ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

April 2012 | Vol. 4, Number 4

ASN Partners with Campaign to Cut Wasteful Health Care Spending and Improve Care

By Kurtis Pivert

The American Society of Nephrology recently joined forces with other leading medical organizations in a campaign to identify and reduce wasteful health care spending while improving patient outcomes at the same time.

Called Choosing Wisely, the campaign is part of a multiyear effort spearheaded by the American Board of Internal Medicine (ABIM) Foundation "to help physicians be better stewards of finite health care resources," according to the foundation's website, www.abimfoundation.org. Together with eight leading medical specialist organizations and *Consumer Reports*, ASN is part of the first wave of the ABIM Foundation's campaign and was set to participate in a press conference unveiling the effort in Washington, DC, on April 4.

"ASN's dedication to this important effort reflects the society's commitment to curing kidney disease and the leading role ASN and its members play in improving the kidney health of nearly 30 million Americans," said ASN President Ronald J. Falk, MD, FASN.

Spiraling costs of care

The cost of health care in the United States has grown exponentially, burdening patients and providers alike. A recent report from the nonpartisan Congressional Budget Office estimated that up to 30 percent of health care charges are spent on procedures that are redundant, not necessary, or potentially harmful—jeopardizing patient safety and squandering resources. Failure to reduce this needless spending could lead to a dramatic increase in medical costs. The Centers for Medicare & Medicaid Services predicts that if no action is taken to reduce expenditures, health care spending will balloon to 19.3 percent of the U.S. gross

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Better Lab-Based Physician Reminders No Guarantee of Improved Kidney Patient Care

By Tracy Hampton

Enhanced laboratory-based treatment prompts may improve primary care physicians' prescribing habits in some situations, but that does not seem to be the case when it comes to prescribing recommended medications for elderly patients with chronic kidney disease (CKD). That was the conclusion of a study in the April *Clinical Journal of the American Society of Nephrology*.

"KDIGO [Kidney Disease: Improving Global Outcomes] guidelines on the care of patients with CKD will be released this year, and they will recommend a more complicated system of staging for people with the disease," said lead author Braden Manns, MD, of the University of Calgary and Alberta Kidney Disease Network, in Alberta, Canada. "Our research suggests that the use of more complex laboratory prompts may not improve care or outcomes."

Lab prompts for patient care

Effective treatments exist for patients with CKD, who are at risk for progression to end stage renal disease (ESRD) and cardiovascular disease. But these patients often do not receive optimal therapy. Perhaps physicians do not recognize earlier stages of the disease or are unaware of the serious complications that can arise as it progresses.

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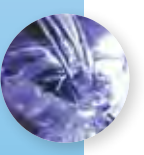

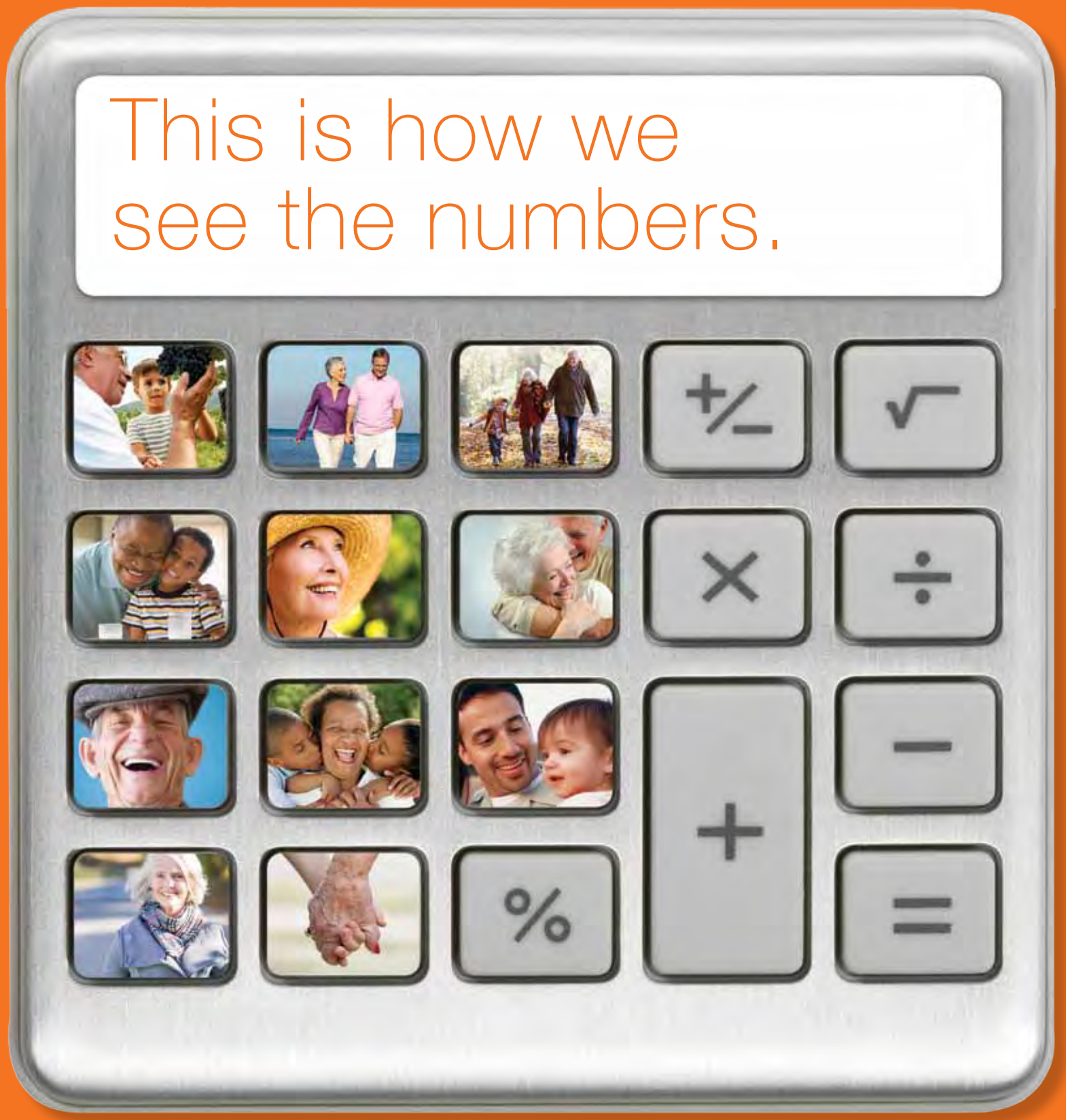

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Physician Reminders

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Clinical decision supports, such as laboratory prompts, have been shown to change physician practice in many randomized trials across a wide range of conditions and interventions, although only a handful of studies have noted an improvement in patient outcomes.

No randomized clinical trials have examined whether providing management-based recommendations along with laboratory reports of kidney function, measured as estimated GFR (eGFR) can help improve care for patients with CKD.

To investigate, Manns and his colleagues conducted a cluster randomized trial, which included patients treated at 93 primary care practices in Alberta, Canada, to test the effect of an enhanced eGFR laboratory prompt for patients with CKD managed by primary care physicians who ordered serum creatinine measurements. The enhanced prompt was compared with a standard laboratory prompt.

Care for CKD

During the study, which included 5444 patients 66 or younger with diabetes or proteinuria and available medication data, the researchers assessed the proportion of patients who received an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). "Nearly 20 percent of people over the age of 65 have CKD, and primary care physicians care for over 95 percent of these patients, without the involvement of specialists," Manns said.

The use of ACEi/ARB in the subsequent year was 77.1 percent in the standard group and 76.9 percent in the enhanced prompt groups. The researchers noted no difference in ACEi or ARB use between the standard and enhanced prompt groups when they repeated the analysis and considered only patients who were not using an ACEi or ARB at baseline. Nor did they see any difference when they considered the subgroup of patients with significant proteinuria in whom ACEi or ARB use could be considered standard of care. Also, when they considered the subgroup of 5055 elderly CKD patients with diabetes or proteinuria who had two eGFR measurements that were less than 60 mL/min per 1.73 m^2, in whom the diagnosis of CKD was confirmed according to clinical practice guidelines, they again noted no difference in ACEi or ARB use.

The investigators did note a significant difference in patients with severe CKD. In the subgroup of elderly patients with an eGFR of less than 30 mL/min per 1.73 m^2, ACEi or ARB use was 13 percent higher in the enhanced prompt group than in the standard prompt group.

"While we were hoping to increase the use of effective medications, we showed no difference in care or outcomes in the overall population," said Manns. "We did see a suggestion of benefit in the subgroup of patients with more severe kidney failure, perhaps because primary care doctors may have recognized that these patients were at particularly high risk; therefore, doctors may have been more responsive to management suggestions."

In a secondary analysis of 22,092 patients with CKD aged 18 years and older, the investigators found no difference in the likelihood of a composite clinical outcome (death, ESRD, doubling of serum creatinine, or hospitalization for myocardial infarction, heart failure, or stroke) with or without the enhanced prompt over an average of 2.1 years. Most of these individuals did not have available medication information because drug coverage is provided only for Albertans older than 65 years by the provincial health ministry,

"Automated reminders like this hold the promise of changing prescribing, lab ordering, and other behaviors with relatively little investment of time and money compared with other knowledge translation strategies, said Kaveh Shojania, MD, who was not involved with the work and is the director of the University of Toronto Centre for Patient Safety, in Ontario, Canada. "In practice, though, these reminders often have small effects (or nil effects, as in this case), as we showed in a meta-analysis in the *Canadian Medical Association Journal* a few years ago."

The data from this study suggest that enhanced management-based laboratory prompts cannot currently be recommended for routine use in all patients with CKD.

"We often think that all we have to do is publish 'high-quality clinical practice guidelines' and the job of improving care and outcomes is done; however, changing care and outcomes is challenging, even when the evidence is strong," Manns said.

The authors speculated on why the enhanced laboratory prompt was not effective, noting the possibility that no further improvement in primary outcome was possible, given the high baseline use of ACEi and ARB in both groups (approximately 77 percent) or that the enhanced prompt might not have been more useful than an already effective standard prompt. Physicians in the standard prompt group could access further information and management recommendations by visiting a website suggested in the laboratory report.

Also, the enhanced eGFR prompt might have been too complex, or physicians might have been overwhelmed with the number of patients receiving a prompt, the authors said.

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Kidney News

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-659-0599

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

Choosing Wisely

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domestic product, or $4.3 trillion, by 2019.

