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Kidney News

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Empathy and Communication are Critical Skills that Can Improve Care

By Eric Seaborg

During her nephrology fellowship, Jane Schell, MD, was surprised at how unprepared she felt to talk with elderly and very ill patients about their poor prognoses and the probably disturbing trajectory of their diseases.

Her personal discomfort led her into a research project where she discovered that her sense of a lack of preparedness—leading to a hesitancy to engage—was widely shared even among her older, established colleagues. And patients reported that this failure of communication left them feeling uncertain, confused, and not ready for the challenges they faced.

A regular part of nephrology practice is delivering emotional news and guiding patients as they deal with life-and-death topics like dialysis initiation and withdrawal. Yet nephrologists do not receive education in skills—communication and empathy—that should be considered as important as other aspects of their training, according to Schell, who is now a practicing nephrologist and palliative care physician at the University of Pittsburgh.

"Most physicians are not adequately prepared to have these kinds of conversations with seriously ill patients," said James A. Tulsky, MD, chair of the department of psychosocial oncology and palliative care at the Dana-Farber Cancer Institute and a pioneer researcher in clinical empathy and communication. "There is very little in any of their training—whether it is medical school residency or fellowship—that focuses on communication skills in these difficult situations."

Patient outcomes: for better or worse

This training absence spans most specialties, despite strong evidence that physician empathy and communication improve patient care. A Joint Commission on Accreditation of Healthcare Organizations report found that communication failures were a root cause of more than 70 percent of serious adverse health outcomes in hospitals.

And conversely, studies show a clear association of clinical empathy with better patient outcomes. In two studies of

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Research on Crystal-Induced Cell Death Could Pave Way for New Molecular Targets for Treating Kidney Diseases

By Timothy O'Brien

Crystals play a role in the development and progression of a wide range of diverse diseases, from gout to atherosclerosis to kidney disease. New experimental findings suggest that these crystallopathies may involve a "regulated process" of crystal-induced cell death called necroptosis, according to a report in *Nature Communications*.

The study also clarifies the steps in the pathway leading to necroptosis, suggesting promising new therapeutic targets to limit crystal-induced cytotoxicity and tissue injury. Necroptosis is just one of several recently recognized categories of "necroinflammation"—with distinct molecular pathways—potentially relevant to a wide range of kidney diseases.

Led by Prof. Hans-Joachim Anders of Ludwig-Maximilians-Universitat in Munich, the researchers performed a series of experiments to understand the types and mechanisms of cell death in crystal-induced tissue injury. Various crystallopathies share common features, suggesting a similar underlying pathogenesis. Crystal-induced inflammation has been considered the main mechanism by which cell death occurs.

But recent studies have identified new pathways of "regulated necrosis"—in which cell death results from active processes leading to cell necrosis that, in turn,

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Inside

Empathy

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diabetes patients, researchers administered the Jefferson Scale of Empathy to physicians and grouped them according to whether they scored high, medium, or low on empathy skill. The researchers studied diabetes because it has clear patient outcomes that can be tracked in electronic health records.

In a study of 29 family physicians and 891 diabetic patients, the patients of physicians with high empathy scores were significantly more likely to have good control of their hemoglobin A1c and LDL cholesterol compared with patients of physicians with low empathy scores. The second study included more than 240 physicians and examined the incidence of hospitalizations among 20,000 diabetic patients. The rate of hospitalizations due to acute metabolic complications in diabetic patients was much lower for patients of high-empathy physicians compared with patients of low-empathy physicians.

Hands-on training

When nephrologists learn the key skill of putting in lines, they learn through a carefully organized process of observing a senior person, then performing the procedure themselves with an attending hovering over their shoulder and giving them feedback, Tulsky said. "If they have trouble doing it, they wouldn't hesitate to ask one of their more senior supervisors, 'How should I do this better?' That doesn't happen for communication," he said. "It is unlikely that before they go in to share news with a patient as a fellow that their seniors will talk to them about it beforehand or that [their attending] will observe them and give feedback."

A successful program

"People think that there is a hard part and a soft part of medicine, and that communication is the soft, fuzzy part. But effective communication is just as hard as knowing how to remove a gall bladder," said Nirmal Joshi, MD, chief medical officer of Pinnacle Health System in Harrisburg, PA.

Joshi instituted an empathy and communication training program for physicians at Pinnacle Health because of low patient ratings of doctor-patient communication. His team created a one-hour training exercise that began with the physicians talking for 10 to 15 minutes to a patient-actor trained on a script and the patient's "family." The actors then provided feedback on how well the physician performed on specific measures of communication. The physicians next viewed a 20-minute film on best practices to improve doctor-patient communication.

In addition to this training, Joshi made communication improvement an ongoing part of the hospital's focus by hiring a coach who periodically sits in on patient encounters and gives real-time advice on how physicians can improve. He hired Stacia Melenchek, M.Ed., to be the physician coach because she had a master's degree in education but little background in healthcare so would bring a consumer's perspective to the task.

About 350 physicians have been through the training, and over two years patient satisfaction scores increased a remarkable 40 percentile points. "In some disciplines, the scores are now in the 90th percentile, and in other instances they are between the 50th and the 90th percentile," Joshi said.

Some of the steps emphasized at Pinnacle seem simple: introducing yourself and explaining your role in the context of all the other providers a patient sees in a hospital, and sitting down rather than towering over the bedside.

But Melenchek also coaches clinicians on making an empathic connection by listening carefully to patients and reading their body language and facial expressions. She emphasizes the importance of noticing when a patient is feeling emotional and overwhelmed, and thus will have a hard time processing the information a clinician is eager to impart. Melenchek also stresses giving medical information in plain English. "I educate them to use a fifth to eighth grade reading level," she said.

The patients are not the only ones who benefit from improved communication, according to Esther Tucci Thoman, manager of physician training at Pinnacle. The physicians have noticed that if they listen carefully and communicate clearly, not only is the patient more likely to adhere better to the plan of care, but it's less work for them in the long run because they get fewer calls and questions from nursing later on.

Not easy to learn

Some of these tasks seem so simple that physicians are surprised to learn that they are not actually performing them, according to Kathryn Pollak, PhD, professor in community and family medicine at Duke University, where she also coaches physicians. She records patient-doctor encounters, and when she plays them back, physicians are surprised at the number of times they miss opportunities to respond empathetically.

Particularly in a specialty like nephrology—in which the news is often laden with heavy emotional content and the patient needs to buy into a treatment plan—physicians need to get away from their prescriptive mode of laying large amounts of information on patients and tailor their approach to the individual.

Nephrologists need to remember that "the information that they are giving is highly emotional for patients," Schell said. "Giving the diagnosis of kidney disease for us seems like an everyday activity. But for a patient, it means that something has changed. They may be dying. They may not know what to expect."

Schell compared watching for emotion with looking for other kinds of clinical data like vital signs. "We should be watching how our patients respond, whether it is nonverbal and looking away, whether it is showing shock, or whether they say words that are emotion cues, [such as] 'I can't believe this.' When patients are emotional, cognitive data generally doesn't go through. Not only do they not hear it, but [we] miss an opportunity to attend to our patients' emotions so that we help them process the emotion."

Schell and Tulsky recommend a process they call "ask, tell, ask" for entering into conversations about serious illnesses. "You always need to ask a patient their understanding before giving them information," Tulsky said, because finding out how much or how little they know should affect what information you give them and how you give it. "You then give information in short bite-size chunks. [It is] very important not to use jargon and not to talk too much. Then the final 'ask' is to ask about their understanding of what you just explained."

Tulsky was one of the founders of a project called VitalTalk, which offers multi-day courses and an online course on communication. Its website offers free "talking maps" for addressing a variety of sensitive subjects as well as videos illustrating how to deal with a variety of patient situations (www.vitaltalk.org).

Schell participated in the development of VitalTalk, and led the development of NephroTalk, which began as a half-day workshop and has developed into a three-day workshop held annually in Pittsburgh. Open to fellows across the country, it focuses on communication tools for challenging topics with practice opportunities with simulated patients. (For information: http://renalfellow.blogspot.com/2015/11/attend-nephrotalk-2016-to-improve-your.html) Schell is continuing to develop the curriculum under a grant from ASN.

"Communication is just another procedure you need to learn, and it is just as hard," according to Duke's Pollak. "When you first start, you are going to make mistakes. You are going to think, 'Why have I forgotten how to talk?' Then it just becomes second nature."

Techniques to start improving communication

A map for conversations on goals of care is called REMAP:

- **R** = Reframe. "I think we are in a different place now."
- **E** = Expect emotion. "I can see that this is really hard for you."
- **M** = Map out patient's goals. "What is most important to you right now?"
- **A** = Align with those goals. "I hear what you are saying is these things are most important."
- **P** = Plan treatments. "Based on what you are telling me about what is most important to you, these are the treatments I would recommend."

A map for responding to emotional concerns is NURSE:

- **N** = Name the emotion: "You seem worried."
- **U** = Understand: "I see why you are concerned about this."
- **R** = Respect: "You have shown a lot of strength."
- **S** = Support: "We will get through this together."
- **E** = Explore: "Tell me more."

