min per 1.73 m^2.

The effects of "immediately modifiable personal behaviors" on CKD risk were analyzed using 5.5-year follow-up data. CKD was defined as moderate to severe albuminuria or at least a 5% annual decline in eGFR. The analysis accounted for competing risk of death.

During follow-up, 32.5% of patients developed albuminuria, 55.2% had a 5% or greater decline in eGFR, 12.3% met both CKD criteria, and 14.8% died. Daily physical activity was associated with reduced risk of both outcomes: PAF of 5.1% for CKD and 12.3% for death. Dietary improvements also had a significant effect—particularly increased consumption of vegetables.

Less than optimal diet, body weight, physical activity, tobacco use, and size of social network were associated with PAFs of 13.3% for CKD and 37.5% for death. Extrapolated to the US population of 17.8 million middle-aged adults with diabetes over 5.5 years, the findings suggested that achieving one modifiable lifestyle factor could reduce CKD incidence/progression by 274,0000 and avoid 405,000 deaths.

Unfavorable dietary and lifestyle factors seem to be major contributors to the risk of CKD events and death among middle-aged Americans with type 2 diabetes. Although some of the PAFs reported in this study are not large, the results suggest that healthier diet and lifestyle changes could have a "substantial impact on population kidney health" [Dunkler D, et al. Population-attributable fractions of modifiable lifestyle factors for CKD and mortality in individuals with type 2 diabetes: A cohort study. *Am J Kidney Dis* 2016; 68:29–40].

Telemedicine and EHRs

Telemedicine and Nephrology: The Slow Revolution Continues

By Eric Wallace, MD, FASN

Almost 25 years after the Texas Telemedicine Project, one of the first major telemedicine initiatives, we are still trying to determine where and how telemedicine fits into modern nephrology.

Increased access to care is just one of many potential advantages of telemedicine. However, at a time of increasing healthcare costs, policymakers and payers ask, "What is the added value?" Furthermore, debates about acceptable means of providing telemedicine care rage on. Legal battles waged between providers of telemedicine and state medical boards have provided further hesitancy on the part of physicians to incorporate telemedicine into their daily practice. Many of the concerns surrounding telemedicine could take another 25 years of study to answer. However, for many patients, telemedicine is not needed for mere convenience or easy access to treatment for sore throats. It is needed to extend substandard access to subspecialty care, as well as expanded treatment options, and it is needed now.

Telemedicine has been primarily used to bridge geographic disparities in access to care, and has been focused mainly on provision of care in rural areas. Approximately 25% of the US population lives in areas considered rural, and rural location has been associated with increased incidence of end stage renal disease (ESRD). Thus telemedicine provides a means to improve access to care where the need is greatest. Luckily, the rural patient is considered the most appropriate recipient of telemedicine visits. In large part, Medicare and Medicaid already cover telemedicine for standard outpatient visits for this population, as do many other private insurers in states with existing telemedicine parity laws. Telemedicine for this population not only serves to increase access to subspecialty care, but also increases the comfort levels of rural primary care physicians who are otherwise practicing in medical deserts with little to no subspecialty support.

While standard outpatient subspecialty visits are covered, coverage of home dialysis follow-up visits is another story. Prior to January 2016, there was no coverage of any telemedicine visits for the home dialysis population. The 90963-90966 outpatient home dialysis codes appeared in January of 2016 as a covered telemedicine code for Medicare. Unfortunately, this coverage excludes home hemodialysis patients (or even peritoneal dialysis patients) with a vascular access as it is stipulated that an in-person face-to-face visit must be provided to examine any vascular access. Still, acceptance of the 90963-90966 codes by the Centers for Medicare & Medicaid Services (CMS) represents a large step for telemedicine in the provision of rural peritoneal dialysis.

Rural patients are the natural focus of telemedicine services, but should rural areas be the only focus

of telemedicine? For many patients living remotely from care but in a metropolitan area, the answer is no. Certain super-subspecialized care might only be achieved in tertiary referral centers or university settings. Patients who might fall into this category include those with rare diseases, pediatric nephrology patients, and transplant recipients. These patients currently have no option for telemedicine. Furthermore, for the elderly and those with limited mobility of all ages living in metropolitan areas, telemedicine might limit non-emergent ambulance transport to and from clinic visits and improve the ability of these patients to make appointments that might thwart frequent hospitalizations. This feature of telemedicine is even more applicable for the home dialysis patient population with limited mobility. Unfortunately, owing to CMS's geographic restrictions on telemedicine, patients such as these do not have access to telemedicine services. Thus a large barrier for many applications of telemedicine lies in the removal of the rural restrictions on telemedicine services.

Improving quality of care

Telemedicine may be a means to not just improve access to care but to also to improve quality of care through remote monitoring and by facilitating the creation of centers of expertise. Already remote monitoring—such as Bluetooth-enabled blood pressure monitors and weight scales—is being used to improve our ability to manage hypertension, for example. Furthermore, the chronic care management code (90940) allows for reimbursement of remote monitoring in select populations. Notably, however, ESRD is excluded from coverage.

Remote monitoring for the home dialysis patient may provide the means to truly have an impact on outcomes such as hospitalizations. Systems providing real-time evaluation of vital signs and real-time therapy monitoring provide a means to intervene with patients to avoid hospitalizations for hypertensive emergencies and volume overload. Remote monitoring, however, is not without its issues. With remote monitoring comes the need for increased nursing and physician time. Only human or computer analytic interpretation of data and intervention paired with remote monitoring can have an impact on outcomes. Furthermore, questions about liability regarding remote monitoring remain. Carefully designed studies to determine appropriate clinical algorithms that maximize outcomes without overwhelming both nurses and physicians with a massive influx of data are needed to guide the use of these exciting technologies.

Telemedicine may also improve quality of care by serving as a way to link centers of expertise with the patients they serve. Certain types of super-subspecialized care might be best achieved by centers of expertise. In this way, adequate staffing, multidisciplinary teams, and continued education can allow patients to receive cutting-edge care. However, patients may only be able to take advantage of centers of expertise if they can make the commute to one. Telemedicine may serve to bridge this gap, thus enabling centers of expertise to ensure patient access.

The designation of "rare" in the US is defined as affecting fewer than 200,000 patients at any one time. By this definition, home dialysis could also be considered rare. It has been shown in 4 separate studies that larger home dialysis units achieve better outcomes for their patients than smaller units. Much of the advantage of larger units is thought to result from their ability to maintain adequate patient volumes, allowing dialysis staff and nephrologists to hone the skills and knowledge required to care for this relatively small group of patients. Still, a large percentage of home dialysis units have fewer than 5 patients. Telemedicine may provide a means by which smaller home dialysis units might benefit from nursing and physician expertise in larger units to improve patient outcomes. However, currently a home dialysis unit is not a covered originating site according to the Centers for Medicare & Medicaid Services.

Telemedicine may further increase uptake of home dialysis modalities by improving patient comfort and knowledge regarding the modality via teleeducation, engagement, and care coordination. More confident providers and patients should be the result of telemedicine-enhanced communication

Much has changed since Jack Moncrief, MD, one of the primary drivers of the Texas Telemedicine Project and pioneers in home dialysis, began the Texas Telemedicine Project. At the time of the project, telemedicine cost over $50,000 per site for capabilities that now can be achieved using technology that many carry in their pockets every day. But the

revolution is far from over. Should the patient's home be considered an originating site? Must each site be required to have the capability to do a full physical exam? How can a telemedicine clinic be incorporated into an already busy physician schedule? What are the liabilities?