Choosing Wisely aims to start a conversation among patients, health care providers, and other stakeholders about using the most appropriate tests and treatments and avoiding care whose harm may outweigh the benefits. In addition to ASN, other medical societies announced as partners in the program's first wave include the American Academy of Allergy, Asthma & Immunology, American Academy of Family Physicians, American College of Cardiology, American College of Physicians, American College of Radiology, American Gastroenterological Association, American Society of Clinical Oncology, and the American Society of Nuclear Cardiology.

Organizations joining Choosing Wisely as part of a second wave include the American Academy of Otolaryngology–Head and Neck Surgery, American Association of Hospice and Palliative Medicine, American College of Rheumatology, American Geriatrics Society, American Society for Clinical Pathology, American Society of Echocardiography, Society of Hospital Medicine, and the Society of Nuclear Medicine.

Consumer Reports, the nation's leading independent, nonprofit consumer organization, will help the effort by partnering with other consumer groups to distribute patient-friendly resources to spark discussion about the need—or lack thereof—for many tests and procedures frequently ordered in the United States.

The Choosing Wisely goals align closely with ASN's mission. ASN regularly advocates for improved care for patients, better health for populations, and lower health care costs.

"The campaign reflects my personal commitment that ASN and its members work in partnership with patients and others to see that those managing their kidney health achieve the best possible quality of life now," Falk said. "ASN's focus on innovative approaches such as Choosing Wisely will lead the way to future cures."

ASN's "Five Things"

As part of the campaign, participating medical societies each came up with a list of five medical tests or procedures commonly used in their field that merit questioning and discussion (see sidebar, page 5).

In tackling issues such as avoiding nonsteroidal anti-inflammatory drugs (NSAIDS) in those with hypertension, heart failure, or chronic kidney disease (CKD), or not placing peripherally inserted central catheters (PICCs) in stage III–V CKD patients, ASN's choices for tests or procedures worth questioning will provoke dialogue both inside and outside the world of kidney disease.

Amy Williams, MD, chair of the ASN Quality and Patient Safety (QPS) Task Force, predicted that "it's going to shake up the medical community a bit and will make nephrologists as well as other physicians aware of specific kidney safety concerns."

Compiled by leaders in the field of kidney disease who have a thorough understanding of the evidence-based medicine behind the list, ASN's *Five Things* may help modify how other providers as well as nephrologists and team members treat patients with kidney disease. Incorporating changes into the work flow will require some adjustments, but "overall we are decreasing the number of unnecessary tests, decreasing harm to patients, and, if you look at it financially, we will be saving a lot of money. It's a win-win," Williams said.

ASN's *Five Things* aligns the highest level of patient care with evidence-based medicine, and may not reflect prevailing practices and structures. Williams described the current system as disjointed, adding that "we're reimbursed for the intensity of services that we provide the patient instead of being reimbursed for the outcome or the value of the care provided."

To those outside the kidney community, some recommendations may at first appear controversial. The recommendation to not perform routine cancer screening for dialysis patients with limited life expectancies with no signs or symptoms of cancer may raise eyebrows. Yet existing guidelines for cancer screening were not designed for those with chronic illnesses like kidney disease. They were designed for the general population and need to be tailored to fit the needs of patients with kidney disease. Treatment of pain and anemia also must be calibrated to meet the unique needs of the kidney patient, while following accepted guidelines.

Early involvement of the nephrologist is crucial for improving outcomes in patients with kidney disease, especially those undergoing dialysis. Whether preserving vasculature for future dialysis or deciding when to initiate the treatment, the nephrologist has to be part of these important conversations. The fourth recommendation—to avoid placing PICC lines in patients with stage III–V CKD without consulting nephrology—highlights the need for nephrologists to be involved with the kidney patient's care early on. Using PICC lines can lead to complications of the peripheral vasculature, which serve as the patient's "lifeline" (arteriovenous fistula) once they've started dialysis. ASN's *Five Things* list also emphasizes the critical partnership of patients, families, and the nephrology team in shared decision-making, such as whether to initiate dialysis and when to do so.

ASN's methodology

ASN's QPS Task Force—comprised of one member of each of the 10 ASN advisory groups, as well as ASN President Falk, ASN Public Policy Board President Thomas H. Hostetter, MD, and ASN Manager of Policy and Government Affairs Rachel Shaffer—addressed the ABIM Foundation's request for a *Five Things* list (see box, page 5). Together with Shaffer, members consulted with their respective advisory groups about the Choosing Wisely initiative and its goals, and were asked to submit tests and procedures that should be reconsidered or ceased altogether within their specific area of expertise in nephrology.

More than 100 ideas were submitted for review, which were narrowed to 20 potential items that the QPS Task Force believed were most influential. In an online survey the task force voted for what they considered the seven most important points and then narrowed the field to six top contenders, all of which received at least 50 percent of the votes.

The ASN Public Policy Board (which oversees the QPS Task Force) examined the six final potential items, and after weighing their potential impact on patient care unanimously voted to eliminate one item and approve the remaining five. With the list finalized, two members of the task force drafted evidentiary statements and a list of the primary organizations whose resources or research evidence supported each item.

ASN encourages members to continue the discussion about tests and procedures whose merits should be questioned and to share their opinions about the *Five Things* and ASN's methodology by contacting communications@asn-online.org.

Raising awareness

Partnering with the Choosing Wisely initiative is just one part of the ASN QPS Task Force's campaign to raise awareness about quality and patient safety issues in the kidney population and to develop and promote resources to help address them. They are consulting with ASN's 10 advisory groups to identify specific patient safety issues relevant to all areas of nephrology practice. The Task Force is also examining approaches to promote research in the field, including designing tools to help kidney care professionals address potential patient safety problems, and authoring position papers on key points. Another important step is educating patients and their families about their roles in promoting safety and quality, and including them as members of the nephrology team. Among other things, the Task Force is investigating the possibility of recommending that ASN participate in the Department of Health and Human Services Partnership for Patients to continue raising the profile of kidney patient safety.

The Choosing Wisely initiative and ASN's *Five Things* aim to start the conversation between patients and physicians on making informed choices to deliver the most appropriate care. To learn more about the ABIM Foundation and its Choosing Wisely campaign visit www.ChoosingWisely.org.

ASN Quality and Patient Safety Task Force Outlines Top "Five Things" List for Choosing Wisely Campaign

Aim Is to Foster Communication Between Doctors and Patients About Appropriate Tests and Procedures

The ABIM Foundation asked each partnering society to review its current practices and suggest five items that, based on the latest evidence on disease management and treatment, are overused or misused or could jeopardize patient safety and care. Each society submitted its list of *Five Things Physicians and Patients Should Question*.

ASN's *Five Things* list includes tests or procedures regularly performed whose value should be weighed and discussed among patients and providers to determine whether they are appropriate for their individual care.

1 Don't perform routine cancer screening for dialysis patients with limited life expectancies without signs or symptoms.

Due to high mortality among end stage renal disease (ESRD) patients, routine cancer screening—including mammography, colonoscopy, prostate-specific antigen (PSA), and Pap smears—in dialysis patients with limited life expectancy, such as those who are not transplant candidates, is not cost effective and does not improve survival. False-positive tests can cause harm: unnecessary procedures, overtreatment, misdiagnosis, and increased stress. An individualized approach to cancer screening incorporating patients' cancer risk factors, expected survival, and transplant status is required.

- **Sources:** U.S. Renal Data System, American Society of Nephrology, American Society of Transplantation, *Archives of Internal Medicine, Seminars in Dialysis.*

2 Don't administer erythropoiesis-stimulating agents to chronic kidney disease patients with hemoglobin levels greater than or equal to 10 g/dL without symptoms of anemia.

Administering erythropoiesis-stimulating agents (ESAs) to chronic kidney disease (CKD) patients with the goal of normalizing hemoglobin levels has no demonstrated survival or cardiovascular disease benefit, and may be harmful in comparison to a treatment regimen that delays ESA administration or sets relatively conservative targets (9–11 g/dL). ESAs should be prescribed to maintain hemoglobin at the lowest level that both minimizes transfusions and best meets individual patient needs.

- **Sources:** U.S. Food and Drug Administration, *The New England Journal of Medicine* (multiple publications).

3 Avoid nonsteroidal anti-inflammatory drugs in individuals with hypertension or heart failure or chronic kidney disease of all causes, including diabetes.

The use of nonsteroidal anti-inflammatory drugs (NSAIDS), including cyclo-oxygenase type 2 (COX-2) inhibitors, for the pharmacological treatment of musculoskeletal pain can elevate blood pressure, make antihypertensive drugs less effective, cause fluid retention, and worsen kidney function in these individuals. Other agents such as acetaminophen, tramadol, or short-term use of narcotic analgesics may be safer than and as effective as NSAIDs.

- **Sources:** National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) *Clinical Practice Guidelines for Chronic Kidney Disease; Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral;* American Heart Association*; Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; Scottish Intercollegiate Guidelines Network on Management of Chronic Heart Failure.*

4 Don't place peripherally inserted central catheters in stage III–V chronic kidney disease patients without consulting nephrology.

Venous preservation is critical for stage III–V chronic kidney disease patients. Arteriovenous fistulas (AVF) are the best hemodialysis access, with fewer complications and lower patient mortality, versus grafts or catheters. Excessive venous puncture damages veins, destroying potential AVF sites. Peripherally inserted central catheter (PICC) lines and subclavian vein puncture can cause venous thrombosis and central vein stenosis. Early nephrology consultation increases AVF use at hemodialysis initiation and may avoid unnecessary PICC lines or central/peripheral vein puncture.

- **Sources:** *Fistula First Breakthrough Initiative–National Coalition Recommendation for the Minimal Use of PICC Lines; American Society of Diagnostic and interventional Nephrology: Guidelines for Venous Access in Patients with Chronic Kidney Disease; Seminars in Dialysis; National Kidney Foundation Clinical Practice Guidelines for Vascular Access; The Renal Network, Inc. PICC Line Resource Toolkit; Clinical and Experimental Nephrology.*

5 Don't initiate chronic dialysis without ensuring a shared decision-making process among patients, their families, and their physicians.

The decision to initiate chronic dialysis should be part of an individualized, shared decision-making process among patients, their families, and their physicians. This process includes eliciting individual patient goals and preferences and providing information on prognosis and expected benefits and harms of dialysis within the context of these goals and preferences. Limited observational data suggest that survival may not differ substantially for older adults with a high burden of comorbidity who initiate chronic dialysis versus those managed conservatively.