Cell Death

Continued from page 1

promotes inflammation. In their experiments, Prof. Anders and colleagues focused on the pathway of necroptosis: a regulated process of necrotic cell death specifically dependent on receptor-interacting serine-threonine kinase 3 (RIPK3) and mixed lineage kinase domain-like (MLKL).

The investigators exposed in vitro kidney epithelial cells to four types of crystals involved in human crystallopathies: calcium oxalate (CaOx), monosodium urate, calcium pyrophosphate dihydrate, and cystine. Under all conditions, cells died by primary necrosis. Flow cytometry showed that CaOx-induced cell death occurred without signs of apoptosis involving caspases.

Rather, all four types of crystals induced proteins involved in the necroptosis pathway: RIPK1, RIPK3, MLKL, and tumor-necrosis factor receptor 1 (TNFR1). Furthermore, crystal-induced cell death was at least partially prevented by exposure to necrostatin-1, a RIPK1 stabilizer. In cells exposed to CaOx crystals, necrostatin-1 completely prevented crystal-induced death.

Further studies were performed in a mouse model of crystal nephropathy, in which oxalate exposure leads to crystal-induced tissue injury and organ failure. Oxalate induced CaOx deposits in *Ripk3*- and *Mlkl*-deficient mice, as in wild-type animals. However, all functional and structural indicators of crystal nephropathy were significantly reduced in the *Ripk3*- and *Mlkl*-deficient mice—including serum creatinine levels, markers of tubule necrosis, and neutrophil recruitment.

Additional experiments suggested that necroptosis is responsible for inducing inflammation in the presence of crystal nephropathy, as inhibiting necroptosis also prevented inflammation. There was also evidence of secondary necroptosis driven by TNF.

The findings add to a growing body of evidence on the bidirectional causal associations between kidney injury and inflammation. Prof. Anders is also coauthor of a recent review in the *Journal of the American Society of Nephrology* that highlights the growing body of evidence for a "genetically determined and regulated process" of necroinflammation. (Co-authors of the *JASN* review are Drs. Shrikant R. Mulay of Klinikum der Universität München and Andreas Linkermann of Christian-Albrechts-University Kiel.)

The concept of necroinflammation provides a unifying theory of the relationship between kidney injury and inflammation, which are "reciprocally enhanced in an autoamplification loop," according to the *Nature Communications* study. Just in the last few years, researchers have made progress toward outlining a number of different molecular pathways by which necrosis induces inflammation and inflammation induces necrosis.

By showing that crystal-induced cell death occurs through a regulated process and identifying the mediators involved in necroptosis, the new study identifies some potentially effective new therapeutic targets. In vivo experiments showed reduced evidence of crystal nephropathy in animals treated with necrostatin-1; as well as etanercept, which blocks TNF-α; and R-7050, a TNFR internalization inhibitor.

What's the relevance to human kidney disease? On review of a large series of human kidney biopsies, Anders and colleagues found CaOx crystals in association with acute tubular injury in 10% of 4125 cases of acute kidney injury. On immunostaining, crystal-induced cytotoxicity in human cells appeared similar to that in mouse cells, including activation of MLKL.

Alberto Ortiz, MD, PhD, of Fundacion Jimenez Diaz and University Autonoma of Madrid noted, "Indeed, oxalate may cause acute kidney injury in 'juicers'—individuals who may inadvertently consume huge amounts of oxalate-rich fruit and vegetables by juicing these in the course of 'healthy' dieting."

The results may help to refine understanding of the process leading to crystal-induced cell death in several human diseases. "Cell death in this context has hitherto been regarded mainly as a passive process of cell loss due to irreparable damage," Anders said. "But we have now demonstrated that it is the outcome of a regulated process, which actively eliminates cells."

Treatments focusing on specific mediators of the necroptosis pathway could offer important advantages, compared to previous strategies directed at the inflammatory reaction. If blocking those mediators can prevent crystal-induced cell death, it might also impede the development of chronic inflammation—with potentially important implications for management not only of acute kidney injury, but also other conditions such as gout and atherosclerosis. Prof. Anders and colleagues write, "Together, TNF-α/TNFR1, RIPK1, RIPK3, and MLKL are molecular targets to limit crystal-induced cytotoxicity, tissue injury, and organ failure."

In addition to necroptosis, the *JASN* review describes five additional pathways of necroinflammation: ferroptosis, mitochondrial-permeability transition-medicated regulated necrosis, pyroptosis, "NETosis" involving neutral extracellular traps, and mitotic catastrophe. These regulated processes of necroinflammation could contribute to a wide range of other important kidney diseases, such as sepsis/urosepsis, acute tubular necrosis, rapidly progressive glomerulonephritis, and thrombotic microangiography.

Together, all of these processes suggest an extensive list of molecular therapeutic targets with the potential to interrupt the process of necroinflammation. A key issue will be whether delayed treatment aimed at inhibiting these regulated processes of cell death will be able to prevent kidney injury in AKI and other conditions. Mulay, Linkermann, and Anders concluded, "The various aspects of necroinflammation offer great opportunities for novel discoveries and eventually also for novel treatment options for patients with kidney disease."

"The impact of an improved understanding of the molecular drivers of regulated necrosis and subsequent inflammation may extend well beyond the kidneys," Ortiz said. He pointed out several systemic diseases in which crystals play an essential role in pathogenesis, and which may be amenable to new treatment approaches targeting regulated necrosis and inflammation: "These include oxalate crystal deposition, which is systemic in oxalosis; atheroembolism, which consists of systemic cholesterol crystal emboli and currently has no specific therapy; and cystinosis, a systemic disease in which cysteamine therapy delays but may not completely prevent systemic complications."

Mulay SR, et al. Cytotoxicity of crystals involves RIPK3-MLKL-mediated necroptosis. *Nat Commun* 2016; 7:10274. doi: 10.1038/ncomms10274.

Mulay SR, et al. Necroinflammation in kidney disease. *J Am Soc Nephrol* 2016; 27:27–39.

Getting JE, et al. Oxalate nephropathy due to 'juicing': case report and review. *Am J Med* 2013; 126:768–72.

Online ASN Communities Expand Member Communication Options

By Zach Cahill

During the past five years, the American Society of Nephrology has seen significant membership growth. ASN now represents a more complete picture of the nephrology community, including a significant international presence and health professionals across many job roles and interest areas. To engage with this diverse membership, ASN has established a new member benefit: ASN Communities.

ASN Communities provide an online platform for discussion, networking, and collaboration among nephrologists around the world. Unveiled in March 2016, the Communities allow members to connect to each other, to the society, and to the broader kidney community. Every ASN member has access to the ASN Communities and may log in through the ASN website with the same username and password they already use.

By providing many options for engaging with colleagues, the Communities are designed to fit the busy lifestyle of ASN members. Daily digest emails summarize the latest conversations, allowing members to keep up with discussions on their own time. Members may respond to or begin a new thread via email from any device. The site also includes a resource library, allowing members to share presentations, documents, videos, and more. The site even recommends contacts based on individual interests, institution, or geographical area.

For the past two months, the society has tested the site with a small group of members in an effort to create an easy-to-use and valuable platform. During that time, members have used 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. Kidney professionals from around the world—including Bahrain, China, India and Italy—have all engaged with ASN Communities, interacting with professionals at all levels, from nephrology fellows to "seasoned" nephrologists. ASN members engaged in the Communities represent all the different facets of nephrology: PhD basic researchers, academics, practicing nephrologists, and many more.

As engagement grows, the Communities will become a venue for topical debates, "Ask the Expert" opportunities, and journal article discussions. Over the coming months, ASN plans to introduce interest-based communities, which will serve as a virtual home for members interested in in-depth discussions about a specific subject area with like-minded peers. Every member interested in a subject area will be able to join the group and be a part of exciting, relevant discussions led by engaged and respected Community leaders. Once established, each community will be able to have a voice in selecting its own leadership. The ASN Communities will also streamline member input on important topics, such as integrated care delivery models, maintenance of certification, and educational interests. The Communities will ensure ASN activities and priorities accurately reflect the vast interests of the society's growing membership.

To explore the new ASN Communities site, visit community.asn-online.org and join the conversation.

Zach Cahill is ASN Communities Associate.