The questions don't stop there. The Kidney Health Initiative (KHI) Workgroup project on Advancing Technologies to Facilitate Remote Management of Patient Self-Care in Renal Replacement Therapy aims to develop an understanding of and solutions to these issues.

The dream of Dr. Moncrief is literally at our fingertips with a new age of smaller, faster, and much less expensive technologies. Opportunities to improve patient care, and access to that care, must be harnessed. It is our obligation to patients to accelerate and through experience guide this slow revolution that holds so much promise to improve their lives.

Eric Wallace, MD, FASN, is affiliated with the Division of Nephrology, University of Alabama at Birmingham.

Could CKD Become a Model for Use of EHRs for Quality Improvement?

By Bridget M. Kuehn

Electronic health records (EHRs) have made it much easier for physicians treating patients with chronic kidney disease (CKD) to collect data, including glomerular filtration rate (GFR), creatinine, blood pressure, cholesterol, anemia, and bone health, said Joseph Nally, MD, Director of the Center for Chronic Kidney Disease at the Cleveland Clinic. But they don't always make it easy for physicians to use the data to improve patient care.

"The EHR has simplified the process in terms of information gathering, but it is still up to the physicians and caregiver team to do all the right things to optimize patient care," Nally said.

It can be an exercise in frustration for clinicians to access the data. Physicians may have to visit multiple screens and may not be able to easily look at trends in the data over several months, said Paul E. Drawz, MD, a nephrologist at the University of Minnesota. The "holy grail" for CKD patients would be to develop a care plan that makes all the critical clinical information and patient preferences easily accessible, said Nally.

To make such a patient plan a reality, Drawz, chair of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Health Information Technology Working group, is working with Nally and other nephrologists and technology experts from across the country. Building off progress made at a meeting held at NIDDK last October, the working group has begun to develop the plan and other tools that will help nephrologists and their institutions better leverage EHR data to improve patient care (Drawz PE, et al. *Clin J Am Soc Nephrol* 2015; 10:1488).

The "holy grail"

For patients with CKD, it is especially important for a care plan to be portable. The plan needs to be able to follow the patient from the dialysis unit, to the emergency department, to the hospital, and back to their physician, said Andrew S. Narva, MD, Director of the NIDDK's National Kidney Disease Education Program.

"The CKD patient in many ways is the perfect storm of the patient who suffers from not having something like this," said Narva. "These patients are on a lot of medicines, they are very complicated, and they get their care in many different places that don't usually talk to each other."

The NIDDK working group is working closely with the Office of the National Coordinator for Health Information Technology, which is working on developing electronic care plans for many conditions as a way to boost evidence-based care, improve outcomes, and lower care costs, noted Jenna Norton, a project manager aiding the effort at NIDDK.

"We are having a rapidly escalating collaboration with them to do this because they now understand that CKD patients are sort of a model chronic disease patient likely to benefit from this," Narva said.

For patients, the care plans will help ensure that their desires and goals stay at the forefront even as they transition between care settings. For example, if a patient ends up in the emergency department in need of dialysis, there will be something in the care plan that indicates the patient's preferences regarding dialysis modality, Narva said.

"It will allow the oatuebts; not to have to repeat themselves over and over and to have more of a voice in their care," Drawz said.

To ensure that patients' needs are considered, the working group includes representatives from the American Association of Kidney Patients.

"It's not happening in a vacuum," Narva said. "We all understand that patient input and the patient voice is key."

Initially, the care plan document will be physician-facing, Norton said. But eventually the working group would like to provide a way for patients to see their information in one place or to engage their physicians. One possibility is creating a mobile application so the patient can navigate his or her care, Norton said.

Challenges ahead

But creating such a care plan is not an easy process. The plan can't be so long or complex that physicians won't use it, Narva said. It also must avoid being "nephrocentric." He explained that most patients with CKD die from heart disease, so other specialists like cardiologists must be able to use it as well. It must be designed to avoid having different recommendations, for example for blood pressure, given by different specialists.

"There's a long way to go before we have a digital information system that really works for patients and clinicians," Narva said.

One of the first hurdles will be deciding how to define CKD. One of the reasons EHRs are particularly useful for CKD care is that the diagnosis of the disease is based on objective laboratory values, which can be identified in EHRs, Narva said.

"CKD is a great example of a computable phenotype that can be a prototype for other conditions moving forward," Drawz said.

The working group is currently hammering out what the "computable phenotype" for CKD diagnosis will be. For example, what are the cutoff readings for laboratory values that indicate CKD? The group is also working on an electronic profile of CKD patients at risk of progression. Already, the group has made substantial progress toward these goals, Drawz said.

Interoperability problems between organizations' electronic records systems are another challenge the working group is trying to address.

"The data doesn't move between providers," Drawz explained. "Just about every single EHR has so many homegrown aspects it is difficult to collaborate across sites."

Blueprint for population health

Finally, the working group is developing a business case for why health systems should invest in the tools and upgrades necessary to use health information technology for population health management.

For example, most patients with CKD go undiagnosed, even though the data needed to identify these patients is in their EHRs. Large organizations like the University of Minnesota's health system have been able to develop tools that can extract this kind of data from their electronic medical record systems to drive quality improvement efforts and research, said the University of Minnesota's Drawz. But it wasn't an easy process. It took hours of a computer programmer's time and the resulting programs can't easily be shared with other institutions, he said. So, many smaller systems go without such tools, leaving CKD patients unrecognized. Or other large systems have to duplicate these efforts.

"You have hundreds, if not thousands, of programmers around the country doing these one-off designs," he said. "If a system were built so it could be exported from one institution to another there would be tremendous savings."

The working group hopes to enable that kind of sharing. The tools developed as a result will help health systems adapt to the ongoing shift toward accountable care organizations and value-based payments from public and private insurers, for example, by helping systems identify CKD patients at risk of hospitalization or those receiving contraindicated medications, Drawz said.

"Once these new payment systems are in place it becomes something that saves money and improves the health of the population," he said.

Ultimately, Drawz said the goal is to provide nephrologists with a blueprint for population health and the tools to implement it.

"The bottom line is we can't improve care without data, and if we can't find CKD patients we can't get the data," Narva said. "These tools are critical as we move forward."

EHR-Based Research Yields Insights on CKD

By Bridget M. Kuehn

Patients with chronic kidney disease who also have chronic obstructive pulmonary disease (COPD) have a 41% increased risk of death, according to a recently published study that relied on electronic health records (EHRs) (Navaneethan SD, et al. *Am J Nephrol* 2016; 43:39–46).

The finding is part of a growing body of evidence demonstrating the power of EHR-based studies to help elucidate the many factors that contribute to poor outcomes for patients with CKD. The technology is also being used to help test ways to improve their care.

Joseph Nally, MD, a coauthor of the COPD study and Director of the Center for Chronic Kidney Disease at the Cleveland Clinic, and his colleagues began exploring electronic data for CKD research nearly a decade ago. There were a few "false starts" using billing data before the multidisciplinary team eventually created a CKD registry using EHRs, Nally said. Their registry now includes 110,000 patients, he said.