- **Sources:** Renal Physicians Association End-of-Life Care Guidelines, *Pediatric Nephrology, Clinical Journal of the American Society of Nephrology, Journal of Pediatrics, Nephrology Dialysis Transplantation, Archives of Internal Medicine, The New England Journal of Medicine, Palliative Medicine.*

ASN Quality and Patient Safety Task Force

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- Allison Eddy (Physiology and Cell Biology Advisory Group)
- Ronald Falk (ASN Council Liaison)
- Jeffery Fink (CKD Advisory Group)
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MicroRNAs Grab Scientific Spotlight in Kidney Disease Research

The scientific spotlight in genomics research is no longer aimed solely at DNA. It is now being shared with DNA regulatory elements such as microRNAs (miRNAs), a family of small, noncoding RNAs that control gene expression by inhibiting translation of their target RNAs.

In new research, investigators found that gene expression for one miRNA—miRNA-21—was greater in renal fibrosis than in normal kidneys. The hope is that one day anti–miRNA-21 therapy could benefit patients with chronic kidney disease.

The research, conducted with laboratory animal models of kidney disease and with human tissue samples, was published in the February 15, 2012, issue of *Science Translational Medicine* (STM). The article is titled "MicroRNA-21 promotes fibrosis of the kidney by silencing metabolic pathways."

Since the 2000 discovery of miRNAs in the human genome, scientists have uncovered evidence of their contribution to the pathophysiology of diseases ranging from cancer to kidney disease. About 1000 miRNAs have been identified in the human genome thus far.

In kidney research, miRNAs are being pursued in areas as diverse as transplant immunology, podocyte development, polycystic kidney disease, renal failure, and fibrosis. In the STM study, scientists at the University of Washington and Regulus Therapeutics, Inc., found that although miRNA-21 does not cause renal fibrosis, it amplifies the kidney's responses to injury, resulting in the development of fibrosis.

"MicroRNA-21 of itself does not create injury and fibrosis, but it worsens it," said Jeremy S. Duffield, MD, PhD, coauthor of the STM article and associate professor of medicine in the division of nephrology at the University of Washington.

A total of 24 miRNAs were initially identified by the University of California–Regulus research group when they conducted gene expression profiles to determine the most commonly upregulated regulatory elements in kidney fibrosis.

The investigators tested the role of several of these miRNAs, but miRNA-21 became the lead target because it was upregulated consistently in the animal models for kidney fibrosis and also in tissue samples from kidney transplant patients with nephropathy. Moreover, a previous study at another laboratory linked miRNA-21 to cardiac fibrosis. That research was published in *Nature* in 2008.

In fact, 24 miRNAs were initially identified by the University of California–Regulus research group when they conducted gene expression profiles to determine the most commonly upregulated regulatory elements in kidney fibrosis. They decided to focus on miRNA-21 because a previous study at another laboratory had linked it to cardiac fibrosis, and it was upregulated consistently in the researchers' animal models for kidney fibrosis and in tissue samples from kidney transplant patients with nephropathy.

Data suggest that anti–miRNA-21 could have a therapeutic benefit in patients with chronic kidney disease.

Induced kidney injury linked to miRNA-21

In normal kidneys of laboratory animals, Duffield and his colleagues detected miRNA-21 expression in the medulla and papilla and in some perivascular cells. However, miRNA-21 expression becomes widespread in kidneys with experimentally induced injuries. The researchers also found that miRNA-21 was markedly upregulated in the pericyte precursors of the scar-forming myofibroblasts in the kidney, and miRNA-21 expression was much higher in inflammatory macrophages than in resident macrophages.

The researchers also found that miRNA-21 was upregulated in the kidneys of laboratory animals soon after experimentally induced renal injury but before the development of fibrosis. Levels of miRNA-21 were much higher in prospectively collected tissue samples from the transplanted kidneys of patients with nephropathy than in tissue samples from healthy individuals. These results suggest that miRNA-21's upregulation is an early response to injury.

To define the precise role of miRNA-21 in kidney fibrosis, the researchers knocked out the gene that codes for miRNA-21 in laboratory animal models and then induced kidney injury. Less interstitial fibrosis occurred in the miRNA-21 knockout mice than in their miRNA-21 intact litter mates.

The miRNA-21 knockout mice were healthy, with normal fertility, body weight, and life span of at least 6 months of age. Although surprising, the finding perhaps can be explained by the activity of miRNA-21 in laboratory animals with normal kidney functioning. "Our work shows that miRNA-21 is not active despite being highly expressed in normal kidney," said Duffield.

The animals' surprisingly good health is consistent with the "lack of activity" of the miRNA-21 in normal healthy mice, Duffield said, on the basis of observations that the molecular signature of normal unstressed kidney does not indicate miRNA-21 deficiency. The molecular signature of miRNA-21 deficiency is only apparent in response to stress, he pointed out.

In the laboratory animals with experimentally induced kidney fibrosis, the scientists systemically administered proprietary oligonucleotide drugs targeting miRNA-21. The experimental anti–miRNA-21 therapy also reduced the extracellular matrix proteins that contribute to fibrosis, as well as reducing protein leakage into the urine, a marker of chronic kidney disease.

"Genetic deletion of miRNA-21 in preclinical models protected kidneys from fibrosis, and treatment with anti-miRNAs targeting miRNA-21 also blocked fibrosis in preclinical models," said Duffield. "Taken together, these data suggest that anti–miRNA-21 could have a therapeutic benefit in patients with chronic kidney disease."

Compounds are now being screened to identify potential candidates for clinical studies. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are currently the main therapies for kidney fibrosis.

Daniel R. Salomon, MD, who was not involved in the research, said that he applauds the University of Washington–Regulus work as "good science. . . done using cutting-edge methods."

However, because the expression of miRNA-21 is not limited to the kidney, the development of an anti–miRNA-21 therapy—and any miRNA-targeted treatment—must consider the systemwide effects of blocking an endogenous factor "which is a normal response to injury" in every single tissue in the body, said Salomon, who is program medical director of the Scripps Health Center for Organ Transplantation and professor and director of the Laboratory for Functional Genomics of The Scripps Research Institute in La Jolla.

Because human biology is so complex, one factor rarely is responsible for a biological process as central to health and tissue integrity as fibrosis, added Salomon, who heads a study on miRNA expression in human immunity sponsored by the National Institutes of Health.

In addition to avoiding systemwide effects, anti-miRNA therapies must use safe and reliable delivery methods specific to the kidney and avoid toxicity derived from off-target effects and from activation of the innate and adaptive immune response, wrote Jordan Yz Li, PhD, and colleagues in a review article, "The role of microRNAs in kidney disease," published in 2010 in *Nephrology*.

Avenues for drug discovery

Duffield and his colleagues identified other possible avenues for drug discovery in kidney disease by performing gene expression profiles on the miRNA-1 knockout mice. Upregulated in the knockout laboratory animals were groups of genes involved in metabolic pathways, including lipid metabolism and enhanced oxygen radical production. The analysis revealed that peroxisome proliferator-activated receptor-α (PPARα) and Mpv17l metabolic pathways are critical miRNA-21 targets, the researchers reported.

Peroxisome proliferator-activated receptors are a group of nuclear receptor proteins that act as transcription factors regulating the expression of genes. The researchers determined that PPARα is a major upstream regulator of lipid metabolism. MicroRNA-21 repressed Mpv171, a mitochondrial inhibitor of reactive oxygen species generation, correlating closely with enhanced oxidative kidney damage.

"It is likely that regulating metabolic pathways including lipid and fatty acid oxidation will become new targets for therapeutics in kidney disease," Duffield said, noting that the University of Washington–Regulus study was the first to show that metabolic pathways contribute to the development of kidney disease.

"These are important pathways that prevent damage in the kidney," Duffield said. "MicroRNA-21 blocks these pathways. The repression of these networks of genes leads to further injury to the kidney epithelium."

The gene expression profiles produced another unexpected finding: before experimentally induced injury, the kidneys of both miRNA-21 knockout mice and miRNA-21 intact mice shared similar genetic profiles.

Only in the injured kidney was miRNA-21 able to repress the critical genes that drive kidney disease. Duffield and his colleagues predict that the therapeutic strategies that target miRNA-21 will be specific because in healthy cells of other organs, miRNA-21 is likely to be inactive.

In the animal models, kidney injury was induced by either unilateral ureteral obstruction of the flow of urine or unilateral ischemia reperfusion injury. The slow initial injury of unilateral ureteral obstruction accelerates with time. In ischemia reperfusion injury, a temporary occlusive clamp is placed on the renal artery for about 30 minutes, followed by restoration of the flow before surgical closure. Severe injury accompanies the reperfusion, with only partial repair.

National Implementation of CROWNWeb Imminent

The national rollout of CROWNWeb for all federally certified dialysis clinics will soon be complete, according to the Centers for Medicare & Medicaid Services (CMS). A requirement of the Conditions for Coverage (CfC), CROWNWeb (Consolidated Renal Operations in a Web-Enabled Network) is an online gateway that securely transfers data to the CMS for processing claims and tracking patient outcomes and facility performance.

The implementation comes after a long trial run with both large and small dialysis providers. CROWNWeb is designed for end stage renal disease (ESRD) dialysis providers to comply with the CfC's electronic submission requirement. It replaces paper forms with a web-based environment that gives patients and researchers access to information on dialysis centers (through Dialysis Facility Compare) and, for the first time, the complete ESRD population. By migrating online and using electronic medical records (EMRs), the CMS hopes to reduce the costs of reporting compliance while improving patient care using real-time data.

A clinical manager from the FMC-NA dialysis facility in Maplewood, NJ, said she "much prefers CROWNWeb to the old paper forms; the system is fast, time-saving, and crystal clear. When I start entering a 2728 form, half of the information is already there as the result of the batch download process."

The data—including patient characteristics, dialysis values, and CMS facility reports—will be stored in a central location and can be securely accessed anywhere online. This always-on access will be critical for continuity of care in patients who move or are temporarily displaced from their dialysis clinic. The CROWNWeb transient patient feature gives providers current patient and dialysis information so they can make informed treatment decisions.

The FMC-NA clinical manager noted that "in addition we can use CROWNWeb to check that the patient census is correct and to transfer patients from one facility to another. We have found that the printed 2728 forms are much more readable when we receive the copy of a form from another facility. This will be more of a benefit once all facilities are on CROWNWeb."