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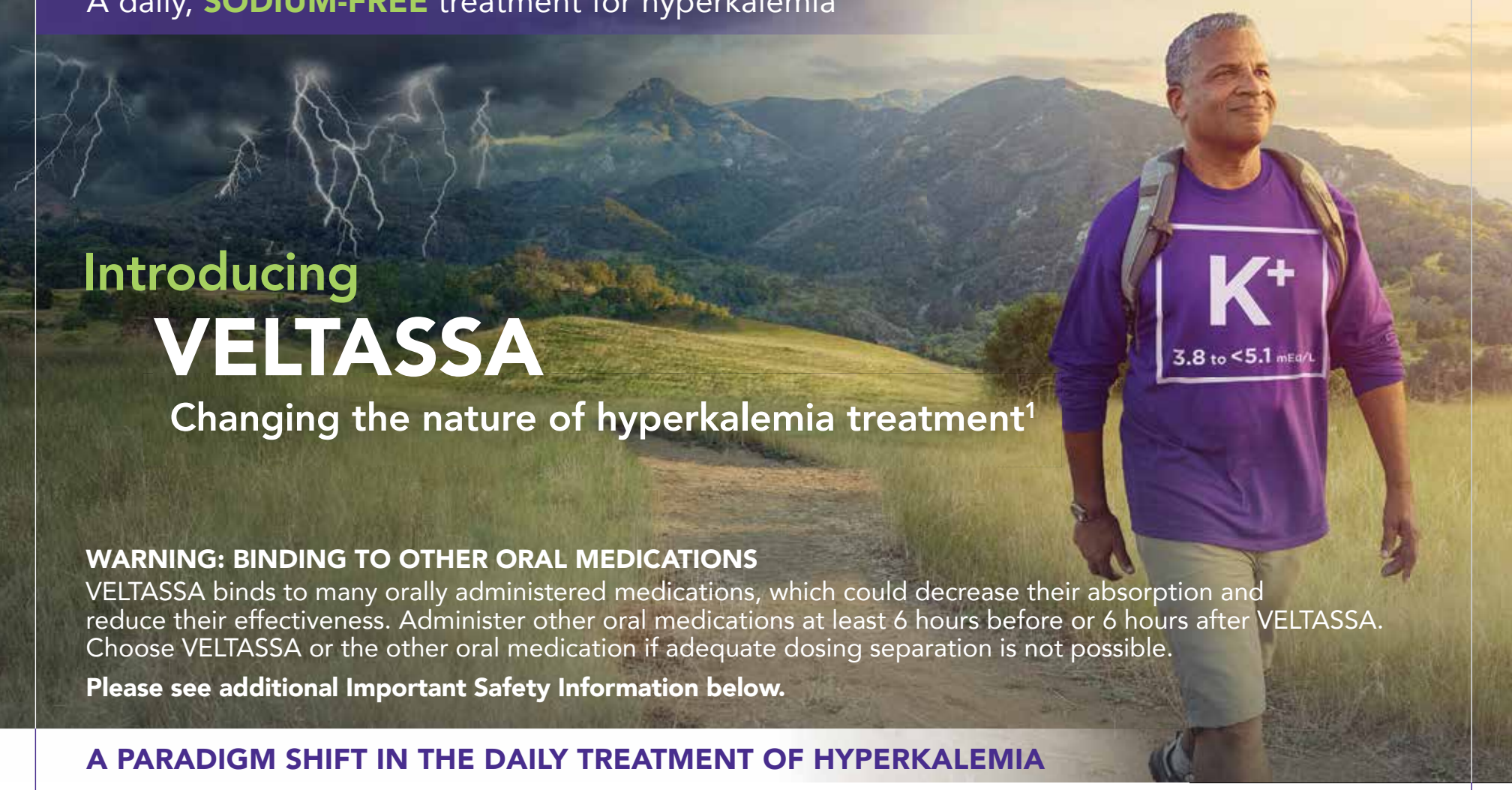

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Reference: 1. Bakris GL, Pitt B, Weir MR, et al; for AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-161.

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Policy Update

ASN, AAKP Join Forces to Advance Living Donor Protection Act

Kidney transplantation is the optimal renal replacement therapy for the majority of people with kidney failure—yet the nearly 110,000 Americans on the kidney wait list face significant barriers to receiving a transplant. The Living Donor Protection Act aims to eliminate some of these barriers and increase transplantation by strengthening and protecting the rights of living organ donors.

A top priority for the ASN Public Policy Board, the Living Donor Protection Act was introduced in the US Senate as S. 2584 by Senators Mark Kirk (R-IL) and Kirsten Gillibrand (D-NY), and in the US House of Representatives as H.R. 4616 by Representatives Jerrold Nadler (D-NY) and Michael Burgess, MD (R-TX). Building Congressional support and cosponsorship for this important legislation will be the focus of ASN's annual Kidney Health Advocacy Day on Thursday, April 21, 2016.

In partnership with the American Association of Kidney Patients (AAKP), ASN Kidney Health Advocacy Day will bring nearly 50 patient and health professionals from around the country to Washington, DC, to meet with their members of Congress and ask for their support for the Living Donor Protection Act. The introduction of this bill and the April advocacy effort build on Kidney Community Advocacy Day 2015, when ASN convened 16 kidney patient and health professional organizations in Washington,

DC, to urge members of Congress to introduce the Living Donor Protection Act. ASN and AAKP will now work collaboratively with other stakeholders in the kidney and transplant community to advance and ultimately enact the bill.

The Living Donor Protection Act would eliminate barriers and safeguard the rights of living donors in three ways:

- **Prohibiting discrimination against living donors** No laws currently exist that prohibit life, disability, or long term care insurance companies from denying or limiting coverage to people who have donated an organ. A 2007 study demonstrated that more than 10% of living donors encountered challenges in obtaining or paying for insurance post-donation owing to these discriminatory policies.
- **Providing job security to living donors during recovery** Four to six weeks are typically required for recovery from living organ donation, so job security can be a serious concern for potential living donors. The Living Donor Protection Act would clarify that living donors can utilize protections under the Family and Medical Leave Act to ensure that their employer cannot penalize them for time spent away from work recovering from the donation surgery. Although this provision would not reimburse donors for lost wages, it would provide job security and reassurance that employment will be waiting upon recovery.
- **Updates educational materials** The US Department of Health and Human Services (HHS) plays an integral role in educating kidney patients and their families about all types of donation and the treatment options available. If the Living Donor Protection Act is enacted, HHS would be called upon to update its materials regarding living donation to reflect these new protections and encourage more Americans to consider becoming living donors.

The Living Donor Protection Act would also help save Medicare money. ASN Public Policy Board member Kevin F. Erickson, MD, conducted an analysis that concluded that by increasing living donation by just 10%, the Living Donor Protection Act could save Medicare $560 million to $1.2 billion over 10 years.

"Organ donation saves Medicare millions of dollars every year," said Rep. Nadler. "It cuts health care costs as much as two-thirds by reducing the need for dialysis and other expensive medical interventions to treat chronic illnesses. Yet, after taking this heroic step to save a life, living organ donors may unfortunately face discrimination when they try to take medical leave or buy insurance. Our bill would address that injustice."

"This bill will cut costs and make it easier for healthy people to donate living organs without fear of losing their jobs or their paychecks," commented Sen. Kirk.

Kidney News readers can learn more and join ASN in advocating for this important legislation by visiting ASN's Legislative Action Center or visiting the ASN Advocacy and Public Policy website.

President's 2017 Budget Cuts VA Kidney Research

By Grant Olan

The Department of Veterans Affairs (VA) helps fund more than 3400 investigators around the country who conduct cutting-edge veteran-focused research in many areas, including kidney disease. More than 3000 veterans are diagnosed with kidney failure each year, and 30,000 veterans are on dialysis.

The list of VA investigator contributions to research during the agency's 90-year history is lengthy and includes the first long-term successful kidney transplant. The VA research program was a big winner in the 2016 budget deal, which increased its funding by $42 million, a 7.1% increase. In his 2017 budget proposal, President Barack Obama is again asking Congress for an increase of $30 million, 5% over the 2016 budget.

None of that funding would go to kidney research. In fact, the President's budget proposal cuts kidney research funding in 2017 by more than $500,000, because the budget would invest an additional $65 million in the Million Veteran Program (MVP) in 2017. MVP will be the world's largest genomic database, with the goal of studying how genes affect veterans' health. To date, the VA has collected DNA samples from nearly 500,000 veteran volunteers. Most of the $65 million would be used for sequencing those DNA samples.

Since the President's requested $30 million increase for the VA research program in 2017 would only fund half of the $65 million increase for MVP, the budget proposal cuts funding for kidney research and most other research areas to pay for the balance. ASN President Raymond C. Harris, MD, FASN, strongly denounced the proposal.

"While MVP is a worthy and noble initiative, investigator-initiated grants for kidney research and other VA research priorities shouldn't be sacrificed to pay for it," Dr. Harris said. "Too many veterans have kidney disease. We need better therapies for treating them, and the President's 2017 budget request would evaporate the 2016 budget gains."

Instead, the Friends of VA Medical Care and Health Research (FOVA) advocacy coalition is asking for the $30 million increase *plus* an additional $65 million for MVP so it does not come at the expense of other important veteran research like kidney disease. ASN serves on the executive committee of FOVA, which represents 80 academic institutions, patient organizations and medical professional associations, and veterans service organizations.

Have questions about kidney research funding or the federal budget? Email Grant at golan@asn-online.org. Your question could be the basis for the next *Kidney News* policy article.

Correction: *Kidney News* regrets an error in the March Detective Nephron column in which text was incorrectly repeated on the first page. The corrected text appears here.

Nice Glom (the new medical student) enters the room along with L.O. Henle to present a case.

Nephron What do you have for me today Henle?

Henle looks at Glom

Glom I have a 65-year-old man with a serum sodium concentration of 112 mEq/L.