One of the reasons EHRs are particularly useful for CKD research is that objective laboratory values found in EHRs can identify patients even if they haven't been diagnosed, said Jesse D. Schold, PhD, of the Cleveland Clinic's Quantitative Health Sciences Department.

"That allows you to identify patients who haven't been recognized through other traditional means," Schold said.

This is particularly important in CKD patients because only about 10% have CKD listed as a condition in their records (Jolly SE, et al. *Am J Nephrol* 2014; 39:288–96). Patients who aren't listed as having CKD are less likely to see a nephrologist and receive recommended testing, and are more likely to receive contraindicated medications, Nally noted.

Another factor that aids EHR-based kidney disease research is the ability to access data from the United States Renal Data System, which provides a census of all patients with end stage renal disease in the US, Schold said. Nally noted that his team also taps data from the Ohio Death Index, which can provide cause-specific deaths for CKD patients (Navaneethan SD, et al. *J Am Soc Nephrol* 2015; 26:2512–2520).

Having a CKD registry also makes study recruitment more efficient. "The CKD registry is a spectacular vehicle for recruitment into research studies and randomized controlled trials," Nally said.

Currently, Nally and his team are using their registry for continuous quality improvement efforts (CQI). For example, they have compared the outcomes of 500 CKD patients who receive care in a CKD clinic, which uses nurse practitioners and algorithm-based care, with 1500 matched CKD patients receiving standard nephrology care. So far, the CKD clinics have performed better on patient processes of care and patient education, but whether it translates into better outcomes is unknown, Nally noted.

The team is also exploring the use of EHR-linked technologies for patient engagement through an ongoing randomized trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The Cleveland Clinic's CKD-enhanced patient portal allows patients to access their lab results, request appointments or prescriptions, or send messages to their clinicians. It also provides CKD-stage–specific information. For example, stage 4 patients may receive information about managing anemia or dialysis options.

"There is momentum in health care to facilitate transparency, which allows for joint decision-making [among] patients, caregivers, and providers," Schold said. "The proliferation of [electronic] data and technology will facilitate that and [help us] understand best practices."

Commercial Online Health Data Research: Weighing Privacy Concerns against Potential for Medical Insights

By Bridget M. Kuehn

Search engines are one of the first places many Americans turn when looking for health information, according to a 2013 survey by the Pew Research Center. But what they may not know is that the data from these searches is collected by the search engine and is increasingly being used for health research and public health surveillance.

The data has enormous potential to help researchers better understand pressing public health issues and perhaps even to identify individuals at risk of developing serious disease. But this emerging venue for health research also poses new questions about what constitutes consent for research use of online health information and what role corporations, who own the data, should play in the process.

"Innovation is crucial in our world, and these approaches that have shown promise should be pursued if we develop appropriate methods to ensure the benefit to society and individual patients," said Mauricio Santillana, PhD, a member of the faculty at Boston Children's Hospital and an associate at Harvard's Institute for Applied Computational Science.

Emerging field

Epidemiologists have been at the leading edge of using search data, often combined with data from electronic health records or social media sites, Santillana said. His group at Harvard University has partnered with Google to use its data for tracking and forecasting epidemics of the flu and other infectious diseases.

While initial attempts to develop a Google search–based flu-tracking system were stymied, methods have improved substantially since then (Yang S, et al. *Proc Natl Acad Sci USA* 2015; 112:14473–14478). Now, Santillana and his colleagues can produce very accurate outbreak estimates in real-time and accurate forecasting of flu trends about 1 to 2 weeks ahead.

"The field has evolved quite a bit," Santillana said. "We basically show data from Google searches may be noisy and may not be straightforward to interpret, but by developing robust methods we can minimize the effect of the noise and produce accurate forecasts."

Other types of research are also being explored that are more longitudinal and focus on individuals. For example, researchers from Microsoft recently showed that Bing search data might be useful to identify individuals with symptoms of pancreatic cancer even before diagnosis (Paparrizos J, et al. *J Oncol Pract.* pii: JOPR010504 [Published online June 7, 2016]). Such early identification might help improve patient outcomes, because many patients with pancreatic cancer receive diagnoses too late to be treated effectively, wrote lead author John Paparrizos, MSc, a computer scientist at Columbia University and his colleagues from Microsoft.

"The results highlight the promise of using Web search logs as a new direction for screening for pancreatic carcinoma," the authors wrote.

Privacy and oversight

But concerns have been raised about protecting individuals' privacy and the oversight of online health data research.

"People have a very different sense of privacy around their medical data," said Elizabeth Buchanan, PhD, an ethicist at the University of Wisconsin-Stout in Menomonie, Wisconsin.

They may also have different expectations for privacy depending on whether they are posting health information on a social media site or whether they are conducting a search, Buchanan said. Most companies' terms-of-use policies outline that user data will be logged and possibly used for research or other purposes, including commercial ones, Buchanan said.

"We should be aware that third party apps are collecting, repackaging, and repurposing our data whether it is posted in a public space or if it is something we consider more private like a search query," she said.

It's important to be aware of how this data might be used in ways that are beneficial, for example, for disease surveillance or for patient outreach, while also understanding the ways that composite online health data might be used to identify an individual or even used to harm them, Buchanan said.

"The promise of personalized medicine and predictive analytics is that it can help," she said. "But we want to be careful of the larger more dangerous uses of these kinds of data," she said.

Santillana said his group protects the privacy of searchers' health information by using aggregate data and trying to ensure that individuals can't be re-identified through the data.

"We do our best to maintain the anonymity of the population we are trying to help," he said.

Other potentially promising uses that track an individual's search behavior may trigger greater public concerns about privacy, Santillana said. For example, what if insurance companies got access to the information and used it to refuse to sell the person insurance?

"If a patient is identified as likely to get a diagnosis

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Commercial Online Health Data Research

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based on search history, who gets the information?" Santillana said. "The benefit could be great, but the implementation is not clear."

He emphasized that he supports industry-academic partnerships provided the goals are very clearly outlined.

"I'm a big supporter of innovation and a big supporter of partnering with industry with the understanding that the goal is to improve social good and patient-centered care," he said.

There are also questions about oversight of search-data–based research. In traditional biomedical studies, academic scientists and medical professionals at universities must get approval from institutional review boards (IRBs) (Vayena E, et al. *Am J Public Health* 2012; 102:2225–2230). Corporations may have less strict review processes, said Buchanan.

For population-level or aggregate data research, such as that done by Santillana's group, IRB approval is not required even at academic institutions.

Government oversight of such research is limited. The Department of Health and Human Services' Office of Human Research Protections (OHRP) has published non-binding recommendations about online health data research, which Buchanan co-authored. The recommendations call on researchers to be sensitive to the unique privacy and security concerns associated with online health data.

The US Department of Health and Human Services National Coordinator for Health Information Technology has issued recommendations for "Big Data" health research that call for more transparency about the computer algorithms used to collect and analyze health data online. The recommendations also call for policies to protect online health data that would fall outside of the Health Insurance Portability and Accountability Act (HIPAA).

The European Union (EU) has been ahead of the curve in regulating the use of search data (http://ec.europa.eu/justice/data-protection/) and ensuring that the public is informed, Santillana said. For example, on a recent trip to England he searched for information about fevers on Google and immediately received a notification that his information could be used for research purposes, and was given the option of saying yes or no to that use of his data.

