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Young Adults with Kidney Failure Found to Have High Cardiovascular Mortality

Close to 40% of deaths in young adult patients with kidney failure (ESRD) result from cardiovascular disease (CVD), according to an analysis of US Renal Data System data published in *JAMA Cardiology*.

Lack of preemptive transplantation and lack of pre-ESRD nephrology care are strongly associated with a higher risk of cardiovascular mortality in the 22- to 29-year-old ESRD age group, reports the study by Zubin J. Modi, MD, a pediatric nephrologist at the University of Michigan, Ann Arbor, and colleagues. They write, "We show that young adults began ESRD care with a higher burden of preexisting CVD and CVD risk factors, which may present a target for earlier intervention to improve outcomes."

The researchers analyzed data on approximately 33,000 patients, aged 1 to 29, who started renal replacement therapy for ESRD from 2001 through 2013. About 20,000 patients were young adults, in whom ESRD onset occurred between ages 22 and 29. Their characteristics and cardiovascular outcomes were compared with those of 10,000 adolescents with incident ESRD, aged 12 to 21 years, and 3000 children aged 1 to 11 years. The researchers hypothesized that young adults in whom ESRD developed would have a different set of risk factors and higher cardiovascular morbidity and mortality compared with pediatric patients.

Young adults with ESRD: CVD rates and risk factors

The data showed significant demographic and clinical differences for young adults with ESRD compared with younger age groups. About 39% of young adult patients were black, compared with 29% of adolescents and 19% of children. At ESRD onset, about 78% of young adult patients had hypertension and 22% had diabetes. They also had a higher rate of comorbid CVD, including an 8% rate of heart failure and a 5% rate of coronary artery/cardiac disease.

Most often, ESRD in young adults was due to hypertension or large vessel disease (30%) or diabetes (30%). Two-thirds of patients with ESRD secondary to diabetes had type 1 diabetes mellitus. Only about 6% of young adults had congenital, hereditary, or cystic disease as the

Continued on page 3

Physicians File Lawsuits against Boards over Maintenance of Certification

MOC critics charge specialty boards engage in anti-competitive practices

By Eric Seaborg

Critics have expanded their tactics challenging maintenance of certification (MOC) requirements by filing several class-action lawsuits against the boards that administer MOC tests and programs.

The first of these suits was filed in December 2018 against the American Board of Internal Medicine (ABIM) by four internists who allege they have been harmed by ABIM's anti-competitive practices regarding MOC.

On Feb. 19, 2019, three physicians in California proposed a class-action lawsuit against the American Board of Medical Specialties, American Board of Anesthesiology, and American Board of Emergency Medicine for antitrust violations. On Feb. 26, 2019, a radiologist in Tennessee filed a similar class-action suit against the American Board of Radiology. And on March 6, 2019, two psychiatrists filed suit against the American Board of Psychiatry and Neurology.

Continued on page 3

Inside

Findings
High-dose NSAIDS may increase kidney disease risk

KidneyX
Read our interviews with two recipients of KidneyX Redesign Dialysis Phase I Awards. More coverage in KNO.

Moving into Management
KN interviews a practicing nephrologist about his move into management

Detective Nephron
Detective Nephron and acolytes unravel a case of proteinuria, hematuria, and increased creatinine

Deemed Status
Accreditation for outpatient dialysis facilities takes off

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USMP/MG120/18-0006a(1) 1/19

High Cardiovascular Mortality

Continued from page 1

primary cause of ESRD, compared with 16% of adolescents and 34% of children.

The outcomes in young adults with ESRD reflected their higher rates of CVD and risk factors. At 1 year, the adjusted rate of hospitalization for CVD in the young adult group was 138 per 1000 patient-years—significantly higher than in adolescents (hazard ratio [HR] 0.86) and in children (HR 0.41). Over 5 years, the rising hospitalization rates in adolescents converged with the high but stable rates in young adults.

Differences in management were also related to CVD outcomes. About 5.5% of young adult patients received preemptive transplantation, compared with 13.5% of adolescents and 27% of children. Hemodialysis and peritoneal dialysis were strongly associated with increased rates of CVD hospitalization: by 14-fold and eightfold, respectively. The CVD hospitalization rates were also higher for black patients, women, patients who were receiving public insurance or were uninsured, and patients with ESRD from causes other than congenital, hereditary, or cystic causes. Patients with comorbid CVD, hypertension, or diabetes at the time of ESRD onset were also at higher risk.

Young adults with ESRD "more comparable with older adults than children"

CVD accounted for 39% of deaths in young adults with ESRD. In this age group, cardiovascular mortality increased over time—from 11 per 1000 patient-years at 1 year, to 37 per 1000 at 3 years, to 70 per 1000 at 5 years—and was higher than in adolescents or children. Citing national vital statistics for 2014, Modi and coauthors write, "[Y]oung adults with incident ESRD had a 143 to 500 times higher risk for CVD mortality than the age-matched general population."

As for hospitalization, the risk of cardiovascular mortality was higher for patients starting hemodialysis or peritoneal dialysis: about 13 and 8 times higher, respectively, compared with preemptive transplantation. Race, sex, insurance status, and comorbidity were also associated with increased cardiovascular mortality. Young adults with a more recent year of ESRD were at higher risk of cardiovascular hospitalization (HR 1.11) but a lower risk of cardiovascular morbidity (HR 0.67).

Fewer than half (47%) of young adult patients received nephrology care before ESRD diagnosis, compared with 57% of adolescents and 74% of children. Young adults who did receive pre-ESRD care were at lower risk of cardiovascular death (HR 0.77). Modi and coauthors write, "Lack of adequate insurance prior to ESRD onset implies limited access to pre-ESRD care, with concomitant risks of delayed diagnosis and insufficient opportunity to provide optimal management during times of less severe kidney disease."

Consistent with previous studies, cardiovascular morbidity and mortality were higher in patients with preexisting coronary and cardiac disease, diabetes, and heart failure. The causes of ESRD also showed a possible association with the risk of CVD hospitalization and death: "[G]lomerular diseases were associated with adolescent or young adult ESRD onset and a higher risk of CVD mortality," according to the authors. "It is possible that glomerular diseases increase systemic inflammation and thereby contribute to a higher CVD burden."

For both children and adults, CVD is a leading cause of morbidity and mortality associated with ESRD. However, relatively little is known about the burden of CVD in young adults with ESRD. Recognizing the "unique challenges" in this group of patients, the US Renal Data System has recently started reporting surveillance data specific to the young adult ESRD population.