The CMS began testing CROWNWeb with large dialysis organizations (LDOs) and built in an electronic data interface (EDI) to facilitate batch processing of large amounts of patient and facility data. However, with smaller dialysis providers unable to use the LDOs' EDI, alternate methods were needed. To address this, the National Renal Administrators Association (NRAA) created a health information exchange (HIE).

"Our members anticipated the rollout of CROWNWeb," said NRAA Executive Director Marc Chow," but they've had concerns about the system's stability and functionality, as well as the expense of manual data entry."

The NRAA HIE, an information routing hub, lets small and mid-sized facilities transmit data to the CMS through the CONNECT gateway and the Nationwide Health Information Network.

The NRAA HIE is participating in the CROWNWeb Phase III Pilot with four EMR vendors and eight dialysis facilities, with additional EMRs preparing for certification. "NRAA members want an effective way to submit CROWNWeb data," Chow said, "and we believe dialysis centers with EMRs will utilize the NRAA HIE instead of the Single User Interface, which requires manual data entry.

"Because the HIE function is new, we expect to gradually roll it out to new users and facilities in order to repair any technical issues and ensure the new service is stable," said Chow. He noted that the February 29, 2012, extension of the Phase III Pilot "will give CMS adequate time to continue working toward a successful integration of the LDOs' EDI, the Single User Interface, and the NRAA HIE in CROWNWeb."

A rocky road

In 2009, *Kidney News* spoke with Ellen Wood, MD, of SSM Cardinal Glennon Children's Medical Center in St. Louis about how the new CfC would impact her practice. Since then, her pediatric nephrology unit has been preparing for CROWNWeb's rollout, but she and her staff have faced challenges acquiring information for personnel access; scheduling the mandated training; and adjusting to, and repeating tasks for, each new go live date.

"The new reporting system clearly takes more time, which takes nurses and our social worker away from patient-oriented activities," Wood said. "So far we have seen none of the benefits that we eventually hope to see."

Such concerns are echoed by other providers, some of whom have encountered difficulties in activating QualityNet Identity Management System (QIMS) accounts. Modeled to allow facilities to manage their CROWNWeb access, QIMS requires that each dialysis center have at least one designated Security Official account and one End User Manager account, with neither position being held by the same person. The clinical manager from FMC-NA said "I absolutely love CROWNWeb, but it was a nightmare to sign up. It took several weeks and many phone calls to the CROWNWeb help desk to get my log-in working. At one point the system was down for 3 weeks, and I had to start the process all over." She added that "it has been frustrating that system problems with receiving the batch downloads have been delaying completion of 2728 forms for new patients, a process that was working in prior pilots."

Although the rollout has been delayed by the extension of the Phase III Pilot, CROWNWeb is just one of several recent CMS mandates to affect dialysis providers. These include the ESRD Quality Improvement Program (QIP), necessitating use of the Centers for Disease Control and Prevention National Healthcare Safety Network to report infections in dialysis patients, and the evolving use of bundled payments, all of which create new challenges for dialysis facilities large and small. To learn more about CROWNWeb and its requirements, visit the website http://www.projectcrownweb.org.

Accountable Care Organizations: Who Can Join and What Will They Mean for Nephrology?

Ever since the Centers for Medicare & Medicaid Services (CMS) released the Accountable Care Organization (ACO) final rule in October 2011, the American Society of Nephrology (ASN) has been analyzing the rule to determine how it may affect patients with kidney disease and the nephrologists who care for them. In the second of a series of Q & A articles with members of the ASN ACO Task Force, Amy Williams, MD, Dan Weiner, MD, and Emily Robinson, MD, answer questions about who can join ACOs and about other new care delivery models.

Can my nephrology practice join an ACO?

Amy Williams: Nephrologists and nephrology practices are eligible to join an ACO and have patients assigned to them according to the two-step process described in the first article of this series (March *Kidney News*). If the patient received any primary care services from a primary care provider in an ACO, but has received most of these services from a specialist (e.g., a nephrologist) eligible to have patients assigned to them as part of an ACO, the patient will be assigned to the specialist and his or her ACO.

ACO providers that are not eligible to have ACO patients attributed to them (medical and surgical specialists or acute-care hospitals) will be able to participate in more than one ACO. Thus, if a nephrologist associated with an ACO is not identified to be the provider of primary care services attributed to any patient in the ACO, that nephrologist is eligible to participate in more than one ACO. However, if the primary care services of the nephrologist are used to assign the patient to the ACO, the nephrologist must be exclusive to that ACO for the purposes of the Shared Savings Program ACO. The ACO will report the Tax Identification Numbers (TINs) and National Provider Identifiers for each practice and individual provider associated with them to the CMS.

Can dialysis organizations join an ACO? Would they want to?

Dan Weiner: Dialysis organizations cannot form an ACO themselves, but they can be a part of a larger ACO structure. Similarly, individual nephrologists can and will be part of ACOs, primarily as specialists and, in rare occasions, as designated primary care providers. In fact, if nephrologists bill under more than one TIN, they can be included in more than one ACO. Given that nephrologists do, in some circumstances, act as primary care physicians and that their group of primary care patients will be far smaller than that of most primary care providers, this policy may enable nephrologists to maintain the primary care relationships with some patients, albeit with some administrative uncertainty.

In one sense, dialysis providers will definitely want to participate in ACOs, and ACOs should want the input of dialysis providers. The dialysis team has far more contact with a dialysis patient than any other medical provider the patient is likely to encounter, and the dialysis provider is uniquely positioned to monitor health and health interventions that are most relevant to a dialysis patient. Additionally, given that the major health care issue for a dialysis patient is almost always the sequelae of kidney failure and kidney failure itself, the expertise of the dialysis provider in managing these issues is critical for optimizing patient success. Finally, even though the ACO final rule specifically mentions antitrust concerns, dialysis providers will not want to lose possible patients to other nearby facilities, suggesting that, if possible, the providers will want the opportunity to collaborate with local ACOs. However, there are inherent problems.

First, dialysis patients make up a small proportion (only about 1 percent) of Medicare beneficiaries, suggesting that ACOs will not develop efficient practices for caring for these patients. Second, given the varying catchment areas of dialysis facilities and of ACOs, it is likely that a single dialysis facility will end up working with multiple ACOs. With each ACO having its own administrative and information technology infrastructure—not to mention the CMS infrastructure and reporting requirements for dialysis units (e.g., Consolidated Renal Operations in a Web-enabled Network [CROWNWeb]), their chain affiliations (if present), and local departments of public health—the administrative burden could be substantial. Third, the quality metrics for dialysis units under the Quality Incentive Program (QIP) and for ACOs within the final rule are inherently different, and quality indicators for the general population often are not applicable to dialysis patients.

What will it mean for me as a nephrologist if my dialysis patients are attributed to an ACO?

Emily Robinson: As with patients, there will be pros and cons for nephrologists if their patients are attributed to an ACO. It is hoped that improvements in communication and coordination of care plans will help the nephrologist as well as the patient.

However, nephrologists will need to be increasingly diligent in ensuring that medication changes and screening tests ordered by primary care physicians to meet quality guidelines are actually appropriate for each individual patient, and they may have to spend more time talking with patients and other physicians about the appropriateness of these interventions.

Dialysis centers have already set up reporting systems for documentation in dialysis patients, but these are different from the systems used for ACO reporting. Thus, a nephrologist/dialysis unit that joins an ACO may be required to use multiple reporting systems for documentation, increasing work, confusion, and financial burden to put the systems in place. Although there are no specific provisions of the ACO that counter the Prospective Payment System bundle and QIP, the amount of effort to satisfy both systems is quite large. It also would remain to be seen whether referral patterns to nephrologists would change. Although patients in a specific ACO do not need to see all of their specialists in that ACO, primary care physicians might urge them in that direction.

How does CMS plan to coordinate the ACO reporting and quality measurements with the QIP program reporting and quality measurements?

Dan Weiner: Unfortunately, no coordination is planned for data reporting or quality metrics between these two CMS programs. This is somewhat ironic, given the time and expense that CMS has devoted to developing dialysis-specific reporting (in the form of CROWNWeb) and dialysis-specific quality measures. The most notable item here is the lack of applicability of the ACO performance measures to a dialysis population.

For example, colorectal cancer screening and breast cancer screening likely are neither cost effective nor beneficial for dialysis patients aged 50 to 75 years who are not eligible for transplantation and therefore have life expectancies of less than 5 years. Similarly, there are no evidence-supported blood pressure (BP) targets, hemoglobin A1C targets, or low-density lipoprotein cholesterol targets for dialysis patients, and no data to support the supposition that any intervention to address BP levels, diabetes control, or hypercholesterolemia has a benefit to the dialysis population. In theory, one could be concerned that ACOs will aggressively pursue these performance metrics at increased cost and increased burden both to the health care system and to individual patients.

Is CMS going to allow formation of renal ACOs?

Emily Robinson: At this time, the answer is no. In the final rule the CMS did not allow for the formation of any specialty ACOs, including a renal/ESRD ACO, stating "although we do not see the need to design distinct ESRD or cancer specific ACOs, neither of these provider types are in any manner excluded from participation in an ACO." So, for the time being, the only types of ACOs that can form are "general" ACOs.

What other kinds of new care delivery models exist?

Amy Williams: The ACO model is not the only one being considered to improve the value of care provided. The Federally Qualified Health Center (FQHC) Advanced Primary Care Practice Demonstration's Patient Centered Medical Home (PCMH) program is another primary care–based comprehensive, coordinated care model sponsored by the CMS in collaboration with the Health Resources Services Administration (HRSA).

As with the ACO model, responsibility for chronic care is centered on the primary care team with the goal of providing patient-centered care by improving care coordination and promoting health while decreasing the overall cost of care. During the demonstration period, individuals with ESRD are excluded. The PCMH involves the subspecialist by designating the subspecialist a PCMH Neighbor with a well-defined graduated role in the care of PCMH patients with subspecialty illnesses. This model would designate the nephrologist as having primary responsibility for patients with acute complicated renal disease

as well as chronic complicated subspecialty care needs, such as those receiving dialysis or having undergone renal transplantation.

Emily Robinson: In addition, the Centers for Medicare and Medicaid Innovation (CMMI) has statutory authority to test new innovative models of care and could potentially conduct a demonstration or pilot project on a renal-specific care delivery model.