"The EU based on their history has become very aware of the harmful potential of having a single entity control information that is sensitive," Santillana said.

While debate continues about the regulation and uses of personal data in the US, Santillana said, "People should be informed."

Buchanan agreed. "It comes back to our communal sense of data and social media literacy," she said. "All of us need to understand what is happening behind the scenes. We need to be aware of the trails of data we are creating and how they are being used."

Expanded Access To CMS Claims Data Offers Benefits and Risks for Patients

By Bridget M. Kuehn

A new rule from the Centers for Medicare & Medicaid Services (CMS) would extend access to CMS claims data to support quality improvement efforts. But the increased access to personally identifiable claims—including to for-profit companies—may pose privacy risks for patients.

The rule, released July 1, 2016, will allow organizations that the CMS has certified as "qualified entities" to share or resell CMS claims data analyses to clinicians, health care organizations, or other organizations, including for-profit ones, to be used for quality improvement efforts. The new rule also outlines privacy and security requirements for the organizations receiving patient-identifiable or de-identified data.

"Increasing access to analyses and data that include Medicare data will make it easier for stakeholders throughout the healthcare system to make smarter and more informed healthcare decisions," said CMS Chief Data Officer Niall Brennan in a press release.

For example, CMS noted that qualified entities could analyze the care received by chronically ill populations to boost quality and possibly drive down the cost of care for these individuals. This might be particularly useful in improving care for patients with chronic kidney disease (CKD) or end stage renal disease. Patients with CKD now make up about 10 percent of the Medicare population, but account for about 20% of Medicare costs, according to an analysis from the United States Renal Data System (http://bit.ly/29ODoit).

Extending data access

The Affordable Care Act of 2010 required CMS to make claims data more accessible to enable measurements of clinician and supplier performance. To qualify for the program, organizations must have experience with performance measurement, be able to handle and combine large datasets, allow clinicians to review and correct performance reports, and meet strict standards for data privacy and security (http://bit.ly/29ELnOK). Initially, CMS only allowed the data to be accessed by non-profit organizations and required public reporting of analyses. But the new rules will extend access to for-profit entities and allow resale of analyses.

To maintain patient privacy, the new rule requires organizations receiving the CMS claims data to use data privacy and security protections "at least as stringent" as that required of organizations covered by the Health Insurance Portability and Accountability Act (HIPAA).

Although CMS has placed some limits on the use of the claims data by for-profit organizations in the new rule, some privacy advocates are concerned identifiable health data might eventually wind up in the hands of companies selling the data for marketing purposes.

"The for-profit change opens the door to a lot of problems," said Pam Dixon, executive director of the World Privacy Forum, a public interest research group based in San Diego, CA.

Many of the for-profit companies that are sophisticated enough to analyze the information-rich CMS claims data also have data brokering divisions, explained Dixon. These data brokering endeavors infer health information about individuals using data sets, like magazine subscriptions, and combine that with other marketing data for resale. The data gathered about an individual through these enterprises is often riddled with errors. For now, CMS has been conservative, only approving a small number of highly vetted for-profits, Dixon said.

"I'm really concerned about who might be approved down the line," Dixon said. "Right now, it does not seem to be really problematic for for-profits [approved by CMS], but that doesn't mean there won't be [problems] in the future."

New protections in the rule, such as requiring qualified entities and those they share data with to meet HIPAA standards for privacy and security, are good steps, Dixon noted. But they are not foolproof. For example, HIPAA allows de-identified patient data to be shared. Studies have revealed, however, that it is very easy to re-identify individuals in such data sets (Sweeney L. *Journal of Law, Medicine & Ethics* 1997; 25:98–110). Large for-profits that broker data for marketing purposes in particular could easily re-identify individuals, Dixon noted.

"There is no such thing as anonymous claims data," Dixon said "Our ability to re-identify the data is too strong."

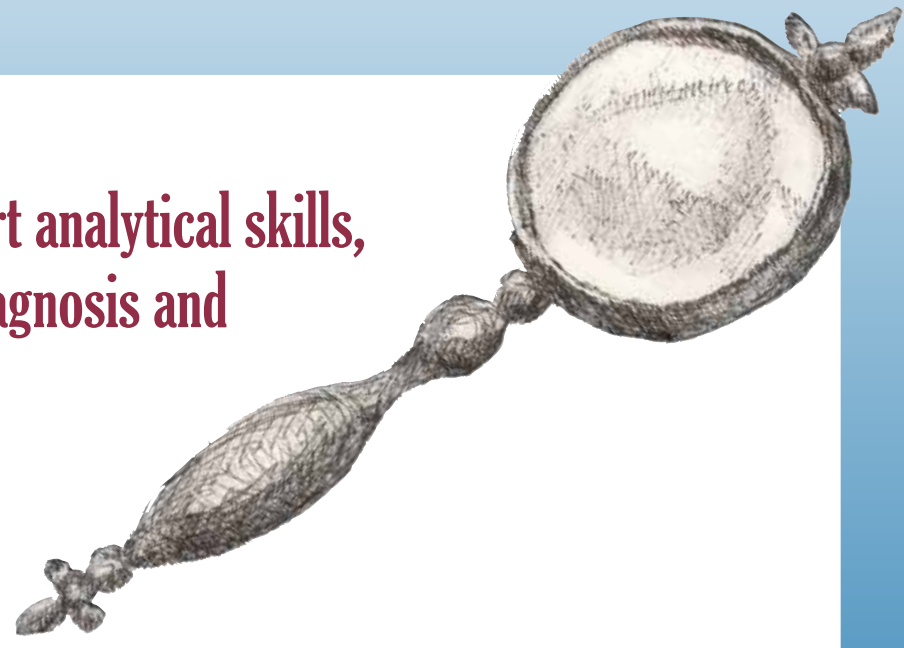
Another concern is that CMS sharing the data with outside organizations increases the risks of privacy breaches.

"If the data is ever breached and goes out in the wild, that is going to be a profound issue for every patient who has their personally identifiable claims data breached," Dixon said.

Finally, CMS will no longer require public reporting of all of the qualified entities' analyses based on the data, although other requirements still apply. This change may reduce transparency, which was part of the initial promise of the program, Dixon said.

"The purpose of this data is to be used for public benefit, not just for enhancing the profits of a for profit company," she said.

Detective Nephron



Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases.

Wildly waving a stack of paper records, budding nephrologist L.O. Henle and medical student Ms. Curious Tubule run down the hall toward Detective Nephron's office.

Henle *(with a smile):* A case, a case!

The detective sits facing the window. He is silent for a moment, then quickly turns around.

Nephron *(curious):* Finally, something that might put an end to this utter boredom.

Henle It's a case of metabolic acidosis.

Nephron *(smiling):* Ah yes. My 8th favorite acid-base abnormality.

Ms. Tubule appears confused. Henle chuckles knowingly and subtly shakes his head.

Tubule *(curious):* 8th?

Nephron *(smiling):* You forget about mixed double and triple acid base disturbances. But please, continue.

Tubule So this is a young female—rather healthy, with only a history of migraines and depression—who presented with one week of progressive shortness of breath, generalized malaise, and loss of appetite.

Nephron How . . . nonspecific! I like that . . . go on . . . .

Tubule She was found to have a serum bicarbonate of 12 mmol/L. Her sodium was 143 mmol/L, chloride was 120 mmol/L. That gives her a serum anion gap of . . . .