The new analysis suggests that patients with incident ESRD developing between ages 21 and 30 have different CVD risks and burdens in comparison with younger age groups. Young adults with ESRD have consistently higher rates of hospitalization and death as a result of CVD than do pediatric ESRD patients. "Their risk of hospitalization and mortality owing to cardiovascular disease is more comparable with older adults than children," Modi and colleagues write.

The study identifies a wide range of risk factors that may aid in developing age-appropriate strategies to improve cardiovascular outcomes in young adults with incident ESRD. "Potentially modifiable risk factors for this young adult population may include optimizing health care for the underlying kidney disease and other coexisting conditions before the onset of ESRD and increasing access to preemptive transplant," the researchers write.

Information on the impact of race, sex, and other nonmodifiable risk factors may lend insights into the genetic, social, and other factors affecting the age-related differences in cardiovascular mortality among young patients with ESRD. "Together, these steps may lead to improved implementation of age-appropriate treatment and patient management strategies and overall cardiovascular health of this unique population," Modi said.

Physicians File Lawsuits

Continued from page 1

The initial suit against ABIM provided a template for the others. The four physicians all passed initial internal medicine boards, as well as those in other subspecialties, such as gastroenterology and infectious disease. The plaintiffs allege they have been harmed by being listed as "not certified" after not passing MOC exams—despite having passed the initial exams that are enough for older, "grandfathered" physicians to maintain their certification.

The suit also alleges that ABIM has illegally tied its initial certification test to its maintenance of certification product, used its monopoly position in the initial certification market to create a monopoly in the MOC market, used various anti-competitive actions to thwart competition from other potential MOC providers, forced physicians to purchase MOC, and charged inflated monopoly prices.

The plaintiffs amended their suit in January 2019 to include a charge that ABIM violated the Racketeer Influenced and Corrupt Organizations (RICO) Act by waging a campaign to deceive the public, hospitals, insurance companies, medical corporations, and media that MOC "benefits physicians, patients and the public and constitutes self-regulation by internists," which misled these entities into requiring "internists to participate in MOC in order to obtain hospital consulting and admitting privileges, reimbursement by insurance companies, employment by medical corporations and other employers, malpractice coverage, and other requirements of the practice of medicine."

Motion to dismiss

ABIM responded to the lawsuit on March 19, 2018, with a motion to dismiss the complaint.

"Plaintiffs may disagree with ABIM and members of the medical community on whether ABIM certification provides them value, but their claims have no basis in the law," said Richard J. Baron, MD, president and CEO of ABIM. "With advances in medical science and technology occurring constantly, periodic assessments are critical to ensure internists are staying current and continuing to meet high performance standards in their field."

"Board certification is a voluntary process, and is not required to practice medicine in any state," ABIM notes in explaining its response to the lawsuit. "Many patients, healthcare institutions, and insurers rely upon certification as a tool that, along with other markers, informs them about a physician's credentials."

This question of whether or not MOC is actually voluntary is a key point on which the lawsuit could turn. Niran S. Al-Agba, MD, a board-certified pediatrician in solo practice in Silverdale, Wash., says that, like other states, Washington has outlawed using MOC as a "requirement for having a medical license, but [it has] not outlawed [requiring MOC] for being on staff at a hospital. So, if you are going to be affiliated with any hospital, you are required to do MOC, and if you are going to contract with certain insurance companies, you are required to be on staff at a hospital."

ABIM responds that the decisions of healthcare institutions and insurers to require certification are independent of any of ABIM's actions.

GoFundMe campaign supports suits

Al-Agba is on the board of directors of Practicing Physicians of America (PPA), a membership organization fighting to end MOC. PPA is sponsoring a GoFundMe campaign to fund federal class-action lawsuits against MOC.

PPA launched the GoFundMe campaign in May 2018 to raise funds to explore the possibility and lay the groundwork for potential litigation. By September 2018, the campaign had met its initial goal of $150,000, enough to launch the lawsuit. By early April 2019, more than 1300 people had donated almost $260,000 toward a new goal of $400,000.

"PPA has created a way for physicians to donate money to their colleagues. We don't take any money off the top of this GoFundMe account. The money is going 100% to help these plaintiffs," Al-Agba said. "Almost 1400 different physicians spread across the country and across many medical specialties [are] supporting plaintiffs that aren't in the same specialty [who] have been harmed by maintenance of certification. That fact alone tells you how unhappy physicians are." The money is funding the lawsuits against ABIM, the American Board of Radiology and the American Board of Psychiatry and Neurology.

Al-Agba hopes there will be some resolution to the ABIM suit by the time of her next 10-year MOC exam in 2022, but an ongoing suit by the Association of American Physicians & Surgeons (AAPS) shows how long the process can be. AAPS, an organization dedicated to "individual liberty, personal responsibility, limited government [and a] free-market medical system," filed a similar antitrust suit in 2013 against the American Board of Medical Specialties (ABMS) for "restraining trade and causing a reduction in access by patients to their physicians. The ABMS has entered into agreements with 24 other corporations to impose enormous 'recertification' burdens on physicians, which are not justified by any significant improvements in patient care," according to its website.

That suit has languished. The merits of the case have yet to be heard, after years of motions to dismiss and responding counter-motions. In the latest action, a judge delayed a status conference on ABMS's motion to dismiss from April 10 to May 3, 2019.

A testing moratorium?

Other forces could well bring major changes to MOC before these lawsuits play out. In response to the report of the ABMS Vision Initiative Commission calling for changes in MOC, the Council of Medical Specialty Societies sent comments that proposed "a moratorium on the use of the high stakes, summative examination for continuing certification until ABMS and its member boards can implement the recommended changes to continuing certification."

The American College of Radiology also sent comments to ABMS endorsing this call for a moratorium "until many programmatic deficiencies are corrected" and noted: "The ABMS and its member boards should carefully consider the anti-trust implications for their actions."

That comment is noteworthy when combined with a question raised on the "Dr. Wes" blog of Westby G. Fisher, MD, a prominent MOC critic and one of the founders of PPA: "How many more ABMS member boards will be sued?"

Kidney News

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Kidney News interviewed Christian Schafmeister, PhD, Department of Chemistry, College of Science and Technology, Temple University, about his KidneyX Prize, "Atomically Precise Membranes for High-Flux and Selective Removal of Blood Toxins" during hemodialysis. Schafmeister presented the work for the Phase I Redesign Dialysis Prize at the inaugural KidneyX Summit in Washington, DC, on April 29, 2019.

KIDNEY X
INNOVATION ACCELERATOR

You learned about the KidneyX Prize through a nontraditional route. Please describe it.