The ASN ACO Task Force and members of the ASN leadership are in an ongoing dialogue with the Innovation Center, as it is known, about potential opportunities and challenges that a nephrology integrated care model could yield. The ASN has developed a series of principles about the formation, structure, and scope of nephrology integrated care models that the society has discussed with the Innovation Center and made available on the ASN home page (www.asn-online.org).

Stay tuned: The next Q & A will focus on nephrology integrated care delivery models and ASN's principles related to a potential pilot project or demonstration project. If you have questions you would like the ACO Task Force to address in this series, please email ASN Manager of Policy and Government Affairs Rachel Shaffer at rshaffer@asn-online.org.

Amy Williams, MD, is affiliated with the Mayo Clinic in Rochester, MN; Dan Weiner, MD, is affiliated with Tufts Medical Center in Boston, MA; and Emily Robinson, MD, is affiliated with the Brigham and Women's Hospital in Boston, MA.

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IMPORTANT DATES (2012)

Abstracts

Wednesday, April 4	**Abstract Submission Site Opens**
Wednesday, June 6	**Abstract Submission Site Closes (11:59 p.m. EDT)**
Wednesday, July 18	Late-Breaking Abstracts Submission Site Opens
Wednesday, September 12	Late-Breaking Abstracts Submission Site Closes (11:59 p.m. EDT)

Registration & Housing

Wednesday, June 6	Registration and Housing Opens
Wednesday, September 12	Early Registration Closes
Friday, September 28	Housing Closes
Wednesday, October 24	Advance Registration Closes
Tuesday, October 30	Onsite Registration Opens

Kidney Week

Tuesday, October 30 – Wednesday, October 31	Early Programs
Thursday, November 1 – Sunday, November 4	Annual Meeting

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Clinical Measure of Frailty Predicts Risk of Delayed Graft Function

A 10-minute bedside test of frailty can predict the likelihood of delayed graft function (DGF) in patients undergoing kidney transplants, according to a new study in the *Archives of Surgery*. Frailty has emerged as an important characteristic of health state in the elderly, but in this study, the effect of frailty on DGF was independent of age.

"It's actually quite difficult to predict who is at higher risk for delayed graft function based on recipient characteristics," said senior author Dorry Segev, MD, PhD, associate professor of surgery at Johns Hopkins School of Medicine in Baltimore. While hyperacute rejection is largely due to known factors such as blood type—"showstoppers," in Segev's words—and long-term organ failure is controlled in large part by how well donor and recipient tissues match, the factors controlling DGF have been harder to tease apart.

Even the underlying cause of DGF is unknown, he said. "That's the million dollar question." The suspicion is that inflammation in the patient causes inflammation in the kidney, resulting in ischemia reperfusion injury. "The thinking is that there is something about the milieu that you're putting that kidney into, some inflammatory state in the recipient, that is causing it."

"Frailty is well documented as an inflammatory state," he went on, leading to the hypothesis that frailty might influence DGF. "It makes sense biologically."

To test that hypothesis, Segev and colleagues prospectively enrolled 183 kidney transplant recipients, all of whom had been cleared by a surgical team for transplantation, and measured their level of frailty immediately before surgery, using a five-part scale:

- shrinking, assessed by asking the patient if they had unintentionally lost more than 10 pounds in the past year.
- exhaustion, assessed by two questions about motivation and effort.
- low physical activity, determined by asking about frequency and duration of leisure activities.
- time required to walk 15 feet, adjusted for sex and height.
- grip strength, measured by handheld dynamometry, and adjusted for body mass index.

"The test is entirely objective and takes about five to 10 minutes to administer," Segev said. The scale has been well validated in the elderly, and is starting to be validated in surgical and kidney disease populations.

In Segev's study, patients had a mean age of 53 years, and had been on dialysis for a median of 2.5 years. He found that DGF occurred in 15 percent of nonfrail patients, but 30 percent of frail patients. The approximately twofold greater risk for DGF remained after adjusting for multiple variables, including patient age, diabetes, and obesity. "Frailty was the strongest predictor of delayed graft function of any factor having to do with the recipient."

The measure of frailty has a number of potential uses, according to Segev. "One question is who is a good candidate for a kidney transplant. We have a fairly poor ability to predict which patients are going to do well and which are going to do poorly," particularly in older adults. "And this is important because kidney transplant is not the only therapy for these patients," since dialysis remains an option.

"The second question is how to optimize someone's transplant care," including organ characteristics. "In a frail patient, I might think twice about putting in a kidney that's been out of the body for 30 hours, while in a non-frail patient I might be more willing to do that, because I know the risk for developing delayed graft function is half that of the frail patient." Decisions about length of hospital stay and medications may also be reviewed based on frailty.

If a patient is frail, can presurgical treatment improve their frail state? "That's the other million-dollar question in this area," Segev said. Work in this field, called "prehabilitation," is just starting to emerge. "It would appear intuitive that such rehabilitation would do something useful, but there are no studies completed to know whether that's true or not."

Doubts remain

"There is a lot of interest in characterizing the underlying health status of patients before they undergo kidney transplants," commented Peter Reese, MD, assistant professor of medicine and biostatistics in the Renal Electrolyte and Hypertension Division at the University of Pennsylvania in Philadelphia.

"There are some patients who are worse off than their ages or comorbidities would lead you to believe, and frailty is potentially a powerful syndrome that could be used to predict which patients are going to do well after kidney transplant."

"But whether or not it would be helpful clinically is unclear," he said, "partially because it's not easy to measure." Most clinicians, he noted, don't routinely perform handheld dynamometry or walking speed, and the measure of weight loss requires longitudinal data that may not be available. "This would significantly add to the burden of preoperative preparation for kidney transplant patients. Something like frailty may be very important. I'm just not sure frailty itself will ultimately be the one we need to measure. We need to compare it to other things," in order to find the one that best combines clinical ease with predictive value, Reese said.

Nonetheless, he said, "some kind of summary measure of the patient's physiologic reserve could be very important, and could add a lot of value" to presurgical planning. "For some patients we might recommend they undergo physical therapy prior to transplant." For others, who don't look like good risks on paper or to the eye, but who are not frail or who have good physical status, "maybe we would accept them, whereas previously we might have turned them down." Whatever the measure of physical reserve that the field chooses, "we are hoping that such measures would allow us to look under the hood."

Journal View

No interactive effect of intensive blood pressure and glycemic control

The combination of intensive blood pressure (BP) control and intensive glycemic control doesn't produce an additional benefit in preventing microvascular complications of type 2 diabetes, concludes a trial in *Kidney International*.

The researchers analyzed data from the randomized ACCORD-BP trial, including 4733 older adults with type 2 diabetes and hypertension. Patients were separately assigned to intensive or standard BP control (systolic BP target <120 mm Hg versus 140 mm Hg) and intensive or standard glycemic control (target HbA1c <6.0 percent versus 0.07–0.79 percent). Microvascular outcomes were assessed, including a composite of renal failure and retinopathy plus nine individual outcomes.

At a mean follow-up of 4.7 years, there were no significant differences in the composite outcome rates between groups: 11.4 versus 10.9 percent with intensive versus standard BP control, and 11.1 versus 11.2 percent with intensive versus standard glycemic control. The risk of microalbuminuria was lower with intensive BP control (hazard ratio 0.84). Intensive glycemic control was associated with a "near-significant" reduction in macroalbuminuria.

There was no evidence that the combination of intensive BP control and intensive glycemic control had any interactive effect. None of the study treatments were effective in preventing renal failure.

Previous trials have shown reductions in the risk of some microvascular complications of type 2 diabetes with intensive BP or glycemic control. The new ACCORD-BP results show a reduced risk of microalbuminuria in patients assigned to intensive BP control, but no effect on other microvascular end points. In the targeted group of older patients with established type 2 diabetes and hypertension, "additional benefit from simultaneous intensive management was not apparent," the researchers conclude [Ismail-Beigi F, et al. Combined intensive blood pressure and glycemic control does not produce an additive benefit on microvascular outcomes in type 2 diabetic patients. *Kidney Int* 2012; 81:586–594].

No increase in cardiovascular events in living kidney donors

Patients selected for kidney donation show no increase in major cardiovascular events at several years' follow-up compared with similarly healthy control individuals, reports a study in the *British Medical Journal*.

The retrospective study included 2028 people in Ontario, Canada, who were selected to become living kidney donors between 1992 and 2009. Provincial health data were used to match this group of donors to 20,280 nondonors, drawn from the healthiest segment of the general population.

The donors and nondonors were compared on a composite outcome of time to death or first major cardiovascular event. The median age at the time of donation was 45 years, and the median follow-up time was 6.5 years.

The primary outcome rate was significantly lower in the living kidney donors than in nondonor control individuals: 2.8 versus 4.1 events per 1000 person-years, hazard ratio 0.66. On a secondary outcome of time to first major cardiovascular event censored for death, there was no significant difference between groups: 1.7 versus 2.0 events per 1000 person-years for donors and nondonors, respectively. For donors and nondonors alike, the risks of death and cardiovascular events were higher for people of older age and lower income.

Cardiovascular disease is a key outcome of interest in assessing the long-term health risks of living kidney donation. This study of recent living donors in Canada finds no increase in the risk of major cardiovascular events within the first 10 years after donation, compared with a group of similarly healthy nondonors. The authors believe their results add to the evidence supporting the safety of living kidney donation as long as rigorous selection criteria continue to be followed [Garg AX, et al. Cardiovascular disease in kidney donors: matched cohort study. *BMJ* 2012; 344:e1203].

Alternative ointment doesn't reduce infections in peritoneal dialysis patients

Polysporin triple ointment (P3) is not superior to mupirocin in preventing infections in peritoneal dialysis (PD) patients and may lead to an increased rate of fungal colonization, reports a trial in the *Clinical Journal of the American Society of Nephrology*.

The randomized controlled trial included 201 PD patients from two centers. Patients were assigned to the routine use of P3 or mupirocin ointment applied to the exit site for 18 months. A composite end point of exit-site infection (ESI), tunnel infection, or peritonitis was compared between groups.

Seventy-five patients had a primary outcome event, including 51 episodes of peritonitis and 24 ESIs. The time to first adverse outcome event was 13.2 months with P3 and 14.0 months with mupirocin. Redness at the exit site was reported by 14 patients in the P3 group versus six in the mupirocin group.