Nephron *(surprised look):* . . .

Tubule . . . an anion gap of 11. So this is a normal anion gap metabolic acidosis.

Henle Her serum pH was 7.25.

Nephron Interesting. So we have a hyperchloremic metabolic acidosis. I'm guessing she doesn't have diarrhea, or else you wouldn't be bothering me with this.

Tubule Well, for hyperchloremic metabolic acidosis, you want to see whether there is a kidney-related cause or an extrarenal cause.

Nephron Remember there are only two body systems in my nephrocentric mind . . . renal and extrarenal.

Tubule Well, the patient hasn't complained of any diarrhea, otherwise . . . I don't know.

Henle *(stepping in):* We calculated the urine anion gap. It was +12 and her urine pH is 6.5.

Nephron I see. Ms. Tubule, Let's take it one step at a time. If you have acidemia, what should the kidney be doing? Should the urine be acidic or alkaline?

Tubule Acidic! The kidney needs to dump that acid to help us cope with this acidemia.

Nephron Good. So if the kidney is able to dump acid and get rid of it, the kidney is doing the right thing, right? In other words, it's not a distal nephron problem (where the fine tuning of acid–base is headquartered). So if you are dumping acidic urine, your problem lies in the gut or the proximal tubule most of the time. If you are having alkaline urine, your problem lies in the distal tubule most of the time. Because if the kidney is the problem and you truly have a nephrogenic tubular acidosis (my term for renal tubular acidosis), it's really a distal tubule problem and you cannot acidify the urine.

Tubule *(happy):* Well said!

Nephron How is the urine anion gap calculated?

Tubule Urine anion gap . . . Oh! So that would be the urine sodium plus potassium, minus the urine chloride. If there is more chloride than sodium and potassium—that is, the urine anion gap is negative—then we presume that extra chloride is balancing high ammonium excretion, which is the proper renal response to acidemia, implying an extrarenal cause of acidosis.

Nephron Right. More precisely, urine anion gap is a surrogate marker for the ability of the kidneys to excrete acid in the form of $NH4^+$. What about the urine pH?

Henle It also represents decreased $NH4^+$ excretion in the kidney.

Nephron *(jumping in):* Careful with that quick reflex thinking. Let's think this through. The kidney can excrete acid in 3 ways: $NH4^+$, titratable acids, and free protons. $NH4^+$ is the main way the kidneys excrete acid and grossly represents about two-thirds of the total acid excretion load. $NH4^+$ excretion requires 3 things: proximal tubular synthesis, medullary recycling, and intraluminal trapping by free H^+ excreted in distal nephrons. We measure $NH4^+$ excretion indirectly with urine anion gap. Free protons represent less than 0.01% of the total acid excretion load. Free protons depend on the activity of the H^+-ATPases in type A intercalated cells. We measure free H^+ with urine pH. So a high urine pH does not really represent problems with $NH4^+$ excretion.

Now, where were we? We have a hyperchloremic metabolic acidosis that we now suspect is nephrogenic in etiology. I presume the patient has normal renal function?

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Detective Nephron

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Tubule Yes.

Henle So now we're entering the land of renal tubular acidoses or in your words—nephrogenic tubular acidosis. Serum potassium is normal. Her urine pH was 6.5. Her urine anion gap is positive. Her fractional excretion of bicarbonate was 17%.

Nephron I take it this was after she was given IV sodium bicarbonate?

Henle Yes.

Tubule They were initially giving her sodium bicarbonate when she first came in the emergency department.

Nephron The clinical characteristics of proximal nephrogenic tubular acidosis will vary depending on whether the patient is at steady state or is actively receiving treatment with bicarbonate. They will also vary depending on if the proximal nephrogenic tubular acidosis represents an isolated problem with bicarbonate reabsorption or is part of a generalized proximal tubular disorder.

Tubule What?

Nephron Remember that with proximal RTA (the way you like it), the defect is a decreased capacity to reclaim filtered bicarbonate in the proximal tubule. The renal bicarbonate losses continue until steady state is reached where the serum bicarbonate—and thus the filtered bicarbonate load—has decreased so much that it is able to be completely reabsorbed. When proximal RTA is in steady state or not treated, and the problem is isolated to bicarbonate reabsorption in the proximal tubule, then there will be no problems with $NH4^+$ production in proximal tubule, so therefore the urine anion gap will be negative. Also, there will be no problems with the H^+ pumps in the distal nephron, so the urine pH should be less than 5.5. However, when the proximal RTA represents rather a generalized proximal tubular problem such as Fanconi syndrome, then the ability of the proximal tubule to synthesize $NH4^+$ will be compromised, and therefore the urine anion gap will be positive and the urine pH will still be < 5.5 since there are no issues with distal acidification. If the patient is actively receiving bicarbonate, the bicarbonate not reclaimed in the urine will be eliminated along with Na^+, which will increase the urine anion gap and make it positive. Also, the bicarbonate in the urine will buffer H^+ in the urine from distal acidification and make the urine pH > 5.5.

In this case, another extra piece of information we need to consider is the elevated fractional excretion of bicarbonate (FE bicarbonate), which only occurs in the presence of bicarbonate supplementation.

Tubule *(relieved):* I see…

Nephron Is there other evidence of generalized proximal tubular dysfunction?

Henle She has no hypophosphatemia or hypouricemia; also no glucose in the urine.

Nephron What do we think?

Tubule I think this is a proximal or type 2 RTA actively treated with bicarbonate, hence the positive urine anion gap and urine pH of 6.5 as she does have the elevated urinary bicarbonate excretion. But I don't know from what.

Nephron Let's stay away from calling thing types 1 and 2. Rather using terms such as proximal and distal is more illustrative of the location and pathophysiology. Numbers confuse physicians – especially nephrologists . . . .

—looking over to Henle: Et tu, Henle?

Henle Well, given the evidence so far, I have to agree with Ms. Tubule that there's definitely some element of proximal RTA. However, the severity of her acidosis is what perplexes me. Normally with proximal RTA, at steady state, the serum bicarbonate is in the 12–20 mEq/L range. Her serum bicarbonate is borderline low and her presentation quite severe for what I would expect.

Nephron Agreed!

Henle So I'm not sure. But in the differential for proximal RTA, we think of congenital transport defects–doubtful for it to present in a middle-aged woman. Lead, mercury, cadmium, copper could also do it, but I don't think she's had any exposure to heavy metals. I don't think she has Wilson's disease, either. Infiltrative conditions–multiple myeloma, amyloidosis–are a possibility as well . . . And your favorite test–serum free light chains–had a normal ratio for her kidney function.

Nephron Are there medications she is taking that are associated with proximal tubular dysfunction?

Henle She's not on acetazolamide, tenofovir, or any chemotherapy agents as she has no cancer.

Tubule Her only medicine is topiramate.

The detective's eyes brighten as he suddenly looks up at Ms. Tubule for a split second, then looks down again.

Nephron Fascinating.

Henle and Ms. Tubule appear puzzled.

Henle and Tubule, in unison What?

Nephron Do we have the pH of the original urine sample? Before bicarbonate infusion?

Ms. Tubule flips frantically through her index cards as though the world were looking on.

Tubule It was 6.1.

Henle Why do you ask?