I was looking for applications where small, atomically precise membranes—a few hundred square centimeters—with very high selectivity and flux could be valuable. I was talking with a group developing a home hemodialysis system about applications of our membranes to dialysis, and was doing some research and wrote a white paper. I then spoke with my colleague Avner Ronen and asked if there was a need for better dialysis membranes and he told me about the KidneyX Prize contest, which was closing the next day. So, I sent in the white paper I had been writing.

How did your work with macromolecules and membranes lead you to look at potential solutions to dialysis?

We are creating large molecules with programmable shapes and looking for applications. These molecules can reach the size of small proteins. Proteins can do amazing things and we hope to develop similar capabilities but in a more "designable" way. There are a class of proteins called "membrane proteins" that act as channels to allow useful molecules to pass in and out of cells. I have thought about making artificial membrane channels for many years.

Your aim is to replicate kidney function by creating chemically synthesized, atomically precise membranes as thin as a single molecule to better replicate the selective membranes in human cells. How does your approach accomplish this?

The thinner a membrane is, the higher the flux will be because there is less resistance for small molecules that pass through the membrane. If channels are constructed that have pores about the size of the molecules and ions we want to pass through the membrane, then the pores will selectively pass their target molecules and nothing else. This is exactly what the membrane channels in the cells in our kidneys (and all cells) do. Very roughly, the kidney is a tube. At the top of the tube, everything in your blood less than about 60 kilodaltons enters the tube. As this fluid (pre-urine) passes down the tube, water, salts, glucose and some other small molecules are drawn back into the blood by highly selective membrane channels. If we can mimic what membrane proteins do, then we can replicate the most sophisticated function of the kidney, which is to pull back from the pre-urine those components that were thrown out in the glomerular capsule.

Please tell us about the "molecular Lego" approach your lab has developed over the past 15 years.

We have designed molecular building blocks that are small rings (molecular Lego bricks). These rings carry two pairs of groups (two amino-acid groups). Each of these amino-acid groups can connect through two bonds to another amino-acid group on another building block. This lets us assemble ladder molecules made up of fused rings. To each building block we can attach other chemical groups that can do things when they are brought together on the ladder backbone. We can assemble short segments and then link those together to create complex three-dimensional structures with enormous control over their shape and what they do.

What is your ultimate goal, and what are the next steps?

We are developing a variety of applications for these molecular Legos. For filtration, we are working to create membranes made out of molecular Lego nanostructures that separate molecules and ions from each other. The ultimate goal is to create membranes that can pull specific small molecules and ions out of mixtures. We are also developing catalysts, molecular Lego nanostructures that build other molecules. This would let us create valuable feedstock molecules in a more environmentally friendly way.

How can the KidneyX partnership between ASN and the US Department of Health and Human Services better encourage and capture the interest of innovators beyond the kidney space?

I don't think a pool of innovators exist that can mimic kidney functions beyond what we have today, without new technologies that let you build things that look like biological membrane channels and integrate them into macroscopic objects. Why? The kidney carries out its most important function at the molecular scale. It must filter large molecules and cells from small molecules without damaging them in the glomerular capsule and then it must pull back valuable molecules from the pre-urine in the tubules. This is as opposed to an organ like the heart—that to a simple approximation is a pump for blood. Wearable dialysis machines, internal artificial kidneys, and home hemodialysis—all of these approaches require better liquid treatment technologies that I believe have to be engineered from the molecules up.

The best way to capture innovators is to engage people, and to ensure funding is available.

Kidney News *interviewed Jeff Ross, PhD, CEO of Miromatrix Medical, about the company's work to bioengineer new kidney grafts consisting of human cells grown in pig extracellular matrix scaffolds. Ross presented the work, "Building New Kidneys," at the inaugural KidneyX Summit in Washington, DC, on April 29, 2019.*

KIDNEY X
INNOVATION ACCELERATOR

KN: Why build new kidneys, and why now?

Dr. Ross The numbers are truly eye-opening—more than 700,000 Americans are living with kidney failure that requires dialysis or transplantation. Unfortunately, less than half of the patients who start dialysis will survive five years, while those fortunate to receive a kidney transplant have a more than 90% survival rate. Our mission is to dramatically reduce the number of patients on dialysis, as well as save millions of lives by eliminating the kidney transplant waiting list.

KN: Please briefly describe your KidneyX 2019 award-winning entry, "Building New Kidneys."

Dr. Ross Our unique perfusion decellularization process essentially washes out the cells from a discarded pig kidney, leaving all the vasculature or blood vessels and microstructures that define the kidney's structure intact. Our groundbreaking technology then introduces human vascular and kidney cells into the decellularized kidney matrix, under defined culture conditions, ultimately recellularizing it. The first step in the process is the introduction of vascular (endothelial) cells to revascularize the kidney matrix and demonstrate that it can be implanted and sustain long-term perfusion. This was our award-winning entry demonstrating we achieved a critical milestone because without an intact and functional vasculature, there is no way to bioengineer a whole kidney. We are now focused on introducing the functional kidney cells to next demonstrate renal function of the recellularized kidney, with our ultimate goal to develop fully functional transplantable kidneys.

KN: You note that the Miromatrix products MIROMESH (soft tissue reinforcement) and MIRODERM (advanced wound care) have been implanted into thousands of patients. How does your approach to building new kidney grafts build on these products?

Dr. Ross Through MIROMESH and MIRODERM, we've been able to demonstrate the vast potential of decellularized porcine matrix. These products are derived from pig livers. Using the same process of perfusion decellularization, we remove all the liver cells while still leaving the overall liver matrix intact, including the vasculature. The decellularized livers are then made into MIROMESH and MIRODERM. So far, thousands of patients have been implanted with our material with no reported adverse reactions related to immunologi-

cal responses. The data helps derisk our approach and provides the initial data to support starting with a pig matrix as a safe approach.

In addition, we recently completed and published our prospective multicenter clinical study evaluating MIROMESH for laparoscopic paraesophageal hernia repair. The two-year follow-up study published in *The American Journal of Surgery* shows GERD patients who underwent laparoscopic paraesophageal hernia repair using MIROMESH saw improved long-term patient outcomes, with no reinterventions, and a 10% two-year radiographic recurrent rate. In the meantime, doctors tested our MIRODERM product against many of our leading competitors in the biological wound matrix field in a case series and published the results in *WOUNDS*. The study demonstrated that our product was able to close at least half of the most difficult diabetic foot ulcers where other treatments failed. We're not only giving those patients new hope, but we're also showing that pig organs can be decellularized, leaving behind all the organ's natural design and architecture.

KN: The kidney is much more complex than these two applications. How can you be sure the kidney product will succeed?