Nephron Hyponatremia! My favorite electrolyte disorder. What is the first question you need to ask?

Henle Whether the patient has symptoms?

Nephron Exactly. Given the severity of this hyponatremia, we need to know if we need to treat immediately with hypertonic saline to avoid life-threatening cerebral edema. Severe symptoms such as seizures and coma indicate significant cerebral edema and require the use of NaCl 3% 100 mL IV bolus, which you could repeat twice if symptoms persist. Moderate symptoms such as confusion indicate a lesser degree of cerebral edema but still significant enough to be dangerous and also require the use of NaCl 3% but in slow infusion. Remember, severely symptomatic or moderately symptomatic hyponatremia are medical emergencies and need to be treated with hypertonic saline.

Henle I interviewed the patient and did a full neurological exam. The patient is asymptomatic.

Nephron *(upset)* That is not entirely true, is it? Evidence has emerged over the last several years suggesting that all hyponatremias are symptomatic to a degree. Even mild chronic hyponatremia in the range of 125 to 135 mEq/L is not only associated with increased mortality but also increased morbidity in the form of subtle attention deficits, gait disturbances, falls, fractures, and osteoporosis.

Glom I did not know that.

Nephron *(smiling)* Are you familiar with the concept of regulatory volume decrease or RVD?

Henle & Glom *(looking at each other)* No.

US Nephrologists Voice Opinions about Certification, Recertification, and ABIM

A recent survey of 1134 US nephrologists who are ASN members provided important insights that will help guide ASN's assessment of approaches to initial certification, recertification, and physician assessment activities, as well as the relationship between the nephrology community and the American Board of Internal Medicine (ABIM).

The survey is part of ASN's larger strategy to help nephrologists maintain career excellence.

About 90% of US nephrologists are ASN members. Nearly 1 in 5 nephrologists who received the survey responded. Most respondents were private practitioners (44.9%), followed by clinical educators (24.8%) and academic researchers (15.1%). Other respondents identified themselves as hospital-based physicians, industry researchers, and administrators (Table 1). Respondents also included those who identified as transplant nephrologist, interventional nephrologist, academic physician, among a few other designations.

The majority of respondents (92%) were board certified through ABIM. For those who were not ABIM-certified, 3 respondents were certified by the American Osteopathic Board of Internal Medicine (AOBIM) and 6 were certified by the National Board of Physicians and Surgeons (NBPAS). Other certifying boards mentioned in the survey's open comments section included the American Board of Pathology, American Board of Pediatrics, board eligible/not certified, and international certification.

"I was pleased to see the number of nephrologists who participated in the survey and provided their opinions about MOC, recertification, lifelong learning, and issues related to ABIM," said ASN Councilor and Education Committee Chair Mark Rosenberg, MD, FASN. "Having this level of information will greatly assist ASN as the society examines options for helping nephrologists maintain career excellence and provide the highest-quality patient care possible."

Table 1
Demographic information of survey respondents

Demographics	Response
ABIM-certified in nephrology	
Yes	1041 (92%)
No	91 (8%)
Practice choice	
Private practitioner	457 (44.9%)
Clinician educator	252 (24.8%)
Academic researcher	154 (15.1%)
Hospital-based physician	132 (13%)
Industry researcher	12 (1.2%)
Administrator	10 (1%)
Year of Board certification	
Before 1990	175 (17.5%)
Between 1990 and 2016	826 (82.5%)

Board certification

When asked if initial board certification is important to the practice of nephrology, 1009 respondents (96.5%) answered "strongly agree" or "agree," and 37 (3.0%) responded "disagree" or "strongly disagree." Following are a sampling of comments made by those who agreed that board certification is important:

- "Board certification has come to mean highly skilled; fulfills basic requirement to practice as a nephrologist."
- "Validation of knowledge base and a public record of achievement."
- "An objective test of the knowledge required to diagnose and treat disorders seen by nephrologists assures training programs have adequately trained fellows and fellows have retained and can apply this information."

Among the 37 respondents who disagreed or strongly disagreed with the statement about board certification were the comments:

- "Board certification is a poor reflection on the individual's ability to be a good practitioner."
- "Board certification is a scam. All that should matter is if you completed a fellowship in an approved training center."

Board recertification

Nephrologists were split in their answer to the question: "Is board recertification important to the practice of nephrology?" Forty-seven percent (491) responded "strongly agree" or "agree" with this statement, and 53% (553) responded "disagree" or "strongly disagree" (Figure 1). In more than 450 open-ended comments, nephrologists stated:

- "[Board recertification] is high stakes with an all or nothing exam that does not reflect real life conditions and is written by people who do not perform the same type of job in a setting similar to most practicing nephrologists."
- "Practicing physicians recertify every day as they see patients and expand their experience and knowledge base."
- "We all need to maintain our knowledge and skills through lifelong learning to provide safe and effective care for our patients. However, the process for this should be completely different from the original certification, which is testing a one-time broad knowledge base and ability to answer test questions. We need to think of recertification as part of team-based practice."

Board certification as a one-time event

When asked if board certification should be a one-time event, 589 (56.8%) respondents said yes, and 448 (43.2%) responded, "It is a credential that should be recertified at regular intervals." Among more than 350 open-ended responses were the comments:

- "A one-time exam to demonstrate achievement and an understanding of one's training seems appropriate. Once you give me the license and certification the Hippocratic Oath takes care of the rest."
- "After my initial certification, I was opposed to mandated recertification; however, after having participated in the recert[ification] process twice now, I can say with reasonable confidence that the preparation (if not the test itself) has made me more current and probably more competent in nephrology. And I do a ton of inpatient consultative nephrology in an academic setting so it's not that I lack for clinical exposure or sharp and helpful colleagues. So if it helps me, it must be helping others."

What activities should count toward recertification?

In the survey's section on recertification, several optional activities that might be part of a recertification process were listed, and participants were asked to select as many options as they felt applied. The results (in rank order) are shown in Table 2.

Table 2
Activities that should be part of recertification

Activity	Response
Accredited continuing medical education (CME)	895
Periodic open-book examinations	543
Performance improvement activities within the context of the health care team and system of practice	167
Peer assessment of performance	162
Practice assessment through practice improvement modules (PIMs)	150
High-stakes, closed-book secure examination	127
None of the above	72
Patient safety initiative documentation	64
Patient satisfaction data collection	53
All of the above	11

In 350 open-ended comments, nephrologists stated:

- "All are valid forms of evaluation."
- "I believe that additional research is needed to . . . determin[e] what techniques are needed to maintain competence, Also, what are the best practices to maintain competency?"
- "I think the goal is lifelong learning. The high stakes exam [that] I just passed is not indicative of physician performance or capability. The practice assessments and performance improvement activities sound like busy work."
- "Most of us in nephrology (and in my case, also transplant nephrology) participate in all kinds of activities which require literature reviews, QAPI projects, etc. Most of us are exceedingly busy. These activities, which are demonstrative of clinical engagement and competence, should count as objective measures of . . . clinical engagement and competence."

What role does CME play in certification?

The survey also asked, "Is documented CME provided by an accredited organization sufficiently rigorous to qualify as the only determinant of recertification?" About 60% (622) of respondents answered "yes," and about 40% (411) answered "no."

In more than 300 open-ended remarks, nephrologists stated:

- "CME is a broad term, but yes, continued education should be the determinant. How to make it rigorous enough to qualify would be subject to some discussion. It should require one to fulfill a variety of areas within the specialty, like not doing all your CME activities on the same topic, say, anemia."
- "What 'recertification' should be testing is whether a doctor is making the effort to be continually exposed to what is new and innovative in the field. How he applies that to his practice is not the point. What you want to weed out [are] those doctors who have become out of touch with the current practice of nephrology."

Time-limited certification

The survey addressed the issue of time-limited certification ("grandfathers and grandmothers"). When asked if nephrologists who earned initial certification before 1989 should participate in recertification, 676 (65.3%) of respondents said yes and 360 (34.7%) said no. In more than 400 open-ended comments, nephrologists stated:

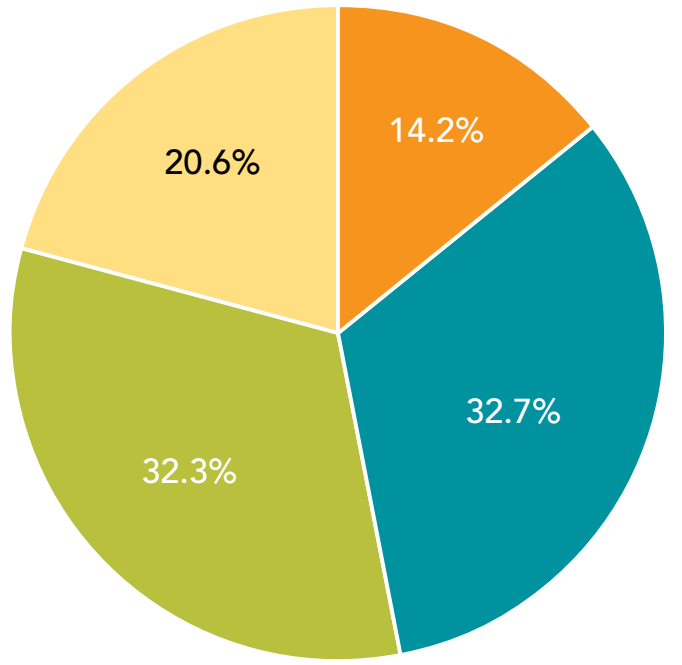
- "I am a grandfather and I feel being formally evaluated like my colleagues is reasonable (you have 'street cred'). I also found participating in a med knowledge MOC activity was educational and worth the time. Online activities which can be completed over multiple sessions are optimal. Would be nice for MOC activities to count toward state licensure."
- "The longer you are in practice, the deeper your knowledge."
- "A deal should be a deal. Do we really want to drive our elder statesmen/women out of practice prematurely by making it even more of a hassle to take care of patients than it already is?"