Nephron So this patient demonstrates the inability to acidify her urine also in steady state conditions. In the face of severe acidemia one would expect her urine to be maximally acidified, and yet this young patient with otherwise normal renal function is unable to get the urine pH lower than 5.5.

Henle A problem with distal acidification. So you're thinking about a distal RTA also?

Nephron Exactly. In fact, a mixed proximal and distal nephrogenic tubular acidosis caused by topiramate. When was the medication started?

Tubule It was for migraine prophylaxis, started several months ago, and why, the dose was recently increased!

Nephron As I suspected.

Henle Let me make sure I understand. To summarize, we have a patient who presented with a hyperchloremic metabolic acidosis, symptomatic for 1 week, with bicarbonate initially of 12. The

history and urine studies suggested a nephrogenic cause of the acidosis. Potassium was normal. Her urine was consistent with a distal acidification defect, but she also demonstrated increased FE bicarbonate after receiving bicarbonate supplementation. And all of these findings are consistent with adverse effects related to topiramate.

Nephron Indeed. And these derangements typically improve with stopping the medication. In addition, topiramate has also been associated with an increased incidence of calcium phosphate nephrolithiasis and osteoporosis.

Tubule Fascinating...

One week later...

Tubule Do you remember the patient we suspected of having mixed RTA secondary to topiramate?

Nephron Of course.

Tubule Right, so on our recommendation the primary team discontinued the medication. She did well with bicarbonate supplementation in the short term and was discharged from the hospital; follow-up labs have completely normalized.

Nephron Very well then. And so, yet again, from a diagnosis of hyperchloremic metabolic acidosis, you have identified an easily reversible cause, and I hope one you will never forget. Let's have some NY style coffee . . . I have a headache!

Special thanks to Dr. Chi Chu, Nephrology Social Media Collective intern and resident at California Pacific Medical Center for submitting this case. A special thanks to Dr. Helbert Rondon, Assistant Professor of Medicine, Renal-Electrolyte Division at the University Of Pittsburgh School Of Medicine and Dr. Rimda Wanchoo, Assistant Professor of Medicine, Nephrology Division, Hofstra Northwell School of Medicine for content editing.

The concept of Detective Nephron was developed by Kenar D. Jhaveri, MD, Associate Professor of Medicine, at Hofstra Northwell School of Medicine and an Attending nephrologist at Northwell Health System, NY. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.

Policy Update

ASN Promotes Additional Federal Investments in Kidney Research

By Grant Olan

On Thursday, July 7, the ASN Research Advocacy Committee participated in meetings at the U.S. National Institutes of Health (NIH) and Department of Veterans Affairs (VA) during the society's annual Kidney Research Advocacy Day (Table 1). ASN Research Advocacy Committee Chair Frank C. Brosius, MD, and ASN Public Policy Board Chair John R. Sedor, MD, FASN, also participated in a first-ever ASN meeting with the White House Office of Management and Budget on Friday, July 8.

The Research Advocacy Committee urged the NIH and VA to pool resources and knowledge toward uncovering new discoveries and innovations for preventing and treating kidney diseases. Meeting topics also included continued collaboration and partnerships with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to eliminate kidney health disparities and increase interest in kidney research careers.

"Kidney Research Advocacy Day is a rewarding opportunity to encourage more kidney research collaborations and initiatives among federal research stakeholders," Dr. Brosius remarked. "Cancer, HIV/AIDS, and other diseases have had great success in part because stakeholders worked together to revolutionize care. ASN hopes to do the same thing for kidney diseases. We've seen too few advances in care, and patients with kidney diseases deserve more and better treatments than the limited options available today."

The Research Advocacy Committee began annual visits to NIH in 2012 to raise the profile of kidney diseases, promote more kidney-related research, and encourage more cross-institute collaboration. In addition to NIDDK, the committee met with leaders of the National Heart, Lung, and Blood Institute (NHLBI); National Institute of General Medical Sciences (NIGMS); National Institute of Minority Health and Health Disparities (NIMHD); National Institute of Biomedical Imaging and Bioengineering (NIBIB); and National Institute on Aging (NIA).

At the VA, the Research Advocacy Committee learned that the highest number of grants during the last funding round went to kidney research, including one of the first five Million Veteran Program grants. The VA Office of Research and Development expressed interest in continued collaboration with ASN and the society's members who are VA clinician-investigators. ASN is a member of the Friends of VA Medical Care and Health Research (FOVA) advocacy coalition. FOVA was founded over 25 years ago to ensure that America's veterans receive high-quality healthcare.

While meeting with the White House Office of Management and Budget, Dr. Brosius and Dr. Sedor discussed the importance and need for more federal investments in kidney research, as well as the status of the Government Accountability Office's (GAO) investigation on the adequacy of federal investments in kidney research. Rep. Barbara Comstock (R-VA), Rep. Tom Marino (R-PA), Sen. Ben Cardin (D-MD), and Sen. Bill Nelson (D-FL) requested the GAO study given the significant societal burden of kidney diseases.

An internal ASN study of kidney research revealed that less than 1% of total Medicare expenditures on care for patients with kidney diseases is invested in kidney research. Altogether, Medicare spends $99 billion annually. The Medicare End-Stage Renal Disease Program—the only disease-specific entitlement program—annually costs $35 billion alone, more than the entire NIH budget. Yet federal investment in kidney research pales in comparison, totaling only $650 million.

The GAO is on track to complete and release the results of its study by the end of 2016. "The GAO report is a crucial first step in understanding the current kidney research landscape, and I anticipate it will confirm what ASN has suspected all along—that kidney research is underfunded," Dr. Sedor said. "I believe the report will pay dividends for research funding down the line. Once complete, ASN looks forward to sharing the results with the entire kidney community."

In the meantime, ASN is working with other stakeholders in the research community to continue building support for another NIH and VA research funding increase in 2017. In 2016, Congress increased the NIH budget by $2 billion to a total of $32 billion, as well as the VA Research Program's budget by $41.8 million to a total of $630.7 million.

Table 1

ASN Research Advocacy Committee

Frank C. Brosius, MD, Chair
Josef Coresh, MD, PhD, FASN
Susan T. Crowley, MD, FASN
William H. Fissell, MD
Jeffrey L. Garvin, PhD
Susan B. Gurley, MD, PhD
David S. Hains, MD
Benjamin D. Humphreys, MD, PhD, FASN
Edgar A. Jaimes, MD
Jordan A. Kreidberg, MD, PhD
John R. Sedor, MD, FASN
Bradley K. Yoder, PhD
Bessie A. Young, MD, FASN, MPH

Practice Pointers

IgA Nephropathy: One Disease or Many?

By Rosanna Coppo, MD, and Jurgen Floege, MD

IgA nephropathy (IgAN) is well identified by dominant IgA glomerular deposits; however, this immunohistologic entity can be an asymptomatic chance finding or present with an extremely variable course. The variable clinical and histologic expressions are likely to be the result of genetic and environmental factors modulating common pathogenetic and progression mechanisms.

Who gets IgAN, and what do we know about the origins?