Dr. Ross As you noted, there is a large difference between a decellularized matrix and a fully recellularized functional matrix/organ. While our commercial products have laid the initial foundation, the work we presented at KidneyX demonstrates our ability to revascularize the whole kidney with human endothelial cells and achieve sustained perfusion, which is a large step forward for regenerative medicine and tissue engineering. We have started seeding the revascularized kidney grafts with functional kidney cells, and we are seeing exciting results that continue to encourage us that we will succeed.

KN: One questioner noted there are approximately 32 cell types in the kidney and asked about the certainty of their roles being preserved once they become part of 3D architecture that's very precise. How would you respond?

Dr. Ross It was a great question and certainly one that is critical given the native architecture and function of the kidney. What we have seen in our development process is the natural homing of the seeded cells to their native microenvironment. We believe this is being driven by the kidney matrix, and the process of perfusion decellularization preserves the intact matrix and associated proteins, providing a repeatable process. We have seen this response both in the homing of seeded cells and cases of functional plasticity in both the kidney and liver.

KN: You stated that Miromatrix is aiming for in vivo functionality by 2020 and that the product could be in humans by 2022. Given the need for trials and regulatory approvals, are these dates realistic?

Dr. Ross The common response when people see our approach and data is, "Wow, that is amazing technology, but it will be 30 years before we see it in the clinic." My response is, "We are a lot closer than you think!" Through our commercial products, initial revascularization, and now focus on achieving in vivo functionality in a large animal model by the end of 2020, we believe our goal of initiating human clinical studies as early as 2022 is a realistic goal. There is still a lot to be done, so it could move some depending on the exact regulatory pathway and data, but we are making great progress, and the future is much closer.

High Dose of NSAIDs May Increase Kidney Disease Risk

Exposure to high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) shows a modest but significant association with kidney disease in a military population, reports a study in the open-access journal *JAMA Network Open*.

The retrospective analysis included data on more than 764,000 US Army soldiers on active duty from 2011 through 2014. Eighty-six percent of participants were men; median age was 27 years. Dispensing and dose of prescription NSAIDs were evaluated for association with incident diagnoses of acute kidney injury (AKI) and chronic kidney disease (CKD).

The participants received a total of 1.6 million distinct NSAID prescriptions during the observation period: mean 2.1 prescriptions per person. Nearly two-thirds of personnel had no NSAID prescriptions in the previous 6 months. About 18% were dispensed 1 to 7 mean total daily defined doses (DDDs) per month, while 16% received more than 7 DDDs. There were a total of 2356 AKI outcomes, affecting 0.3% of participants; and 1634 CKD outcomes, affecting 0.2% of participants.

Participants with 7 or more DDDs per month had significant increases in both kidney disease outcomes: adjusted hazard ratio 1.2 for both AKI and CKD. At this level of exposure, there were 17.6 additional cases of AKI and 30.0 additional cases of CKD per 100,000 exposed individuals. Obese individuals were at significantly increased risk of both outcomes: adjusted hazard ratio 1.5 for AKI and 1.6 for CKD. The hazards were more than doubled for individuals with a history of hypertension and rhabdomyolysis. For diabetes, the hazard ratio was 1.8 for both outcomes.

Most studies of NSAID associations with kidney disease have focused on older adults or patients with chronic diseases. There has been little concern about the renal effects of these widely used medications in young, healthy adults. Some studies have suggested a possible increase in kidney disease risk among NSAID users engaging in endurance exercise.

This large study of Army personnel finds "modest but statistically significant" associations between high doses of NSAIDs and the risk of acute and chronic kidney disease outcomes. "Dosage reduction represents an approach that may decrease associated kidney disease outcome rates," the researchers write. They also note the contribution of modifiable factors such as body mass index and hypertension [Nelson DA, et al. Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults. *JAMA Netw Open* 2019; 2 (2):e187896. doi:10.1001/jamanetworkopen.2018.7896].

Markers of Tubule Cell Dysfunction Predict AKI

Among patients with chronic kidney disease (CKD), baseline biomarkers of tubule cell function are independent predictors of the later development of acute kidney injury (AKI), reports a study in *Kidney International*.

The researchers analyzed data on 2351 participants from the randomized Systolic Blood Pressure Intervention Trial (SPRINT). All had CKD (mean estimated glomerular filtration rate [eGFR] 49 mL/min/1.73 m^2) and hypertension at baseline, but not diabetes. Participants were assigned intensive or standard systolic blood pressure targets: less than 120 versus less than 140 mm Hg. Study outcomes showed lower rates of cardiovascular disease and death with intensive blood pressure-lowering therapy, but a higher risk of AKI.

The current study analyzed baseline data on urinary markers of renal tubule dysfunction (alpha-1-microglobulin [α1m], beta-2 microglobulin [β2m], and uromodulin [UMOD]) and markers of renal tubule injury (kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1]) and chitinase-3-like protein [YKL-40]). The two types of markers were analyzed for association with the risk of AKI, with adjustment for other factors.

Over a mean follow-up of 3.8 years, AKI developed in 184 participants—a rate of 7.8%. Acute kidney injury was more frequent in men and in black patients, as well as those assigned to the intensive blood pressure–lowering therapy.

Two markers of kidney tubular dysfunction—UMOD and α1m—were associated with AKI, independent of eGFR and albuminuria. Hazard ratios were 0.68 per twofold increase in UMOD and 1.20 per twofold increase in α1m. At the highest versus lowest quartiles, baseline UMOD and α1m were more strongly associated with AKI risk (HR 2.04 and 1.57, respectively) compared to the 3-month change in serum creatinine (HR 1.27). In contrast, increases of tubule cell injury markers occurred mainly after the AKI event.

Identifying CKD patients at particularly high risk of AKI may help to inform monitoring and prevention strategies. This study identifies markers of tubule cell dysfunction—lower UMOD and higher α1M—as predictors of future AKI risk. The researchers conclude: "[T]ubular cell function markers may reflect a vulnerable kidney with diminished capacity to counter acute insults and thus identify CKD individuals at heightened risk of future AKI" [Bullen AL, et al. The SPRINT trial suggests that markers of tubule cell function in the urine associate with risk of subsequent acute kidney injury while injury markers elevate after the injury. *Kidney Int* 2019; DOI: https://doi.org/10.1016].

Dual Therapies for Black African Patients: Randomized Trial

Combination therapies including amlodipine improve blood pressure (BP) control in sub-Saharan African patients with hypertension, concludes a trial in *The New England Journal of Medicine*.