The overall rate of fungal ESIs was higher with P3 than with mupirocin: 0.07 versus 0.01 per year, respectively. This led to a fungal peritonitis rate of 0.04 per year in the P3 group, compared with no cases in the mupirocin group.

Topical ointments can reduce the risk of peritonitis in PD patients. New alternatives are being searched for to deal with the potential problem of antimicrobial resistance.

The new trial found no reduction in infectious complications in PD patients using P3 compared with standard mupirocin ointment. The authors express concern over the possible increase in fungal colonization of the exit site with P3 ointment, and they call for further study [McQuillan RF, et al. A randomized controlled trial comparing mupirocin and polysporin triple ointments in peritoneal dialysis patients: the M P^3 study. *Clin J Am Soc Nephrol* 2012; 7:297–303].

Good 3-year graft and patient survival with belatacept

Three-year follow-up results show continued high rates of patient and graft survival in kidney transplant recipients treated with belatacept, reports a study in the *American Journal of Transplantation*.

The researchers present final results from the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression (BENEFIT) study. A total of 666 kidney transplant recipients were randomly assigned to receive the selective costimulation blocker belatacept in either a more-intensive (MI) or a less-intensive (LI) regimen, or standard treatment with cyclosporine. Previous results have shown similar rates of patient and graft survival but with better renal function and improved cardiovascular and metabolic risk profiles in the belatacept groups. Belatacept was associated with an increased rate of posttransplant lymphoproliferative disorder, particularly of the central nervous system.

Four hundred seventy-one patients completed at least 3 years of treatment. The rates of survival with a functional graft were 92 percent with belatacept, both MI and LI, and 89 percent with cyclosporine. At 3 years, the mean calculated GFR was higher (approximately 21 mL/min/1.73 m^2) in the belatacept groups, compared with the cyclosporine group. The calculated GFR increased by 1.0 mL/min/1.73 m^2 per year with belatacept MI and 1.2 mL/min/1.73 m^2 per year with belatacept LI, compared with a decrease of 2.0 mL/min/1.73 m^2 per year with cyclosporine.

There was one case of acute rejection in the cyclosporine group during the third year of follow-up. No new cases of posttransplant lymphoproliferative disorder occurred after 18 months, and there were no new safety signals.

The new report extends the benefits of belatacept through 3 years of follow-up. The rates of patient and graft survival are similar to those of cyclosporine, and kidney function is better. The BENEFIT investigators conclude "the totality of data suggests that belatacept offers an important therapeutic advance in the care of renal transplant recipients" [Vincenti F, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. *Am J Transpl* 2012; 12:210–217].

Something to Say?

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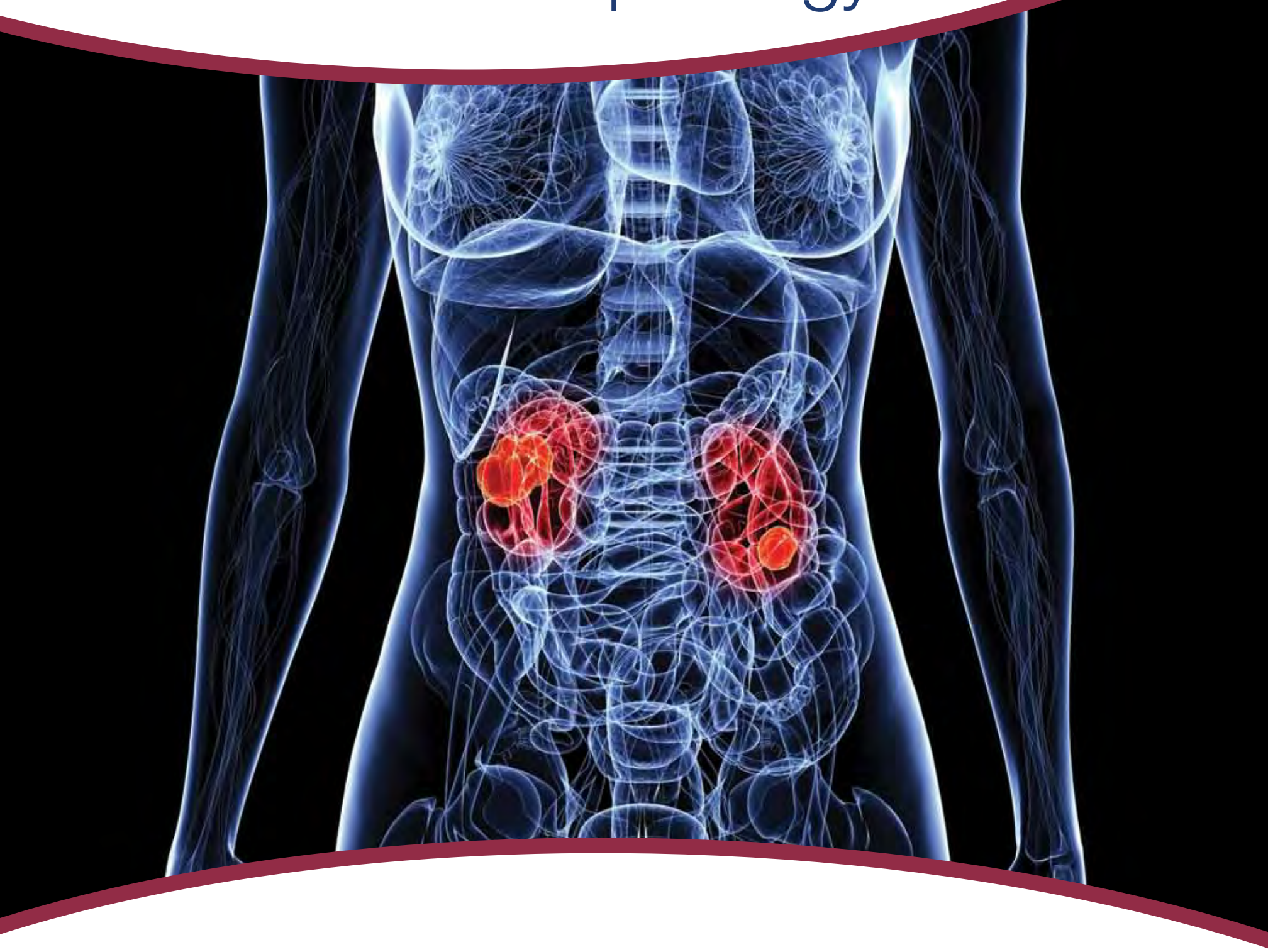

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Industry Spotlight

Abbott Pumps up Activity in Chronic Kidney Disease

Abbott Laboratories (Chicago) currently has about 20 drugs in midstage or late-stage clinical trials, versus about eight in 2009, and these include potential treatments for change to chronic kidney disease (CKD) as well as for multiple sclerosis and liver cancer.

Abbott has more drugs in its pipeline because of acquisitions and licensing deals, according to a report on the *Wall Street Journa*l MarketWatch site. Chronic kidney disease CKD has become an area of focus.

Recently Abbott had success with a midstage clinical trial for CKD patients with the oral drug bardoxolone methyl over 52 weeks, in which kidney function improved. A phase 3 trial is under way. "We had essentially nothing in phase 3 just a couple of years ago," John Leonard, senior vice president of pharmaceuticals, research, and development at Abbott, said. "We've had a very aggressive in-licensing effort." MarketWatch late last year reported that Abbott's research pipeline is filling in anticipation of the loss of patent protection of its top-selling drug, Humira, an antiinflammatory medication.

For kidney patients, Abbott already offers Zemplar (paricalcitol) capsules, a form of vitamin D, to prevent and treat secondary hyperparathyroidism (increased parathyroid hormone levels) in people with stage 3 or stage 4 CKD and in people with stage 5 kidney failure who are receiving dialysis.

Abbott has provided nutritional products for two decades for kidney disease patients, and in its March announcement noted that new formulations have been rebranded as Nepro HP (high protein) and Nepro LP (low protein), formerly Suplena. These two products are available in select markets and will continue to launch globally over the next few years, the company said.

Dialysis Companies Shine in Difficult Economy

Fresenius, DaVita, and American Renal Holdings (parent company of American Renal Associates)—all providers of outpatient dialysis services—announced better than expected financial results for the year ending December 31, 2011.

Fresenius, the largest global provider of dialysis services and products, saw its net profit for 2011 rise 9.6 percent from a year earlier to €205 million (or $269 million). Parent Fresenius's fourth-quarter net profit jumped 14 percent to $310 million, while earnings per share rose 14 percent to $1.02. Fresenius Medical Care's net revenue—dialysis services and products—increased to $3.32 billion in the fourth quarter, up 4.9 percent over the previous year.

Fresenius forecasts 2012 revenue of around $14 billion, helped by acquisitions in the United States and Europe, an 11 percent increase adjusted for accounting changes, and a 13 percent to 15 percent increase in constant currency. The company projected net profit rising to around $1.14 billion in 2012.

Fresenius SE projected sales growth of 10 percent to 13 percent in 2012 and a rise in net income of 8 percent to 11 percent in constant currency, with growth in all business areas.

As of March 31, 2011, Fresenius Medical Care treated 216,942 patients worldwide—a 9 percent increase from the previous year. In North America, they provided dialysis treatments for 138,392 patients, for an increase of 4 percent, with the total number of patients climbing to 139,887 when the 21 clinics managed (and not owned) by Fresenius Medical Care North America are included. The international segment served 78,550 patients, an increase of 20 percent over the prior year.

Rice Powell, who leads Fresenius North America, will succeed Ben Lipps as chief executive and chairman of the management board on January 1, 2013.

The second largest provider, DaVita, reported a fourth quarter profit of more than $148 million, or $1.56 per share, more than doubling the profit reported the year before.

Income from continuing operations attributable to DaVita, Inc., for the year ended December 31, 2011, was $481.8 million, or $4.99 per share. These figures include an after-tax noncash goodwill charge of about $14.4 million for DaVita's infusion therapy business. DaVita annual revenue climbed to $1.86 billion, up from $1.64 billion for the previous year.

The company reported a total of 5,227,167 treatments in the United States for the fourth quarter of 2011—or 66,167 treatments per day—for a per-day increase of 12.4 percent over the fourth quarter of 2010.

Looking ahead, DaVita's operating income guidance for 2012 is expected to be in the range of $1.2 billion to $1.3 billion. Estimated operating cash flows for 2012 are in the range of $950 million to $1.050 billion.