ABIM and MOC

Finally, the survey asked, "Is ABIM the appropriate organization to recertify nephrologists?" In response, 427 US nephrologists (42.1%) said yes, and 587 (57.9%) said no. In more than 550 open-ended remarks, nephrologists stated:

- "ABIM has betrayed the rank and file of physicians and unless it undergoes some major change it should not recertify any specialty. The American Society of Nephrology should be tasked with recertification."
- "With the caveat that they need to right their ship, since the current management and policies are out of touch and there has been a major erosion of trust in the organization, its leadership, and its interests across physicians."
- "ABIM would be perfectly appropriate, if they would reconsider the burdensome and expensive way they provide recertification. Otherwise, we should be open to alternative organizations."
- "I guess … I think the idea of breaking away from the "mothership" and doing our own thing doesn't really solve the fundamental issue of what really makes and keeps a physician board certified and what doesn't. I think we would end up reinventing the wheel if we tried to do it on our own. As long as there is an ABIM that is receptive to positive change, we should put our stakes with a singular governing body and ensure our voice is heard and our ideas applied."

Figure 1
Survey responses to the question "Is board recertification important to the practice of nephrology?



ASN invited survey-takers to make additional remarks about any aspect of certification and recertification and received more than 475 comments; a sampling appears here:

- "1. Stop re-certification/MOC. 2. Have practicing nephrologists more involved in policy or performance measure making. 3. Advocate for setting up oversight for ABIM or NQF, etc. 4. Advocate for legislation to prevent any interruption on physician's practice."
- "For patients to get the best care, we need teams. We need to hold teams accountable for patient safety, satisfaction, and to an increasing extent, better outcomes. We should be thinking about these issues and how to do this better, not trying to make a better mouse trap to evaluate physicians' knowledge."
- "Self-assessment programs that require testing are rigorous enough to meet the purpose of updating and refreshing knowledge."
- "I agree with the need for initial certification but not for recertification. I agree that physicians should continue CME education but not [be] re-examined. It is like getting your driver's license; there is no need to be retested. Experience is something that books cannot test."
- "I strongly hope whatever organization takes the lead in the process, that organization takes into account the tremendous burden this places on the practicing nephrologist and attempts to incorporate the documentation into a meaningful practice with minimal oversight or [documentation] burden."
- "Nephrologists are internists—I want the ASN to continue to work with ABIM."
- "Recertification is useless, waste of money, waste of resources. [I]t does not help patient care. [D]oes not change patient mortality. [S]hould be abolished."

Next steps

ASN is currently forming a task force to identify pathways available for nephrologists to renew their subspecialty board certification. The task force will analyze the MOC survey data, generate a decision matrix of pros and cons for the identified pathways, and report to the ASN Council on findings and recommendations for society actions. The survey results will help guide this process.

To discuss the survey or the task force, to provide comments about the survey, or to ensure your voice is heard concerning certification, recertification, or assessment, please contact ASN at education@asn-online.org, subject: Recertification.

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Collaboration among Industry, Regulatory Agencies, and Professional Societies Drives Progress in Treating Kidney Diseases

By Jeffrey Petersen

In 2014, the Centers for Disease Control and Prevention estimated that there were more than 20 million Americans with chronic kidney disease (CKD) and 661,648 prevalent cases of ESRD (1, 2). In 2013, patients with CKD represented 10 percent of the Medicare population, with expenditures exceeding $50 billion accounting for 20 percent of total expenditures (2). The ESRD population is less than 1 percent of the total Medicare population, with expenditures of $30.9 billion accounting for 7.1 percent of the overall Medicare paid claims (2).

The cost of drugs is an important component of these expenditures, and both public and private payers are moving to bundled payments in an attempt at cost containment. The nephrology community has been in the vanguard of such changes, with a prospective payments system (PPS) for kidney dialysis services introduced in early 2011 (3). Intravenous drugs were included in the bundle for the first time, having previously been reimbursed separately from the dialysis treatment. In the first year after implementation of the PPS, utilization of these drugs declined 34 percent (4). Hirth et al. interpreted this decline as resulting from changes in provider behavior in response to financial incentives within the PPS as well as changes in the label for erythropoieisis-stimulating agents (ESAs) during this time period (4).

Concern has been expressed that the PPS may put at risk the development of innovative therapies or devices. This may add one more potential barrier in exploring new treatments for ESRD patients. Already the number of randomized clinical trials published in nephrology between 1996 and 2010 is lower than other specialties in internal medicine (5). The introduction of several new expensive prescription drugs has rekindled debate over the costs attributed to drug development.

Well designed clinical trials are a key component of marketing approval of any new drug but do not represent the sole cost of developing a new drug. A systematic review of published estimates in 2010 found a ninefold range in the estimates of drug development from $161 million to $1.8 billion of capitalized US dollars (6). The authors concluded that no published estimate of the cost of developing a drug can be considered a gold standard. Tufts Center for the Study of Drug Development announced in November 2014 that the cost to develop and win marketing approval for a new drug was $2.6 billion (7), although this figure has been challenged (8). In the same announcement, the authors noted that the development process often lasted longer than 10 years, however, the lengthening of development and approval time were not responsible for driving up the development costs. The same authors reported that the clinical approval success rate had declined from 21.5 percent in 2003 to 11.8 percent currently, and these drug failures are key contributors to development costs (9).

In September 2012, the American Society of Nephrology, recognizing the lack of clinical trials and the huge unmet need, established, under a memorandum of understanding with the Food and Drug Administration (FDA), the Kidney Health Initiative (KHI) (10). Its mission is "to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products, and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which the FDA and the greater nephrology community can interact and optimize evaluation of drugs, devices, biologics and food products."

One of the key obstacles KHI identified was the lack of well-defined clinical trial end points for studies of treatment of CKD progression that would be acceptable to regulatory agencies for registration. Progression of CKD as measured by loss of GFR is typically 2–5 mL/min per year, and clinical manifestations occur late in the disease. The FDA has previously accepted a doubling of serum creatinine as a surrogate endpoint for assessing a drug's efficacy along with evidence of the drug's effect on all-cause mortality and ESRD (11). A doubling of serum creatinine corresponds to an approximately 57 percent decline in estimated GFR using the CKD-EPI equation.

In December 2012, the National Kidney Foundation and the FDA sponsored a workshop on GFR decline as an end point for clinical trials in CKD. Levey et al. conducted a series of meta-analyses of cohorts and clinical trials and simulations of trial designs and analytic methods (12). They concluded that a confirmed decline in estimated GFR of 30 percent over 2 to 3 years may be an acceptable surrogate end point in some circumstances but that the pattern of treatment effects on GFR must be examined, specifically acute effects on estimated GFR. An estimated GFR decline of 40 percent may be more broadly acceptable than a 30 percent decline across a wider range of baseline GFRs and patterns of treatment effects on GFR. If this surrogate is accepted, there is a potential for studies to be shorter and to enroll fewer patients for outcome trials. The European Medicines Agency also has recognized this problem, having issued a draft guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency in June 2014. It defined treatment goals; study designs; outcome measures, including estimated GFR as an end point; and data analyses (13); it suggests that for smaller studies actual measured GFR using an exogenous filtration marker may be preferable to creatinine-based eGFR. As drug development is global, further clarity on acceptable end points for major agencies must be sought. The draft guideline was open for consultation until January 2015 and a final guideline is pending.

KHI has identified two pilot projects affecting clinical trials (10). A workgroup in partnership with the Lupus Nephritis Trial Network is analyzing existing data to test for clear end points for lupus trials. Pharmaceutical companies have been contacted to discuss the inclusion of their data into the planned analysis. On completion, the workgroup will recommend a core set of outcome measures, biomarkers, surrogate markers, and clearly defined terms that they propose should be incorporated into future lupus nephritis trials. A separate workgroup comprising KHI members from patient groups, health professional organizations, and industry and FDA representatives will examine, define, and explain the major barriers to innovation in kidney health and identify potential solutions to those barriers.

It is important to recognize that any drug approval requires a thorough assessment of benefits as well as risks, and a 2- to 3-year study is usually required to assess long-term safety data.