The randomized controlled "Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans" (CREOLE) trial included 728 black patients with uncontrolled hypertension in six sub-Saharan African countries. Enrolled patients had BP of 140/90 mm Hg or higher on no antihypertensive therapy or a single-drug regimen. The patients' average age was 51 years; 63% were women.

Patients were assigned to one of three antihypertensive drug combinations: the calcium-channel blocker amlodipine (5 mg) plus the thiazide diuretic (HCTZ) (12.5 mg); amlodipine plus the angiotensin-converting enzyme inhibitor perindopril (4 mg); or perindopril plus HCTZ. After 2 months, the dose of each drug was doubled for another 4 months (amlodipine 10 mg, hydrochlorothiazide 25 mg, perindopril 8 mg). Change in 24-hour ambulatory systolic BP from baseline to 6 months was compared between groups.

On analysis of primary outcome data in 621 patients, reductions in BP were greater with the two amlodipine-containing regimens. Compared to perindopril plus HCTZ, between-group differences in systolic BP were 3.14 mm Hg with amlodipine plus HCTZ and 3.00 mm Hg with amlodipine plus perindopril. There was no significant difference between the two amlodipine regimens.

Other outcomes showed a similar pattern, including ambulatory diastolic BP, office BP, and BP response rate. Six-month BP control rates were 76% with amlodipine-HCTZ and 74% with amlodipine-perindopril versus 60% with perindopril-HCTZ. Patients receiving amlodipine-HCTZ had significant reductions in plasma potassium and higher rates of hypokalemia.

Black African patients have a high prevalence of hypertension and typically need at least two antihypertensive drugs to achieve BP control. There is uncertainty regarding the most effective two-drug regimen for black patients with hypertension, reflected by differences in current recommendations.

The CREOLE results suggest a better response with amlodipine, combined with either HCTZ or perindopril, compared to HCTZ plus perindopril in black African patients with uncontrolled hypertension. The researchers note some limitations of their study, including whether the findings can be generalized to black patients with diabetes or those outside of sub-Saharan Africa [Ojji DB, et al. Comparison of dual therapies for lowering blood pressure in black Africans. *N Engl J Med* 2019; DOI: 10.1056/NEJMoa1901113].

Kidney News sat down with Steven G. Achinger, MD, Managing Partner & Chairman of the Board at Watson Clinic LLP in Lakeland, FL, to speak about his recent move into management after 11 years of clinical nephrology practice, including how he made the decision and any advice he has for those considering a similar move.

Watson Clinic was founded in 1941 and is a 100% physician-owned and physician-governed clinic with 169 equal partners. It has 17 locations in Polk, Hillsborough, and Pasco counties that encompass more than 40 medical and surgical specialties.

In 2018, the clinic logged 1,054,031 outpatient visits, 56,422 surgeries, and 197,812 hospital encounters. The clinic has about 1700 employees, including 220 physicians, 171 partners, and 105 mid-level practitioners—making it the 5th largest employer in Polk County and the 6th largest medical group in the Tampa Bay area.

Dr. Steven G. Achinger

KN: How long have you been a practicing nephrologist?

Dr. Achinger: I've been practicing for 12 years, and with the Watson Clinic for 10 years. I have now been managing partner since March 2018.

KN: What is the management structure of Watson Clinic?

Dr. Achinger: The clinic is a for-profit partnership with 171 partners. We're 100% physician-owned and physician-governed. We have a strong administrative team who help guide us and manage the non-physician employees, but as a group, the Watson Clinic partners determine our own direction and priorities. We have a board of directors, who must be partners and full-time practicing physicians, who are elected. The managing partner is also an elected position and acts in the day-to-day execution of the strategic plans and governance of the group.

KN: What made you want to seek the position of managing partner?

Dr. Achinger: There's always change in the economic and regulatory environment around medicine that significantly impacts the work physicians do. We often feel as though we're not able to control most of these factors because we're busy in the patient care aspect. I've always paid attention to the changes in expectations from third-party payers and regulatory bodies that govern the practice of medicine and felt I could add something to my group because of this background. I've not held a previous administrative position beyond committee assignments, but I learned in my first nephrology group practice from 2007 to 2009, where I joined a friend from my fellowship prior to joining the Watson Clinic. There I learned how to grow a medical practice and be competitive in the marketplace. That experience taught me that I had a lot to offer the clinic, and I'm now mapping that into a larger scale.

KN: Did you have any business management education or experience before taking this position?

Dr. Achinger: I had experience in terms of small-group management and practice building, which are still the fundamentals, I believe, of a medical group. You have to be able to keep the business aspects in mind because we have to keep the lights on, pay our employees, and pay our rent. The fundamental thing is always being an excellent doctor and providing good care, and those other things should take care of themselves, but you can't neglect either one.

KN: Do you think your clinical nephrology practice was a springboard into management? In the sense of any lessons or experience you had from practicing that have been useful?

Dr. Achinger: In the practice of nephrology, you encounter large for-profit healthcare corporations, and you learn how to deal and negotiate with these companies. That experience is very useful to me in my current role as managing partner. Being able to understand how corporate business works and how to interact with them as a physician has been an invaluable tool.

KN: What are your goals as the managing partner?

Dr. Achinger: My goals are to 1) Maintain the core identity of the Watson Clinic as a 100% physician-owned and operated medical group, and 2) Provide the highest quality of care to our patients. We also have to demonstrate that we can provide cost effectiveness in the care we provide in order to survive in the future market, which we all feel is going toward a value-based reimbursement model. So, efficiency and cost-effectiveness are going to become more integral to organizations such as ours, and that can't be neglected.

KN: As managing partner, have you planned any changes to the Clinic or the nephrology practice?

Dr. Achinger: Changes are going to come slowly. One of the biggest challenges to overcome is how to coordinate our physicians so the care they provide meets quality improvement targets and is cost-effective, while still maintaining the high degree of autonomy that our physicians, as owners of their own practice, enjoy. What our doctors really love about the clinic is the large degree of autonomy they are granted. Therefore, how do we move our group in a direction that requires us to be moving in sync with each other while still maintaining our autonomy? That's the essential challenge with the position I hold, and my ability to be successful is going to depend upon how I maintain both of those.

KN: What challenges have you encountered in the management position?

Dr. Achinger: The main challenge I've encountered is the difficulty that comes along with making decisions that are in the best interest of the group, but might be unpopular and might put you, at times, in opposition to your peers. That's difficult, and there's no antidote to that. But, you have to look out for the best interest of the group. It is sometimes difficult to make that decision through the eyes of what's best for the group while maintaining your responsibility to represent all partners' interests.

KN: How about challenges in time management while practicing and managing?