American Renal Associates reported revenues for the 3 months and the year ended December 31, 2011, of $93.1 million and $360.1 million, respectively, compared with $81.9 million and $304.9 million, respectively, for the same periods in 2010.

At the end of 2011, American Renal Associates had provided services to 7374 patients at 108 outpatient dialysis centers, an increase over the same time period the previous year when they served 6628 patients at 93 outpatient dialysis centers.

Treatments for the fourth quarter of 2011 totaled 266,313, or 3371 treatments per day: a per-day increase of 11.8 percent over the fourth quarter of 2010. Treatment growth unrelated to acquisitions was 11.3 percent in the fourth quarter.

American Renal Associates Holdings, Inc., is an owner and provider of outpatient kidney dialysis facilities and operates the facilities in partnership with nephrologists throughout the United States.

Excellent Water Quality Key to Safe Dialysis

Ensuring safe procedures in the dialysis unit is essential to the health and well-being of patients. The Practicing Nephrologists Advisory Group this month addresses water quality. Future issues of *ASN Kidney News* will look at other patient safety concerns.

By Andrew Fenves, on behalf of the ASN Practicing Nephrologists Advisory Group

Nephrologists in clinical practice take it for granted that when they arrive for morning rounds the hemodialysis machines will be set up and ready to go, with the water for the dialysate purified and inspected.

In fact, the level of water purity required to ensure patient safety has gradually evolved since hemodialysis was introduced many decades ago. The case study below, from a large community-based teaching hospital, illustrates how water quality can change unexpectedly, and the importance of rapid response to such changes to ensure patient safety.

Case study

At this facility, hemodialysis nurses and dialysis technicians arrive at around 6 a.m. to set up the 10 stationary hemodialysis machines and inspect the two traveling machines for use in the intensive care unit.

The first sign of trouble was an elevated chloramine level in the deionized water. This water came from a central water source one floor above the acute hemodialysis unit. Chloramine levels were repeatedly 15- to 20-fold above the usual levels. All dialysis treatments were put on hold, and staff members contacted the bioengineering department. Soon, the director of the acute hemodialysis unit arrived. By now, two neighboring outpatient hemodialysis units were experiencing water problems as well, and staff members were unable to administer dialysis to their first shift of patients. Two other large downtown hospitals soon followed suit, reporting unacceptably high city water chloramine levels in their acute hemodialysis units.

The medical director and hemodialysis nursing supervisor began to formulate a plan to prioritize the hemodialysis patients by the acuity of their illness. In the meantime, bioengineering staff began inspecting the carbon filters as a first step to diagnose the problem. The medical director notified several nearby community dialysis centers and instructed the charge nurses that patients with emergent dialysis care needs should be diverted to nearby hospitals. In addition, the nephrologists in the hospital were notified of the temporary closure of the hemodialysis unit. These physicians were instructed to see their sickest patients first and to treat them medically if necessary until the unit was functional again.

Fortunately, the majority of patients who needed dialysis that day belonged to one private practice group, and this group used a voicemail system to rapidly spread the message regarding the unit's temporary closure. A second nephrology group was contacted by a regular paging system.

The bioengineering staff established that the essential problem was a large quantity of chlorine and ammonia from the city water supply overwhelming the carbon tanks. They later learned that the city had performed some maintenance work on its water supply equipment and at the conclusion of this exercise elected to cleanse the system with the use of extra chlorine and ammonia. Carbon filters were replaced with new ones within about 3 hours. The subsequent water samples revealed acceptable levels of chloramine, and the dialysis unit was reopened. Even with a 3-hour delay, all patients ultimately underwent dialysis safely that day, and no adverse events were reported. Finally, the bioengineering staff shared their findings with other hospitals and outpatient dialysis units during the course of the day, helping all units regain full function by the end of the same day.

Safety precautions for dialysis water supply

All hemodialysis patients are exposed to very large quantities of water during a standard treatment. Failure to adequately treat water contaminated with chemicals, bacteria, or toxins, or failure to recognize that treatment components are not operating according to strict specifications, can put hemodialysis patients at risk of injury and even death.

Water treatment has evolved over the decades. By the late 1960s it was recognized that in addition to standard water purification systems, a deionizer was required to further purify the water (1). This eliminated the potential problem of methemoglobinemia produced by the traces of copper in certain copper pipes used in some hospitals (1).

In 1973, investigators in Minnesota reported that methemoglobinemia developed in several dialysis patients despite the use of reverse osmosis in purified urban water supplies (2). After some investigation the authors identified chloramine as the culprit for the methemoglobinemia in these patients (2, 3). Chloramine forms when water is treated with chlorine and ammonia, a common treatment technique in municipal water supplies. Chloramine can be removed by charcoal filtration. Hence, modern water treatment facilities now include charcoal filters along with a deionizer. Even with this addition, sporadic cases are reported of methemoglobinemia and hemolysis in some hemodialysis patients, caused by chloramine. These cases may reflect the use of a single carbon filter with insufficient capacity, or at times excessive water flow rates that allow insufficient contact with the carbon particles (4).

The case reported here illustrates how water supply and water quality may suddenly change without prior notification to hospitals or dialysis units. Accordingly, several safety precautions should be in place. First, careful and constant monitoring of water quality is essential. In this case, such vigilance prevented the potential adverse clinical events that would have otherwise occurred in the hospital. Second, it is desirable to have an action plan in place in case the acute hemodialysis unit needs to close temporarily due to similar circumstances. Action plans will clearly differ depending on the particular circumstances of the hospital or outpatient clinic in question, but they should identify key individuals who can implement the actions necessary to assure maximal patient safety.

Here are some key points to remember about water quality and patient safety:

- Excellent water quality remains a key ingredient for delivering safe hemodialysis to our patients.
- Constant and careful monitoring of the water quality is essential.
- Contingency plans for a sudden change in water quality are important to maintain patient safety.
- The use of chloramines in water treatment facilities may pose an unexpected risk to water quality in certain circumstances.

Andrew Fenves, MD, FASN, is with Dallas Nephrology Associates.

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Policy Update

Budget Madness:
Fiscal Year 2013 and Research Funding

By Grant Olan

While the National Institutes of Health (NIH) is still sorting out how to divvy up its funding for fiscal year (FY) 2012, Congress is knee deep in the budget process for FY 2013. In February, the Obama administration released the president's budget for 2013. It includes $71.7 billion for the U.S. Department of Health and Human Services (HHS), an 8.5 percent cut from FY 2012. To put that number in perspective, in 2010, HHS's budget was $84.4 billion. HHS's budget includes funding for many different agencies, including the Centers for Disease Control and Prevention (CDC), the Centers for Medicare & Medicaid Services (CMS), the U.S. Food and Drug Administration (FDA), and of particular interest to investigators, the Agency for Healthcare Research and Quality (AHRQ) and NIH (Figure 1).

Drilling down, HHS's budget includes $408.8 million for AHRQ, an increase of $3.7 million over FY 2012 (Figure 2). On the other hand, HHS's budget for NIH is flat at $30.9 billion, and the National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK) budget was slightly reduced to $1.94 billion, a decrease of $2.80 million from 2012. That compares with budget increases for the National Heart Lung and Blood Institute and National Institute on Aging of $709,000 and $522,000, respectively.

However, Congress still has to have its say. The members of Congress ultimately hold the purse strings, and there is considerable pressure to lower the discretionary spending caps imposed by the Budget Control Act (BCA) last summer. The BCA also forces Congress to find an additional $1.2 trillion in savings by either raising revenues, making additional spending cuts, or a combination of the two. If Congress cannot agree to a plan that achieves that $1.2 trillion savings level (or to repeal the BCA) before January 2, 2013, then across-the-board cuts (also known as sequestration) will automatically go into effect for most discretionary federal spending programs in 2013, including HHS.

The impact on medical research would likely be devastating. NIH Director Francis S. Collins, MD, PhD, estimates that sequestration would result in an 8 percent cut to NIH, translating into reducing the number of grants it funds by 2300. Success rates would similarly drop dramatically.

ASN is working to ensure that Congress strengthens funding for medical research—and specifically kidney disease research—in collaboration with the American Society of Pediatric Nephrology (ASPN) and the Congressional Kidney Caucus, which includes Chairman Rep. Jim McDermott, MD (D-WA) and Vice Chair Rep. Jesse Jackson, Jr. (D-IL). ASN and ASPN are grateful for the support of the Congressional Kidney Caucus, which submitted language highlighting the importance of kidney disease research across the NIH and directed at patients of all ages, to be included in the report the House Appropriations Committee submits to the full House of Representatives. (Appropriations committees write the legislation that allocates federal funds to agencies, including NIH.) This report is vitally important, as it explains to Congress the reasons for including the spending proposals in appropriations bills. In addition, ASN and ASPN worked with the caucus to include a specific funding recommendation for the NIDDK budget—the first time a specific budget level has been supported by the kidney community. This "programmatic request" for NIDDK for FY 2013 was $2.03 billion, or 4.5 percent more than the president's budget requested. This level of funding is critical to sustain the inroads that have been made in kidney research and to protect the pipeline for promising new investigators.

To support this request, ASN collaborated with ASPN to send a letter in support of kidney disease research and robust NIDDK funding to both the House and Senate Appropriations Committees. It was signed by numerous other members of the kidney community, representing patients, providers, and industry.

ASN has taken a number of other steps such as:

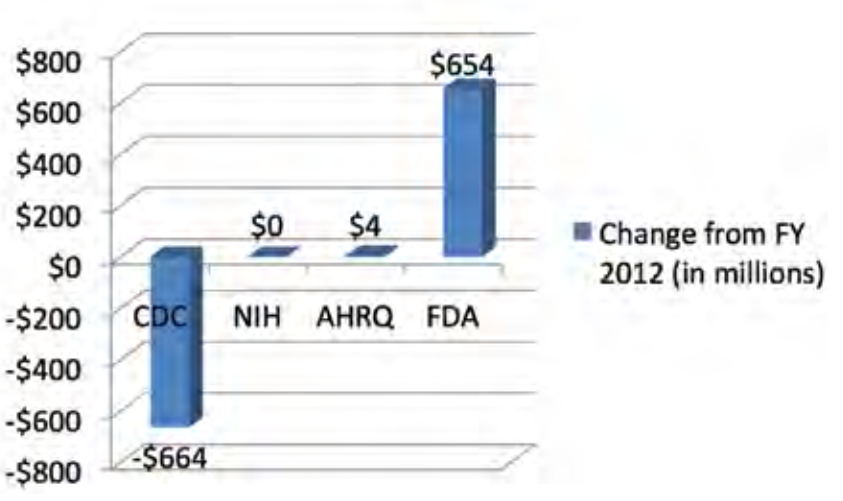
- Joining more than 165 organizations in sending a letter urging Congress to increase NIH funding by 4.5 percent (to $32 billion) over FY 2012 ($30.6 billion) to account for inflation and modest growth.
- Involving the ASN membership in a petition-signing campaign urging the White House to support more funding for NIH.
- Partnering with more than 900 organizations in sending a letter urging Congress to avert cuts to the overall HHS budget.
- Launching an ASN membership email campaign to urge their members of Congress to support more research funding for NIH. Contact your member at http://capwiz.com/asn/home/.