Despite all of these issues, progress has occurred in the treatment of our patients. Unadjusted mortality rates in Medicare patients with CKD have decreased 35.9 percent since 2001, whereas for those without CKD, the decrease was 18.1 percent over the same time period (2). The incidence rate of ESRD plateaued beginning in 2001 and declined in all but one year between 2007 and 2012, and it was essentially unchanged in 2013 (2). Mortality rates for dialysis patients fell by 5 percent from 1996 to 2003 and 23 percent from 2004 to 2013 (2). The recent collaborative efforts of all stakeholders should, in the years to come, affect our common mission of improving the lives of patients with CKD and ESRD.

Jeffrey Petersen, MD, is affiliated with Amgen , and is a member of the Kidney News *Editorial Board.*

References

1. Centers for Disease Control and Prevention (CDC). *National Kidney Disease Fact Sheet. General Information and National Estimates on Chronic Kidney Disease in the United States, 2014*. Atlanta, GA, US Department of Health and Human Services Centers for Disease Control and Prevention, 2014.
2. US Renal Data System. *USRDS 2015 Annual Report. Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethesda, MD, National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases, 2013.
3. *Medicare Improvements for Patients and Providers Act, Pub 1 No. 110–275, 122 Stat 2553*, 2008.
4. Hirth RA, et al. The initial impact of Medicare's new prospective payment system for kidney dialysis patents. *Am J Kidney Dis* 2013; 62:662–669.
5. Palmer SC, Sciancecalepore M, Strippoli GFM. Trial quality in nephrology: How are we measuring up? *Am J Kidney Dis* 2011; 58:335–337.
6. Morgan S, et al. The cost of drug development: A systematic review. *Health Policy* 2011; 100:4–17.
7. *How the Tufts Center for the Study of Drug Development Pegged the Cost of a New Drug at $2.6 Billion*, Boston. The Tufts Center for the Study of Drug Development, 2014.
8. Avorn J. The $2.6 billion pill—methodological and policy considerations. *N Engl Med* 2015; 372:1877–1879.
9. DiMasi JA, Grabowski HG, Hansen RW. The cost of drug development. *New Engl J Med* 2015; 372:1972.
10. Kidney Health Initiative Inaugural Review 2012–2014. https://www.asn-online.org/khi/KHI_YER_2014.pdf.
11. Thompson A, Lawrence J, Stockbridge N. GFR decline as an end point in trials in CKD: A viewpoint from the FDA. *Am J Kidney Dis* 2014; 64:836–837.
12. Levey AS, et al. GFR decline as an end point for clinical trials in CKD: A scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis* 2014; 64:821–835.
13. European Medicines Agency. *Draft Guidelines on the Clinical Investigation of Medicinal Products to Prevent Development/Slow Progression of Chronic Renal Insufficiency (EMA/CHMP/355988/2014)*.

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Iron status should be determined on pre-dialysis blood samples. Post dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

Adverse Reactions

The most common adverse reactions (≥3% and at least 1% greater than placebo) in controlled clinical studies include: procedural hypotension (21.6%), muscle spasms (9.6%), headache (9.2%), pain in extremity (6.8%), peripheral edema (6.8%), dyspnea (5.8%), back pain (4.5%), pyrexia (4.5%), urinary tract infection (4.5%), asthenia (4.1%), fatigue (3.8%), arteriovenous (AV) fistula thrombosis (3.4%), and AV fistula site hemorrhage (3.4%).

References: 1. Rockwell Medical, Inc. Data on File. Independent Market Research Study Conducted in August 2015 with 103 U.S. Based Nephrologists – Based upon efficacy, safety, most appealing aspect, contrast to IV iron and choice between Triferic and IV iron.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions. Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after hemodialysis until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions *[see Adverse Reactions].* Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic in two randomized clinical trials. **Iron Laboratory Testing.** Iron status should be determined on pre-dialysis blood samples. Post dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

ADVERSE REACTIONS: The following adverse reactions are described below and elsewhere in the labeling: Hypersensitivity Reactions *[see Warnings and Precautions].* **Clinical Trials Experience.** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice. In two randomized, placebo-controlled clinical trials, a total of 292 patients were administered Triferic for periods of up to 1 year *[see Clinical Studies in the Full Prescribing Information].* The mean total exposure in the randomized treatment period was 5 months. A total of 296 patients received placebo treatment for a similar time period. In the two studies, 64% were male and 54% were Caucasian. The median age of patients was 60 years (range, 20 to 89 years). Adverse events occurring in 3% or greater of patients treated with Triferic in the randomized clinical trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at Least 3% of Patients Receiving Triferic and at an Incidence at least 1% Greater than Placebo

System organ class Preferred term	**Triferic N=292 n (%)**	**Placebo N=296 n (%)**
Number of patients with at least one adverse reaction	229 (78.4)	223 (75.3)
General Disorders and Administration Site Conditions		
Peripheral edema	20 (6.8)	11 (3.7)
Pyrexia	13 (4.5)	9 (3.0)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Infections and Infestations		
Urinary tract infection	13 (4.5)	4 (1.4)
Injury, Poisoning, and Procedural Complications		
Procedural hypotension	63 (21.6)	57 (19.3)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	28 (9.6)	24 (8.1)
Pain in extremity	20 (6.8)	17 (5.7)
Back pain	13 (4.5)	10 (3.4)
Nervous System Disorders		
Headache	27 (9.2)	16 (5.4)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	17 (5.8)	13 (4.4)

Adverse Reactions Leading to Treatment Discontinuation. In clinical trials, adverse reactions leading to treatment discontinuation included headache, asthenia, dizziness, constipation, nausea, hypersensitivity reactions, intradialytic hypotension, pruritus, and pyrexia. Adverse reactions reported in the treatment extension period were similar to those observed in the randomized clinical studies.

USE IN SPECIFIC POPULATIONS: Pregnancy. Pregnancy Category C. *Risk Summary:* There are no adequate and well-controlled studies of Triferic in pregnant women. In pregnant rats and rabbits, ferric pyrophosphate citrate caused developmental toxicity at maternally toxic dose levels that were higher than the maximum theoretical amount of iron transferred to patients from Triferic. The incidence of major malformations in human pregnancies has not been established for Triferic. However, all pregnancies regardless of exposure to any drug have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Use Triferic during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data:* In a fertility and early embryonic development study in female rats, the maternally toxic ferric pyrophosphate citrate dose of 40 mg/kg administered three times per week by intravenous (IV) infusion was not toxic to the developing embryo. In embryo-fetal developmental toxicity studies, ferric pyrophosphate citrate was administered during the period of organogenesis as a one-hour IV infusion to pregnant rats and rabbits. No maternal or developmental toxicity was observed at doses up to 30 mg/kg/day in rats and 20 mg/kg/day in rabbits. Maternally toxic doses affected embryo-fetal development, resulting in post-implantation loss due to early resorptions, abnormal placentae, decreased fetal body weight and fetal head and vertebral malformations at 90 mg/kg/day in rats and vertebral malformations at 40 mg/kg/day in rabbits. A pre-and post-natal development study was conducted in pregnant rats with intravenous doses of ferric pyrophosphate citrate up to 90 mg/kg/day. The maternally toxic dose of 90 mg/kg/day resulted in reductions in the number of live offspring and lower offspring body weights. There were no adverse effects on survival of offspring at doses up to 30 mg/kg/day, or on behavior, sexual maturation or reproductive parameters of offspring at any dose level. **Nursing Mothers.** It is not known if ferric pyrophosphate citrate is present in human milk. Because many drugs are excreted in human milk and because of the potential for adverse events in nursing infants, a decision should be made whether to discontinue nursing or to avoid Triferic, taking into account the importance of iron to the mother and the known benefits of nursing. **Pediatric Use.** Safety and effectiveness have not been established in pediatric patients. **Geriatric Use.** In controlled clinical trials, 99 (28.6%) patients ≥ 65 years of age were treated with Triferic. No overall differences in safety and efficacy were observed between older and younger patients in these trials *[see Clinical Studies in the Full Prescribing Information].*

OVERDOSAGE: No data are available regarding overdosage of Triferic in humans.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility. Studies examining the carcinogenic potential of ferric pyrophosphate citrate have not been conducted. Ferric pyrophosphate citrate was clastogenic in the in vitro chromosomal aberration assay in CHO cells in the presence of metabolic activation. Ferric pyrophosphate citrate was not mutagenic in the in vitro bacterial reverse mutation (Ames) test or clastogenic in the in vitro chromosomal aberration assay in CHO cells in the absence of metabolic activation or in the in vivo mouse micronucleus assay. In a combined male and female fertility study in rats, ferric pyrophosphate citrate was administered intravenously over one hour three times per week at doses of up to 40 mg/kg. No adverse effects on fertility or reproduction were noted.

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Practice Pointers

Putting SPRINT into Practice

This month, Kidney News *Editorial Board member Edgar V. Lerma, MD, FASN, interviewed George Bakris, MD, FASN, FASH, FAHA, about recent SPRINT (Systolic Blood Pressure Intervention Trial) results. Dr. Bakris is professor of medicine and director of the ASH Comprehensive Hypertension Center at the University of Chicago Medicine.*

KN: Why is the SPRINT study significant?