Dr. Achinger: That hasn't been the biggest problem, to be honest. I do enjoy it and try to maintain a work-life balance with the help of my wife, who is very supportive. On the clinical side, I've had to utilize a nurse practitioner more than I have in the past in order to free up time.

I think those who are looking to step into similar management roles have to do a self-assessment asking, is this the right time in their career to make this transition, and it's not always. If I had the opportunity 8 years ago, for instance, it would not have been the right time for me. That didn't have anything to do with my ability at the time, but more to do with family and other constraints. You have to ask yourself, is this the right time to put this kind of strain on things?

KN: Do you have any tips or recommendations for a nephrologist, or any clinician, stepping into management?

Dr. Achinger: I feel very blessed in this role as I can serve as managing partner, but also continue my clinical practice. If I were confronted with a situation that was an either-or, that's a much more difficult decision to make because I think it would be hard to recoup. As a clinician, you spend a long time building your practice, so if I had to give that up completely, it would have been a much more difficult decision.

So, if you are considering a management role, try as best as you can to continue to see patients, continue to stay engaged in the actual practice of medicine because I think it will make you a better administrator and will also keep you from feeling like it's an irreversible step. If more management roles were structured in a way such that it wasn't all or nothing, and physicians were able to continue their clinical work, I think organizations would get more physician engagement.

I think that if we expect every doctor who wants to move into administration to suddenly give up clinical practice, we're selecting for a particular subset of physicians, so that may not lead to the best physician managers in the long run. Whereas, if there were more opportunities to do both—to be a practicing doctor and to be an administrative leader at the same time—then I think you're going to be selecting from a much larger pool that might otherwise not submit themselves for the running as they don't want to give up their practice.

KN: Any tips for a young nephrologist finishing their fellowship?

Dr. Achinger: I just hear rumors about the nephrology marketplace, but it's getting tough. Maintain your independence as much as possible. I'm a firm believer in private physician groups over hospital-owned practices. I think that wherever those opportunities exist, don't give up your autonomy. Also, of course, understand that it's going to be hard work.

Please contact Info@kidneynews.org if you have any questions or comments for Dr. Achinger.

ASN, HHS, and Members of Congress Share Common Vision for Improvements in Kidney Care

By David White

After years of advocacy from the American Society of Nephrology (ASN) and other members of the kidney community, the Department of Health and Human Services (HHS) and members of Congress are expressing very similar viewpoints to those of ASN and the broader kidney community on some of the major issues confronting the 40 million men, women, and children facing kidney diseases in the United States.

In May 2019, both the administration and members of Congress demonstrated their commitment to change in two critical areas: immunosuppressive coverage and innovation in the kidney space. Building on a speech HHS Secretary Alex Azar gave outlining the department's plans to tackle many aspects of kidney health policy, HHS is expected to unveil an HHS-wide kidney strategy. Among other things, it is anticipated the strategy will include an announcement from the Centers for Medicare and Medicaid Innovation (CMMI) regarding a new kidney care model for testing—for which ASN's Quality Committee and Policy and Advocacy Committee have been recommending elements for inclusion.

Extending immunosuppressive coverage

When ASN and other kidney community stakeholders met with HHS Secretary Azar in February 2019, one of the topics the society highlighted was the need for better data from HHS regarding the likely number of transplant patients who would utilize lifetime immunosuppressive drug coverage were Congress to pass legislation extending it past 36 months.

On May 10, 2019, the Office of the Assistant Secretary for Planning and Evaluation within HHS released an analysis demonstrating that extending Medicare coverage specifically for immunosuppressive drugs for more than 3 years posttransplant would save Medicare at a minimum $73 million over the course of 10 years (1).

"Providing limited Medicare coverage for only immunosuppressive drugs could result in savings associated with preventing reversion to dialysis and may have the added benefit of supporting transplant recipients in deciding to transition off Social Security Disability Insurance and Medicare," according to the report. "This may enable transplant recipients to return to the labor market and possibly enroll in private health insurance coverage, since they may be less concerned about losing coverage for their immunosuppressive drugs. Although these additional savings are not incorporated into the current analysis, given a recent study indicating that a little over 60% of individuals under age 65 who receive a kidney transplant currently continue to be enrolled in Medicare past 36 months, such savings could be substantial."

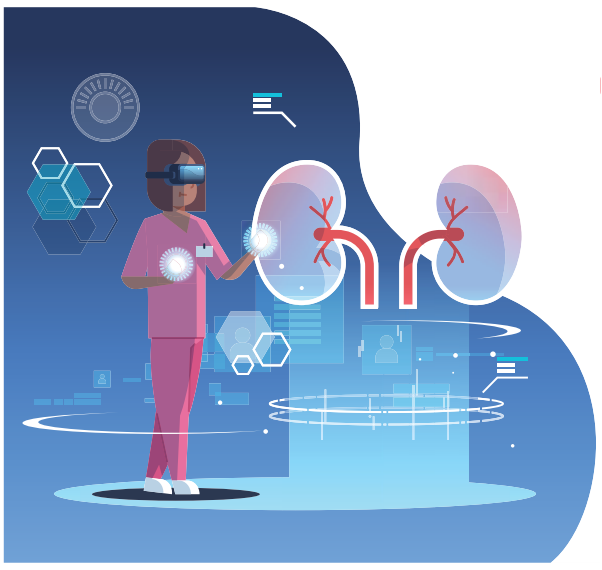
Kidney News Online reported in March 2019 in the article "Extending coverage for immunosuppressant drugs" that in a House Appropriations subcommittee hearing Secretary Azar previewed the analysis in response to a question from kidney care champion Rep. Jaime Herrera-Beutler (R-WA-03), who highlighted that "oftentimes we see people who lose their transplants get back on dialysis, because Medicare won't cover it. And the cost and quality of life issues are ridiculous: it's a lose-lose."

ASN President Mark E. Rosenberg, MD, FASN, responded to Secretary Azar's preview in March saying, "ASN has been advocating for Congress to extend this life-saving coverage for years. In fact, last month, representatives from ASN and other kidney community stakeholders discussed with Secretary Azar and other HHS leadership how helpful obtaining data regarding the potential cost or savings of extending immunosuppressive coverage beyond the three-year window would be." ASN Policy will continue advocating for Congress to extend the coverage.

Spurring innovation

ASN has been actively advocating for multiple pathways that could spur innovation throughout its existence. Keystone moments include former ASN President Sharon M. Moe, MD, FASN, testifying before a 2014 House Subcommittee on Research and Technology hearing on the use of prizes to spur innovation and technology breakthroughs, the creation of the Kidney Health Initiative (KHI) in 2012, and the formation of the 2018 Kidney Innovation Accelerator (KidneyX), a public-private partnership between HHS and ASN to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases. Like immunosuppressive coverage, many of these efforts also came full circle in May.