ASN is also organizing the second annual ASN Hill Day on April 26, 2012. ASN Council, Board of Advisors, and Public Policy Board members will speak with members of Congress and their staff about the importance of supporting innovative kidney disease research that will improve patient care, cut costs, and preserve the investigator pipeline. Stay tuned for more details.

Figure 1
HHS and its agencies

Abbreviations: ACF = Administration for Children & Families; AoA = Administration on Aging; HRSA = Health Resources and Services Administration; IHS = Indian Health Service; SAMSHA = Substance Abuse and Mental Health Services Administration

Figure 2
Funding changes in the proposed FY 2013 budget



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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. L. O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron (angry) My assistant is late today.

L. O. Henle enters the room with excitement.

Nephron What do you want?

Henle I…I have a case for us.

Nephron You are late today.

Henle Hypomagnesemia.

Nephron (with surprise) Excellent! A good case can change my mood.

Henle A 65-year-old man was just seen for fatigue and muscle weakness and found to have a serum magnesium level of 0.6 mg/dL.

Nephron This should be fun.

Henle (with a curious look) For 3 days they tried giving him magnesium replacements intravenously and orally, and although his levels are improving, they can't figure out the cause.

Nephron Ahhah! This is going be exciting.

Henle Just some more information, if you allow, sir.

Nephron Sure—I hope it is the information I am looking for.

Henle He really has no significant medical problems except hypertension and gastric reflux disease. His FeMg was 0.5 percent.

Nephron So it's a gastrointestinal (GI) loss. Why are you bothering me?

Henle He has no diarrhea, and no apparent GI loss can be found. He has no history of alcohol ingestion.

Nephron (very excited) Great job; let's move on. So just because there is no GI loss, it is presumed renal losses? You just told me that the kidney is doing the right thing: the urinary loss of magnesium is very minimal. If I had to guess what the urine magnesium was, it must have been very low.

Henle You are correct.

Nephron Any other electrolyte problems?

Henle (astounded) I am getting to that point. Also, hypokalemia and hypocalcemia.

Nephron (calm) Fascinating!

Henle So far he is not taking any diuretics, he was not aggressively volume expanded and not hypercalcemic, and I don't see anything on his medication list that can cause renal magnesium wasting, like a chemotherapy agent, calcineurin inhibitors, or amphotericin B.

Nephron Ridiculous! Why are you even bothered by those things when the kidney is doing the right thing! This is GI loss to me. Please go back and evaluate his medications, and make sure he is not having any GI losses.

Henle exits, and Detective Nephron resumes drinking his coffee.

Nephron (to himself) Henle seems to be very puzzled by this one. So far, the kidneys are the smarter organ here!

Before Detective Nephron can go get more coffee, Henle returns to the office.

Nephron You're back.

Henle I am puzzled. His magnesium is persistently low, and his repeat urinary FeMg percent level is appropriately low.

Nephron Good!

Henle When we have renal losses, the cause is usually medication, diuretics, certain antibiotics (like gentamicin or foscarnet), or primary renal wasting from syndromes. But, as you said, it is not a renal cause. He has no diarrhea or pancreatitis, and no known or existing malabsorption disease. Also, he has had no known abdominal surgery.

Nephron Great! The magnesium content of upper GI tract secretions is 15 mEq/L compared with 1 mEq/L in the lower tract, so that in general, magnesium depletion due to upper GI tract secretory loss is much more common than that due to lower GI tract disorders. You did some good work. But we still don't have a diagnosis.

Henle Yes, you are correct.

Nephron Look at his medication list and his known diagnosis. He has hypertension and gastric reflux. What is he taking?

Henle Metoprolol and omeprazole.

Nephron (chuckling) All right, then!

Henle What?

Nephron Stop the omeprazole, and recheck the magnesium level in a week.

Henle Really?

Nephron Yes, proton pump inhibitors (PPI) can cause hypomagnesemia, especially with long-term use. Hypomagnesemia in the range seen in this patient, along with hypocalcemia, has been reported with PPI use. Usually the loss is GI, so the urinary magnesium and calcium are low. Hypomagnesemia is associated with hypocalcemia, and this is due to both decreased parathyroid hormone secretion and parathyroid hormone resistance. Hypomagnesemia-induced kaliuresis leading to hypokalemia can be seen with these patients as well. What was the urinary calcium and potassium in this patient?

Henle Low and high, respectively. Given the low calcium, his parathyroid hormone was checked, and it is 30 pg/mL.

Nephron So stop the PPI now!

Henle Why does this happen?

Nephron (with a smirk) It is speculated that the drug might interfere with intestinal absorption. Some data say that there might be a renal effect as well. Data from case reports suggest that a renal effect may also contribute. It is possible that the drug interferes with the maximum tubular reabsorption threshold for magnesium.

Henle This is interesting.

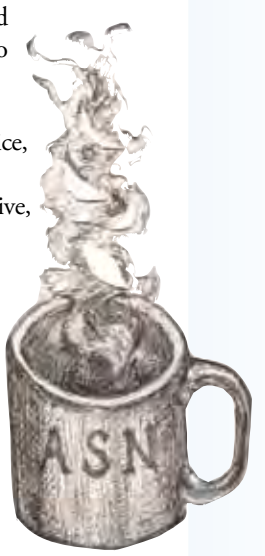
Nephron Let me know in a week.

Henle exits, and Detective Nephron starts reading* ASN Kidney News. *A few days later, as the detective is sipping away at his coffee, Henle enters the office.

Nephron Nothing is better than a cup of hot coffee! And a great case!

Henle Once we stopped the PPI and the magnesium, the patient's calcium and potassium all improved slowly. He is being discharged and advised to not to take these agents any more.

Nephron Great work, Henle. Again, my dear apprentice, from a diagnosis of hypomagnesemia, you found the culprit agent. To be a good detective, always, observe, think, read, and apply. If it doesn't cross your mind, you will never diagnose it. Great case, Henle. The problem is not always in the kidney!



"Detective Nephron" was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine. Thanks to Dr. Rimda Wanchoo, division of nephrology, Weill Cornell Medical Center, for editorial assistance.

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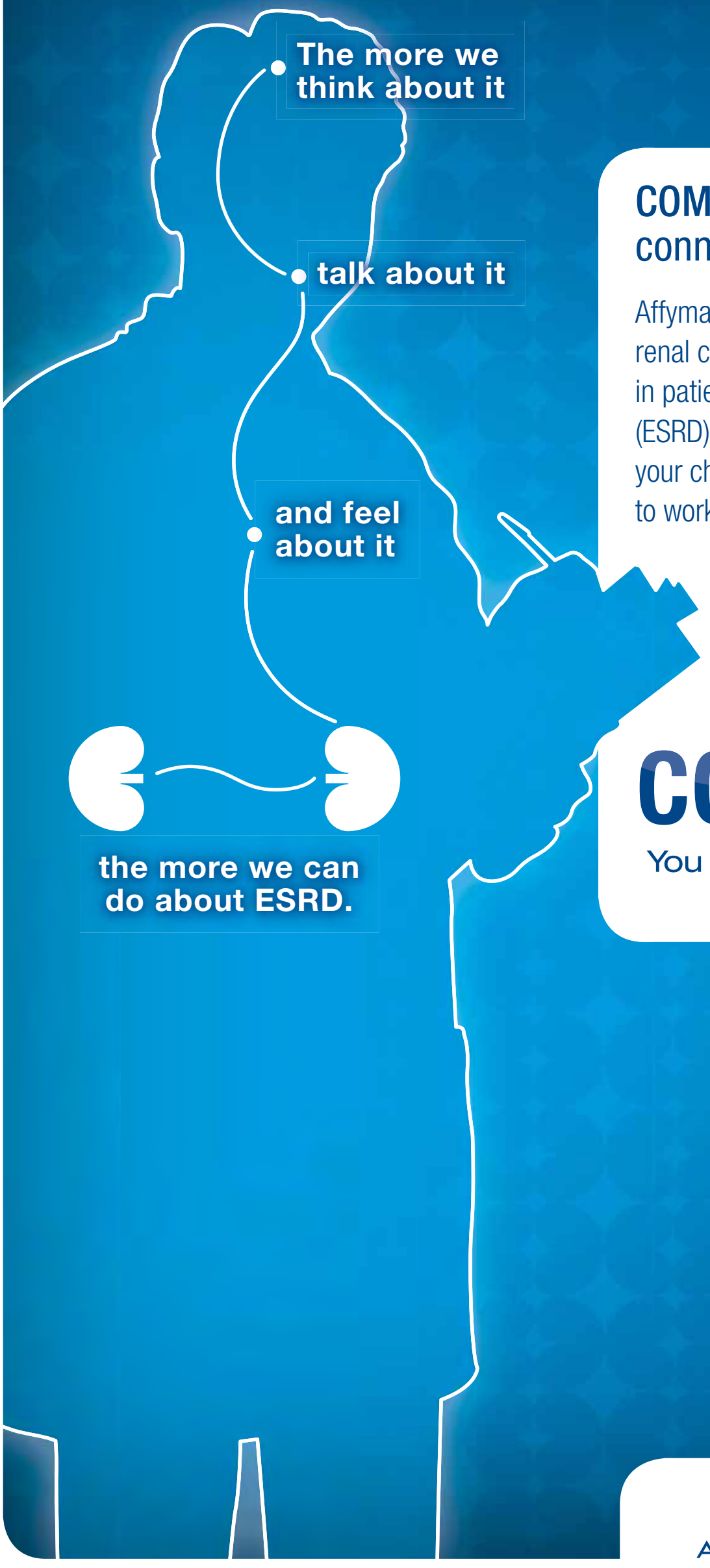

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