There is genetic heterogeneity, and no causal mutation has been detected. IgAN has genetically complex traits, and genome-wide association studies have identified susceptibility variants that are responsible for 6 to 8 percent of disease risk (1). Genome-wide association studies have indicated the involvement of various pathways, including antigen presentation, complement activation, regulation of IgA mucosal synthesis, and innate immunity. These findings suggest a role for mucosal infections and intestinal immunity. The pathogenesis of IgAN is thought to develop on the basis of a genetic predisposition, only partially known, via multiple hits (2). The first hit is an abnormal production of galactose-deficient IgA1, which needs a second hit, represented by the production of autoantibodies directed against galactose-deficient IgA1, followed by the third hit, the formation of immune complexes in circulation. The deposition of complexes in circulation in the mesangium activates complement and other mediators, leading to inflammation and finally ending in fibrosis, which is the fourth hit.

How do patients present?

The clinical presentation can be apparently benign, with isolated microscopic hematuria or bouts of gross hematuria coincident with mucosal infections. The patients presenting these features are often young, with normal glomerular filtration rate (GFR) and normal blood pressure (BP), and spontaneous remission can occur, particularly in children. On the contrary, in several patients, years after unnoticed microscopic hematuria, proteinuria develops, mostly around 1 to 2 g/d. These patients often present with hypertension and mildly reduced GFR. The diagnosis of IgAN can be missed if a renal biopsy is not performed, and some patients enter dialysis and transplantation programs without the recognition of the causal renal disease.

Who is likely to have progressive disease?

The detection, at renal biopsy, of proteinuria, hypertension, and reduced GFR is associated with potential progression (Table 1). However, the most significant risk factor for progression of IgAN is persistent (time-averaged) proteinuria (>1 g/d) and persistent hypertension. Also, mild time-averaged proteinuria (>0.5 to <0.9 g/d) has been associated with progression, indicating the need for renal biopsy and diagnosis of IgAN before the development of heavy proteinuria (3). Time-averaged proteinuria and mean BP over 2 years are predictive of outcome, but clinical decisions are usually taken at biopsy. The added value for individual prognostication of histologic features has been proven by the Oxford Classification of IgAN (4), indicating that the mesangial (M) or endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis lesions predicted renal outcome independent of clinical data at renal biopsy and during follow-up. Addition of M or endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis lesions to baseline GFR, proteinuria, and mean BP improved prediction of patient risk, with accuracy comparable with the 2-year follow-up data (5). Patients with M1 are at risk, even if proteinuria at biopsy is <1 g/d, whereas those with M0 and tubular atrophy/interstitial fibrosis lesions 0 have low risk, even if proteinuria is 1 to 1.5 g/d (Table 1).

Supportive therapy: One for all and what does it include?

Given the usually long course of disease until renal failure develops, nonspecific measures that retard progression are key in the treatment of IgAN patients at risk for progressive loss of renal function. In sum, such measures are referred to as supportive therapy. Key components are the administration of renin-angiotensin system (RAS) blockers (i.e., angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers uptitrated to achieve both sitting BPs in the 120s as well as a proteinuria <1 g/d) (6). Both targets seem of equal importance. Nondihydropyridine calcium antagonists should not be used as first-line agents given their induction of glomerular hypertension. Other important measures are lifestyle changes (in particular, the initiation of a moderate protein diet of 0.8 g protein per 1 kg body weight per day, particularly if GFR is <60 mL/min), salt restriction, nicotine abstinence, and treating all components of the metabolic syndrome (Table 2). In patients with proteinuria that was initially controlled by these measures but subsequently started to increase again, aldosterone breakthrough may have occurred. In such patients, a low dose of an aldosterone antagonist (e.g., spironolactone at 25 mg/d) may effectively reduce proteinuria again; if this approach is used, hyperkalemia is a risk, necessitating frequent monitoring and/or the addition of a loop diuretic.

Who should receive immunosuppression, and if so, which one?

Immunosuppression should only be considered in patients at risk for progression of IgAN (see above). There is relative consensus not to offer immunosuppression to patients with a GFR <30 mL/min at baseline, unless one of the very rare rapidly progressive courses with widespread crescents and glomerular necrosis is present (7). Importantly, the detection of a single crescent in an otherwise stable clinical setting does not warrant immunosuppression but should rather call for RAS blockade. Immunosuppression has mostly relied on systemic corticosteroids, whereas combination therapy, mycophenolate mofetil, and calcineurin inhibitors are discouraged (7). A landmark trial in 1999 (8) as well as some subsequent trials showed that a 6-month course of initially high-dose corticosteroids with tapering can stabilize the course of disease. This trial and the subsequent trials, however, suffered from inconsistent RAS blockade or the requirement to halt RAS blockers before randomization (6). In our recent STOP-IgAN (Supportive versus Immunosuppressive Therapy for the treatment Of Progressive IgA Nephropathy) Trial, a 6-month-long optimization of supportive measures reduced GFR loss so much that no added benefit of immunosuppression on the course of GFR could be detected (9). An effect of immunosuppression on inducing full clinical remission was noted in some patients with a baseline GFR >60 mL/min, but this benefit was offset by a 50% increase in infections and significantly more diabetes induction and weight gain (9). Thus, at present, systemic corticosteroids should be used restrictively in high-risk IgAN patients, only be considered after optimization of supportive measures, and probably be reserved for those patients who still exhibit a proteinuria >2 to 3 g/d despite these measures.

What novel therapies are on the horizon?

Given the uncertainty of the value of systemic immunosuppression in IgAN and our increasing knowledge of the pathogenesis of IgAN, alternative approaches are of great interest. On the basis of a small pilot trial (10), the NEFIGAN Phase II Trial recently

Table 1

Risk factors for progression of IgA nephropathy: Importance as judged by an arbitrary score (0 to +++)

Clinical data at renal biopsy
Reduced GFR (+++)
Proteinuria >1 g/d (++)
Hypertension (++)
Renal biopsy histologic features: MEST score: mesangial hypercellularity (++), endocapillary hypercellularity (±), segmental glomerulosclerosis (+), and tubular atrophy/interstitial fibrosis (+++)
Crescents affecting >50% of glomeruli (uncontrolled data)
GFR at renal biopsy considered together with follow-up (time-averaged) proteinuria and time-averaged mean arterial BP over 2 years (+++; see text for explanation)

Abbreviation: MEST = mesangial or endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis lesions.

Table 2.

Supportive measures in IgA nephropathy patients at risk for progressive disease

Level A recommendations

- Target sitting systolic BP in the 120s
- Initiate RAS blocker; uptitrate dosage targeting the above BP and proteinuria to <1 g/d
- Avoid dihydropyridine calcium channel blockers or use them only after initiating an ACE inhibitor or ARB
- Control protein intake to about 0.8 g/kg per day

Level B recommendations

- Control each component of the metabolic syndrome
- Restrict NaCl intake/institute diuretic therapy
- Nondihydropyridine calcium channel blocker therapy
- Aldosterone antagonist therapy (adapt dose to CKD stage)
- β-Blocker therapy
- Smoking cessation
- Allopurinol therapy (controversial)
- Empiric $NaHCO_3$ therapy independent of whether metabolic acidosis is present (controversial)
- Avoid NSAIDs if possible (if not, use maximally once or twice weekly)

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; NSAID = nonsteriodal anti-inflammatory drugs; RAS = renin-angiotensin system. Modified from Floege and Feehally (6).

evaluated effects of budesonide encapsulated to achieve preferential release in the terminal ileum in high-risk IgAN patients. In data presented at the American Society of Nephrology Kidney Week in 2015, this approach reduced proteinuria and stabilized GFR in the patients. A phase III trial is currently in the planning phase.