KidneyX hosted its inaugural Summit in Washington, DC, April 29–30. The summit was overbooked with members of Congress, the administration, and the kidney community—patients, healthcare professionals, innovators, and investors. Attendees spoke about their sense that kidney issues were receiving unprecedented levels of support, signifying a turning tide in kidney care and hopes that KidneyX could serve as a catalyst for innovation.



The Administration

Ed Simcox, JD, Chief Technology Officer at HHS, and ASN President Mark E. Rosenberg, MD, FASN, kicked off the Summit and announced the 15 finalists for the KidneyX Redesign Dialysis Phase I prize competition. (Abstracts from the 15 finalists may be viewed on KidneyX.org.)

"Being present at the KidneyX Summit was the most exciting and energizing experience I have had as a nephrologist. I could palpably sense the excitement, hunger, and momentum for developing new treatments for kidney diseases," said Dr. Rosenberg. "There was remarkable alignment of scientists, innovators, policymakers, industry, care providers, professional societies, and patients. I left the Summit knowing that we can and will make progress in the prevention and treatment of kidney diseases."

HHS Deputy Secretary Eric Hargan, JD, set the tone for Summit attendees declaring that kidney patients deserved more treatment options and applauded the efforts of KidneyX. Mr. Hargan went on to outline that policy changes are needed in addition to new technologies. "Patients with kidney failure deserve more options for treatment…. Today's policies bias providers toward center-based dialysis and in particular payment incentives probably encourage dialysis [centers] to attract and retain patients rather than allow for the most appropriate mode of care," suggesting that more home dialysis and transplant care is needed. Mr. Hargan was followed by Adam Boehler, Deputy Administrator of the Centers for Medicare & Medicaid Services (CMS) and Director of CMMI, participating in a "fireside chat" during which he discussed how payment policy can help spur innovation. Mr. Boehler is directly overseeing the development of the comprehensive kidney care model referenced earlier.

Members of Congress

The bipartisan, bicameral enthusiasm for KidneyX was on full display at the Summit. Sen. Todd Young (R-IN) provided the Senate's perspective and noted that he will continue to champion KidneyX in the Senate. Congressional Kidney Caucus Co-Chairs Rep. Suzan DelBene (D-WA) and Rep. Larry Bucshon, MD (R-IN) highlighted the need for innovation in the kidney space as well as delivered a remarkable show of support by gathering the signatures of 57 members of the House of Representatives in support of $25 million for KidneyX in the fiscal year (FY) 2020 Labor, Health and Human Services, Education and Related Agencies (LHHS) Appropriations bill.

Owing to the support of these and other key congressional champions like Rep. Terri Sewell (D-AL), and the advocacy efforts of ASN and other kidney organizations, John R. Sedor, MD, FASN, KidneyX Chair, made a surprise and welcomed announcement at the Summit that the House Appropriations Committee included $10 million for KidneyX in the FY 2020 LHHS bill. ASN will continue to engage the broader kidney community to work to ensure that KidneyX receives federal funding in FY2020.

"The excitement and energy in the room was palpable. The interest in KidneyX is tangible proof of the hunger in the community for disruptive change in how we diagnose and manage kidney diseases," said Dr. Sedor. "Our patients are waiting for KidneyX to foster innovation from the bench to the bedside."

Redesign Dialysis Phase II, the second phase of KidneyX's inaugural prize competition, was announced at the Summit. Phase II asks innovators to develop and demonstrate prototype solutions and will award $500,000 to up to three finalists.

The Patient Access to ESRD New Innovative Devices Act (H.R. 2710)

Also introduced in May 2019, the Patient Access to ESRD New Innovative Devices Act calls for the Secretary of HHS to make changes to the Medicare payment bundle for dialysis to "allow a pathway for innovation in new medical devices that improve dialysis treatment and outcomes." H.R. 2710 was introduced by Reps. Danny Davis (D-IL) and Trey Hollingsworth (R-IN).

The bill and an accompanying regulatory outreach effort have been a top policy priority of ASN for years. ASN's letter of support states, "Your important and timely legislation would increase to the House sponsors of the bill patient access to new products that may increase their quality of life or help bring better value to the healthcare system by creating a pathway for new and innovative devices for kidney failure to be reimbursed by Medicare in the bundle."

Reference

1. https://aspe.hhs.gov/system/files/pdf/261746/Savings_From_Extending_Coverage_For_Immunosuppressive_Drugs_Final.pdf

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ACCREDITATION for Outpatient Dialysis Facilities

In February 2018, Congress passed a law allowing deemed status for ESRD facilities, which had been specifically prohibited by the 1972 law that provided Medicare coverage for ESRD. The 2018 law allowed accreditation organizations to apply to the Centers for Medicare and Medicaid Services (CMS) for deemed status. The following is an interview with Glenda Payne, an owner of National Dialysis Accreditation Commission (NDAC), the first accreditation organization to earn deemed status from CMS for survey of ESRD facilities.

Kidney News (**KN**): What is the difference between accreditation and certification?

Glenda Payne (**GP**): Accreditation is awarded to a facility that meets the standards of the accrediting organization (AO). CMS awards certification based on the successful completion of an initial survey by either a state agency, or by an AO with deemed status. Certification by CMS is required to receive payment for care of Medicare beneficiaries.

KN What is "deemed status?"

GP Deemed status means that an AO's standards and survey process have been reviewed by CMS and found to be equivalent to the CMS regulations and survey process for a specific provider type.

KN What does it mean if a dialysis facility is accredited with deemed status?

GP It means that the dialysis facility has successfully completed a survey by an AO with deemed status, that CMS will certify (and pay) the facility for care of Medicare beneficiaries, and that the facility is largely exempt from oversight by the state agency.

KN Are AOs with deemed status contractors for CMS?

GP No. AOs are independent organizations with no direct ties to a government entity. They apply to CMS for deemed status and must report survey information to CMS, but are not a part of a government agency.

KN In the 27 states that require ESRD facilities to be licensed, are AOs allowed to do the state licensing surveys?

GP This varies by state. Most states retain the right to conduct the initial licensing survey, but an AO can do the initial survey for Medicare certification by deemed status after the facility completes licensing requirements and begins to provide service. Several states are open to collaborative agreements with AOs to allow the AO to do subsequent licensing surveys.

KN What are the differences between an AO survey and a state survey?