Dr. Bakris: Because it was an appropriately powered study that addressed questions about the level of blood pressure (BP) control in high–cardiovascular (CV)-risk groups, including a very large group over age 75 and those with chronic kidney disease (CKD) stages 4 and 5. In addition to continuing follow-up of the CKD cohort, SPRINT is also looking at the effects of lower BP on dementia in the SPRINT Memory and cognition IN Decreased hypertension (SPRINT-MIND) trial.

KN: What message should primary care physicians and nephrologists get from the SPRINT study?

Dr. Bakris: UpToDate includes carefully crafted messages for general practitioners and specialists.

Regarding goal BP, major guidelines, published before the ACCORD BP Trial, suggested that the goal BP in patients with diabetes mellitus (DM) is <130/80 mm Hg. However, there are no convincing data supporting this approach, with the possible exception of patients who have diabetic nephropathy and proteinuria, for whom evidence suggests that such a goal may slow the rate of progression of the nephropathy. Thus, we agree with the eighth Joint National Committee (JNC 8) and the European Societies of Hypertension and Cardiology that goal BP in most patients with diabetes is <140/90 mm Hg.

We recommend a goal BP of <140/90 mm Hg compared with higher pressures in all patients (grade 1B).

We suggest (a weaker recommendation) an attempt to lower the systolic BP to <130 to 135 mm Hg if it can be achieved without producing significant side effects (grade 2B).

We recommend a goal BP of <130/80 mm Hg compared with higher pressures in patients with diabetic nephropathy and proteinuria (500 mg/d or more; grade 1B).

For patients who fulfill the entry criteria in the ACCORD BP Trial (type 2 diabetes plus either cardiovascular [CV] disease or at least two additional risk factors for CV disease), the author and reviewers of this topic suggest that the risks and burdens of aiming for a goal systolic BP of <120 mm Hg (more side effects, extra patient visits, and increased cost) plus the lack of experience of almost all clinicians in attaining such a goal may be too great a burden to achieve the small reduction in stroke that may be attained (absolute benefit: 1 in 89 patients at 5 years). However, such a goal may be considered in highly motivated patients who would accept more aggressive antihypertensive therapy to further reduce their risk of stroke.

On the basis of the entirety of the data, including the SPRINT study (although there were no diabetics in the SPRINT study, the meta-analysis performed by Perkovic is compelling [1]), the interaction with glycemic control found in the ACCORD Trial, the ABCD Trial, the post hoc analyses of normotensive subgroups in drug versus placebo trials, etc., do we not have enough evidence to suggest a goal BP similar to the goal BP now recommended for patients who meet criteria for the SPRINT Study?

Please note that, on the basis of BP measurement in the SPRINT study, what is routinely used in the office should give a systolic BP range about 5 mm Hg higher, and therefore, the goal should be 125–130 mm Hg. This is only one part of the UpToDate changes.

KN: What are the limitations of the study (and the implications in the results)? What do you think about the exclusion criteria: autosomal dominant polycystic kidney disease, diabetes, proteinuria >1 g/d, stroke patients, and nursing home patients? Do you think these exclusion criteria affected the results significantly, particularly the study's generalizability?

Dr. Bakris: Limitations of the study are few and clearly stated in the paper. They did not want to look at diabetes because the ACCORD Trial did so, there was a need for CKD data in high-risk groups, and they did not make recruitment very difficult, because CV outcome was the primary end point (that is why high levels of proteinuria were excluded). The data are generalizable if you read the accompanying editorial, which makes the point clear, and we do so as well in UpToDate.

KN: Are the results applicable to CKD patients (with and without diabetes mellitus [DM])? ESRD patients? The elderly?

Dr. Bakris: Absolutely. The level of evidence in CKD is at least 2A if not 1B given factored power calculations. DM is less so, but we think so. ESRD is obviously no, and the elderly is absolutely yes (The results totally discredited JNC 8 recommendation and argue for more aggressiveness).

KN: Does the SPRINT study have any implications for resistant hypertension patients?

Dr. Bakris: Well, this is tough. They did not purposely recruit such patients, but many patients in the study were on three or more medications. The only thing you could say is that this group generally did not have resistant hypertension, because they were mostly well controlled with multiple agents and they took them.

KN: One cannot downplay the BP monitoring/documentation deployed by dedicated individuals involved in the study (e.g., three office BP readings with 5-min rest periods in between readings). Do you think this should be standard practice in all offices?

Dr. Bakris: Good point. Although I do not think that it is practical to do what they did in the study, I do think it is practical to do what I do with all my patients and that is make sure that they have a home BP monitor, know how to take BP, and report data through the Internet to the nurse or doctor, who will have given specific instructions as to when to take the BP (early morning preferred; not everyday but three times a week and after stable, once weekly). There are data that, in stable patients, seven BP readings a month over various times of day are as good as an ambulatory blood pressure monitoring. Patients need to take responsibility for their problem, including following a low-sodium diet.

KN: In this era of electronic medical records (EMRs), ICD-10 documentation, and staffing issues, is there any study looking into how rigorously BP monitoring is actually done in most primary care offices? Nephrologists' offices?

Dr. Bakris: I am not aware of any such data; it will be challenging, especially in underserved populations and free clinics, but this is an opportunity for someone.

KN: The study did not seem to consider diastolic BP in the decision algorithm. Is this a concern?

Dr. Bakris: Well, yes. Interestingly, they did not have many people at all with a diastolic BP <60, even on treatment; however, it is well known that, in the cohort, studied risk is tied to systolic and not diastolic BP (so not inappropriate). I have mentioned in my interviews that physicians should avoid low diastolic BP in people younger than 60 and try to get systolic BP at least to 140–149 mm Hg in this small subgroup.

KN: Are the results going to warrant a revision of the JNC 8 2013 Guidelines? Kidney Disease Improving Global Outcomes (KDIGO) 2012 Guidelines?

Dr. Bakris: KDIGO is already in the process of making an update. Because there are no more JNCs, the American Heart Association/American College of Cardiology is crafting an updated and revised document to the JNC.

KN: How do you apply such results to your own clinical practice?

Dr. Bakris: In general, I was always applying them but not going as low as they did in the SPRINT study. I calculate the ASCVD (atherosclerotic cardiovascular disease) score with the application for all of my patients as I sit with them, and I discuss how much risk reduction they would get with a lower pressure. I then let them choose if they want more medications. Most opt for lower BPs.

KN: If you were to redo the SPRINT study, what would you have done differently?

Dr. Bakris: I was on the original planning committee and would have perhaps added more African Americans and a greater proportion with more advanced CKD, but there was no money to do this. It was a miracle that they funded what they did, and many investigators did this study as a loss. My administrator did not want me doing the study for that reason.

Reference

1. Emdin CA, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 6:603–15.

Findings

Model calculates lifetime ESRD risk from predonation characteristics

A new online risk calculator can assess 15-year and lifetime risk of ESRD among potential living kidney donors, reports a study in *The New England Journal of Medicine*.

The researchers performed a meta-analysis of seven general population cohorts, totaling more than 4.9 million participants. Included subjects were free of absolute contraindications to kidney donation; median follow-up was 4 to 16 years. Models were developed to estimate the combined effects of 10 readily available demographic and clinical variables for estimating ESRD risk among kidney and donor candidates over a 15-year time window. The 15-year projections were compared with actual risk in a population of 53,000 living kidney donors.

Risk of ESRD was significantly associated with estimated GFR (eGFR), noninsulin-dependent diabetes, higher systolic BP, antihypertensive medication use, current and former smoking, and higher urinary-to-albumin creatinine ratio. There was also a small, graded association with obesity. Fifteen-year risk varied by age and race: for a 40-year-old with health variables similar to those of age-matched kidney donors, risk was 0.24 percent for black men, 0.15 percent for black women, 0.06 percent for white men, and 0.04 percent for white women.

Lifetime projected ESRD risks were highest in the youngest age group, particularly among young blacks. In contrast, many older individuals were at lower risk—even in the presence of health issues regarded as con-

traindications to donation. On analysis of observed 15-year ESRD rates among living kidney donors, postdonation risks were 3.5 to 5.3 times higher than predonation risks.

As an aid to evaluating and counseling potential donors, Grams et al. (1) developed an online risk tool (http://transplantmodels.com/esrdrisk/). They note that the magnitude of the additional risk after living kidney donation and the variations in risk associated with health characteristics remain unclear [Grams ME, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med* 2016; 374:411–421].

Belatacept improves long-term kidney transplant outcomes

Follow-up from a previous clinical trial shows improvements in kidney graft survival and function in patients receiving belatacept-based immunosuppression compared with those receiving cyclosporin, reports a study in *The New England Journal of Medicine*.

The researchers presented 7-year follow-up data from the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT). Kidney transplant recipients were randomly assigned to primary immunosuppression with a more intensive belatacept-based regimen, a less intensive belatacept regimen, or a cyclosporin regimen. Patient and graft survival and eGFR were assessed at 84 months.