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Kidney Health Initiative Meeting Highlights Telehealth and Clinical Trial Recruitment, Plus Latest Round of Project Proposals

KIDNEY HEALTH INITIATIVE

By Ryan Murray

The Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology (ASN) and the US Food and Drug Administration (FDA), seeks to encourage innovation and patient safety in kidney disease through its collaborative partnership with the kidney community.

KHI held its Fourth Annual Stakeholders Meeting May 25–26, 2016, in Silver Spring, MD. The annual meeting brought together diverse representatives from the kidney community, connecting members across different fields and allowing them to share ideas, discuss ongoing projects, collect feedback, and collaborate on potential new projects. Of the more than 30 US and international attendees, nearly a third represented FDA and government agencies, a third were affiliated with industry, and a third represented patients and health care professionals.

Following an evening opening presentation and panel that assessed the impact already made by KHI and outlined future opportunities, Thursday's small group breakout sessions allowed members to review current KHI projects and provide feedback. The program also featured presentations and panel discussions on telehealth, new technology to tackle patient recruitment and retention in clinical trials, as well as patient and care partner engagement. The meeting agenda may be viewed at https://www.asn-online.org/khi/meetings.aspx.

KHI advances its mission and objectives through the completion of various projects proposed by members across all areas of the kidney community. KHI held its sixth project proposal submission cycle and collected proposals from members for project ideas via its online web portal in the spring of 2016.

During this cycle, KHI received eight project proposals seeking endorsement by the KHI Board of Directors. The proposals demonstrate their huge potential to make an impact on kidney disease and also reflect the diversity of KHI's membership and interests:

- Clinical Trial Endpoints for Cardiovascular Interventions in Advanced CKD
- Developing a Framework and Evaluating Patient Preferences for Implantable, Wearable, and Portable Renal Replacement Devices
- Developing and Coordinating Best Practices for Systematic Banking of Biosamples for Personalized Kidney Medicine
- Development of a Roadmap for Innovations in Renal Replacement Therapy (RRT)
- Establishing Appropriate Endpoints for Clinical Trials in Hyperoxaluria
- Fostering Development for Fluid Management in Kidney Disease Patients
- Guidelines for the Development of Innovations in Vascular Access Care
- Understanding and Overcoming the Exclusion of Patients with Kidney Disease from Cardiovascular Trials

The KHI Board of Directors is in the process of reviewing the proposals, scoring them based on their feasibility, impact on the field, and ability to meet the KHI mission. The board will determine which proposals will be officially endorsed this summer. Once projects have been endorsed, interested individuals can apply to serve on project workgroups this fall.

The web-based project portal lets KHI members submit brief project proposals and also discuss and refine submissions. KHI's seventh project proposal submission cycle will occur in winter 2016–2017. To learn more about KHI's current projects, workgroup members, and proposals visit KHI online at www.kidneyhealthinitiative.org.

In its fourth year, KHI will continue to strive for continued growth and interaction among its diverse membership to facilitate the efficient passage of drugs, devices, and biologics into the kidney space. If interested in receiving more information about KHI or enrolling as a member organization, please contact the KHI staff at KHI@asn-online.org.

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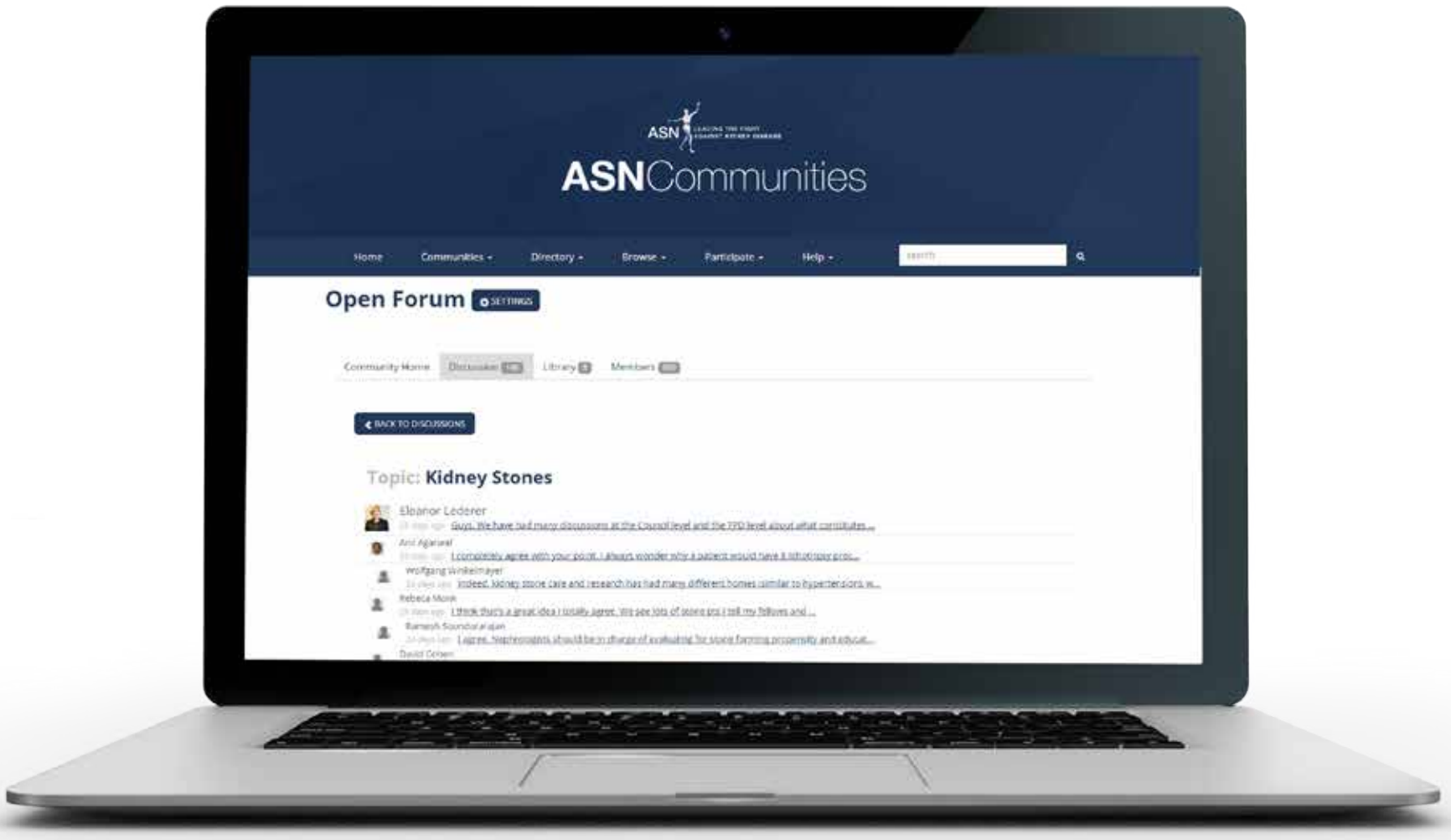

The new ASN Communities site is a members-only platform that allows ASN members from around the world to connect online, join discussions, and share knowledge and resources. Members are already using the Communities to get advice on issues they face in daily practice, to share ideas on addressing nephrology workforce issues, and to provide input to the society on public policy matters.

Visit community.asn-online.org to join the conversation.

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