Of 666 randomized patients, 660 received their assigned treatment. Complete follow-up data were available for 153 patients treated with the more intensive belatacept regimen, 163 patients treated with less intensive belatacept, and 131 patients treated with cyclosporin. Both the more and less intensive belatacept regimens were associated with a lower risk of death or graft loss compared with the cyclosporin regimen: hazard ratio of 0.35 in both groups.

Mean eGFR increased with both belatacept regimens but declined in the cyclosporin group. At 84 months, mean eGFR was 70.4 mL/min per 1.73 m^2 with more intensive belatacept and 72.1 mL/min per 1.73 m^2 with less intensive belatacept compared to 44.9 mL/min per 1.73 m^2 with cyclosporin. The three groups had similar cumulative rates of serious adverse events.

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Long-term follow-up of patients enrolled in the BENEFIT shows a 43 percent reduction in risk of death or graft loss with belatacept versus cyclosporin immunosuppression. Vincenti et al. (2) note that the survival advantage of belatacept emerged as early as 5 years of follow-up. They point out some important limitations of their study, including the lack of comparison with tacrolimus [Vincenti F, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med* 2016; 374:333–343 (Erratum: *N Engl J Med* 2016; 374:698)].

Are we performing too many tests for acute kidney injury?

Patients with acute kidney injury (AKI) undergo a large number of tests, many of which are of limited clinical value, reports a study in *BMC Nephrology* (5).

The retrospective study included 5731 AKI episodes in 4903 adult inpatients at an academic medical center over 1 year. Rates of test performance and abnormal results were calculated for various urine, blood, radiologic, and pathology tests, including differences by AKI stage. Diagnostic yield was determined by manual review of electronic medical records.

The most common known etiologies of AKI were ischemic acute tubular necrosis, prerenal azotemia, nephrotoxic acute tubular necrosis, and cardiorenal syndrome. The most frequently ordered tests were urinalysis and automated urine sediment examination. Ultrasound was performed in 10 percent of patients, and biopsy was performed in 0.5 percent of patients.

For nearly all tests, frequency increased with higher AKI stage. Some tests were more likely to show abnormal results at higher AKI stages, but others were not. The frequency of abnormal results ranged from 0 percent for antiglomerular basement membrane testing to 71 percent for urine protein tests.

For many tests, diagnostic yield was low. Selected blood and urine tests had low effects on AKI diagnosis and management, but radiologic tests were more likely to show clinical utility. The ratio of number of tests ordered to number of tests with clinical utility ranged from 5 for abdominal/pelvic computed tomography to 60 for urine eosinophils.

The optimal approach to diagnostic evaluation of AKI has not been defined; many different tests are available. This new study questions the diagnostic value of many of the large number of tests used in patients with AKI.

Many tests have limited clinical utility, even when the results are abnormal or positive. Leaf et al. (5) highlight the need to develop tests that provide "reliable or actionable data" for AKI diagnosis and management [Leaf DE, et al. Excessive diagnostic testing in acute kidney injury. *BMC Nephrol* 2016; 17:9].

Industry Spotlight

Fresenius, Plaintiffs ask for more time to settle suit

Fresenius is now working to settle a lawsuit brought against it by plaintiffs regarding its dialysate products GranuFlo and NaturaLyte. Although the company notified its own dialysis centers about cardiac arrest events in some patients using the products, it allegedly did not inform other dialysis centers at the same time it sent an internal memo, the *New York Times* reported.

The two Fresenius dialysates neutralize the normal buildup of acid in the blood.

In March 2016, reports noted that the company and plaintiffs asked a district court judge for more time to settle the multidistrict litigation (MDL) before scheduled trials are set to begin.

The company and the plaintiffs asked for a stay until August 31, 2016. "The requested stay of proceedings in this MDL and continuances of the first two bellwether trials are based upon good cause; they serve interests of judicial economy and promote litigation efficiency" as the parties attempt "to bring about a settlement-in-principle," they wrote, as reported in MassDevice.com.

Baxter's New Trial for High-Dose Dialysis

Baxter International Inc. announced in mid-March 2016 it had enrolled the first patient in a US clinical trial for VIVIA, an investigational home hemodialysis (HD) system being developed by Baxter (Deerfield, IL), and DEKA Research & Development (Manchester, NH).

The trial is designed to study more frequent, extended-duration nighttime home HD therapy (high dose HD), which will be performed in dialysis facilities as well as in homes. The study will assess product safety and adequacy of dialysis.

High dose HD therapy is a more frequent therapy usually performed as short daily treatments at least 5 days per week for sessions that typically run less than 4 hours, or as nocturnal treatments wherein sessions are conducted for more than 6 hours while a patient sleeps. High dose HD therapy is associated with improvements in survival and clinically important health measures, including health-related quality of life, compared with conventional hemodialysis, Baxter noted in its announcement.

The VIVIA investigational home hemodialysis system includes an integrated water purification module, safety sensors and one-button fluid infusion. Its use is limited by federal law to investigational use only in the US.

Market Realist, an investment information technology company, reported that Baxter's US peritoneal dialysis business exhibited the highest quarterly growth in the fourth quarter of 2015.

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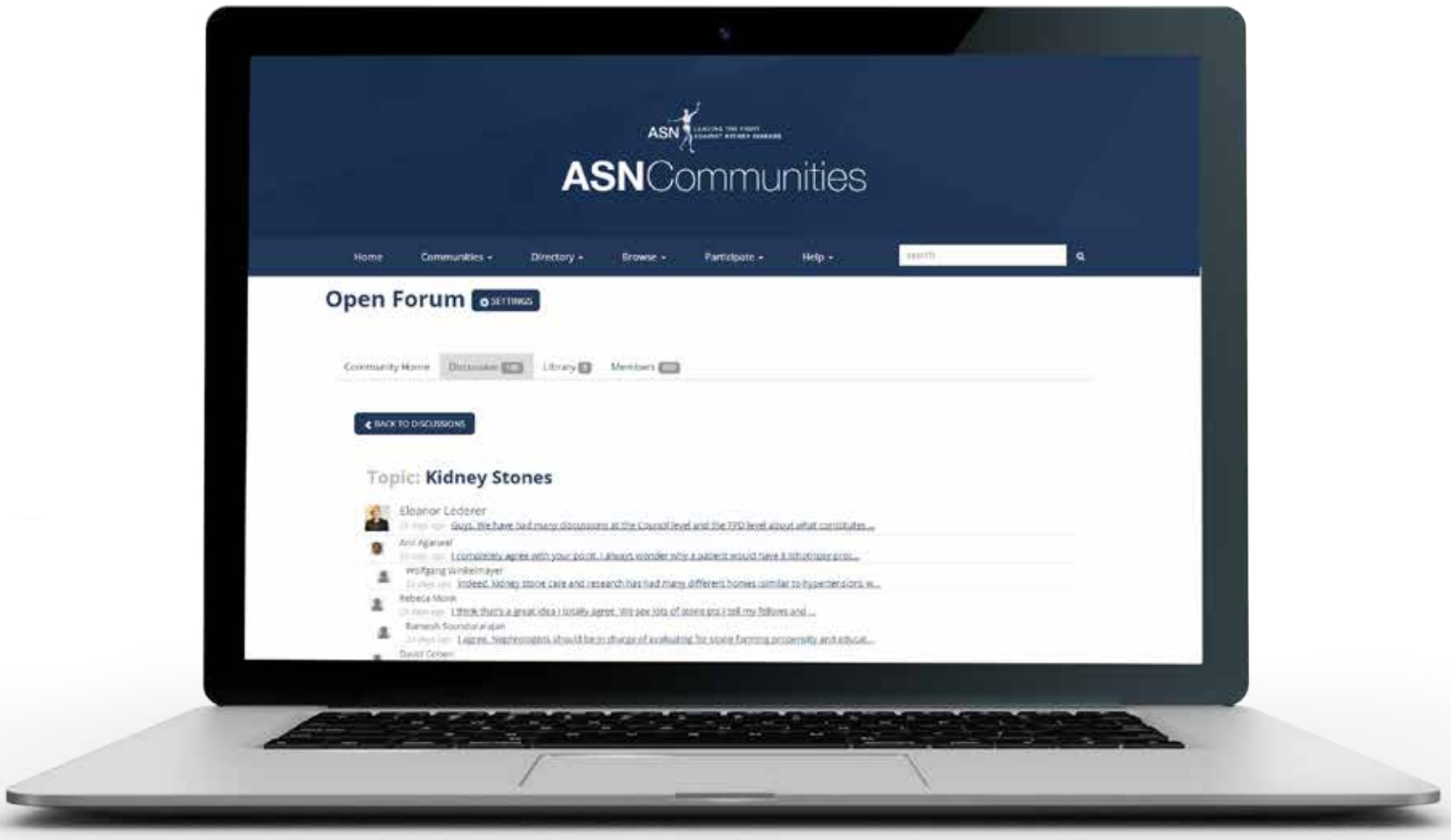

The new ASN Communities site is a members-only platform that allows ASN members from around the world to connect online, join discussions, and share knowledge and resources. Members are already using the Communities to get advice on issues they face in daily practice, to share ideas on addressing nephrology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

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