GP The AO survey process must be equivalent to the CMS survey process. In our case, the NDAC survey process is based on the CMS Core Survey process and uses tools that are very similar to those the state surveyor uses. Another difference with NDAC is that all surveyors have dialysis expertise and there is a centralized review of the findings of every survey.

KN What is the cost of an AO survey?

GP An AO sets the cost of the survey, and the various AOs entering this market may charge different rates. The cost of a basic survey by NDAC covers a three-day survey by an experienced dialysis nurse, a full written report within 10 working days, and upon receipt of an acceptable plan for any cited deficient practices, accreditation with deemed status for three years.

KN Will an AO do complaint investigations?

GP Yes, an AO is expected to be able to investigate all complaints received. Accredited facilities are expected to post a notice with contact information for the AO. If the state agency or CMS receives a complaint with allegations that pose a serious risk to patient health and safety, the state will be authorized to conduct the investigation. Less serious complaints received by the state or CMS are to be referred to the AO.

KN Will an AO be able to do surveys to add services or stations, for example to add home dialysis services?

GP Yes, AOs can do expansion surveys, including surveys to add home dialysis services. This survey would include accreditation of the in-center services if those were not already accredited.

KN Can an AO limit its service area to particular states?

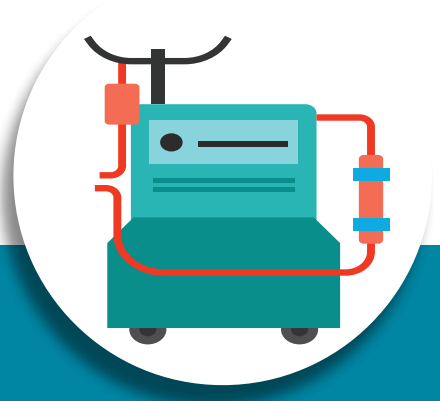
GP No. CMS requires all AOs to provide service to all US states and territories.

KN How long is the accreditation "good?"

GP CMS limits the accreditation period to 3 years. Each accredited facility will need to be resurveyed within 36 months to maintain accreditation with deemed status.

KN How will CMS oversee AOs with deemed status for ESRD?

GP There is a rigorous approval process that is repeated every 4 to 6 years. This includes review of the AO Standards and policies and procedures, surveys completed, qualifications and training of staff, and observation of an actual survey. In addition, CMS reviews the findings and the accepted plan of correction for each initial survey including the first accreditation survey of existing facilities. AOs are required to submit data every month to include surveys completed the last month, the outcomes of those surveys, and the schedule of surveys for the following month. Finally, CMS conducts validation surveys to ensure the AO is continuing to use a survey process that is equivalent to the CMS process.



Accreditation organizations are independent organizations with no direct ties to a government entity. They apply to CMS for deemed status and must report survey information to CMS.

KN Why would a dialysis facility choose accreditation over remaining under state oversight?

GP Our clients have given us several reasons:

- Consistency. Having experienced dialysis nurses conduct the survey and review of the findings centrally means there is assurance that all surveyors follow the AO Standards as written and that there is more likelihood of the "same survey" being done each time, eliminating the survey variance from surveyor to surveyor or from state to state.
- Predictability. Knowing that the surveys will be done within 36 months helps to maintain "survey readiness" at all times.
- Clinical rigor. Having experienced dialysis nurses who know the Standards and apply them fairly in every survey increases the likelihood that serious issues will be identified so that steps can be taken to improve safety and reduce risks of poor patient outcomes.
- Timeliness. While the same law that allowed deemed status also mandates CMS conduct initial surveys of dialysis facilities within 90 days of readiness, shaving just weeks off of that timeline can significantly reduce start-up costs. Since there is no mandate for CMS timeliness in adding services or stations, using an AO for these survey needs can speed up that approval by months.

Note: The Accreditation Commission for Health Care was approved for deemed status in April 2019.

Kent Thiry Resigns as DaVita Chair and CEO

Kent Thiry has resigned as chairman and chief executive officer of DaVita (Denver, CO), one of the largest kidney care services companies in the world. After 20 years in the role, the colorful CEO was practically synonymous with the company.

MarketWatch reports that he will transition to executive chairman of DaVita. Javier Rodriguez takes over as CEO of the company (after serving as CEO of DaVita Kidney Care).

When Thiry took over the business in 1999, it was called Total Renal Care. *Chief Executive Magazine* in 2009 wrote rhapsodically about what the CEO had managed to accomplish in 10 years:

- Employee turnover decreased by 50% between 1999 and 2005.
- A 1999 year-end loss of $417.3 million on revenue of $1.45 billion by the year 2004 was turned into net income of $222.3 million on revenue of $2.3 billion. (At the end of calendar year 2018, DaVita had net income of $333 million and total revenues were $11.4 billion.)
- A 2004 purchase of US clinics from Swedish dialysis firm Gambro nearly doubled the size of the company.

Thiry will be remembered for intimate team-building, as well as for turning around a company in crisis after he arrived in 1999. He also made an impression within the organization—and to outside Thiry-watchers. Employees named the company DaVita (Italian for "giving life"), and the company became known internally as a "village" where Thiry presided as "mayor." Employees were known hence as "citizens" and "teammates."

The New York Times, Denver Post, and others have written about his proclivity for dressing as one of the Three Musketeers and proclaiming, "All for one, one for all."

Thiry's two-decade tenure, begun at age 43, wasn't without controversy. While Thiry led the company, DaVita had to settle several lawsuits, including a recent one for three wrongful patient deaths, another for physician "kickback" practices, and a federal suit that violated the False Claims Act.

Business schools have studied DaVita's somewhat unorthodox approaches to team efforts and success in shaving seconds off dialysis procedures in order to create envied labor-hour-per-treatment statistics.

Kidney Cancer Updates

News concerning combination drugs in the kidney cancer space continues apace. Recently, Merck & Co. and Pfizer obtained approval from the US Food and Drug Administration (FDA) for a combination of Merck's Keytruda (pembrolizumab) and Pfizer's Inlyta (axitinib) as a frontline treatment for patients with advanced renal cell carcinoma.

OncLive reported that the findings from the phase 3 KEYNOTE-426 trial showed that the frontline combination significantly improved overall response rates (ORRs), as well as progression-free and overall survival compared with Pfizer's Sutent (sunitinib), a tyrosine kinase inhibitor. The data showed that the combination reduced the risk of death by 47% versus sunitinib alone (95% CI).

"This is the first anti–PD-1 therapy that is approved as part of a combination regimen that significantly improved overall survival, progression-free survival, and ORR compared with sunitinib in this patient population," OncLive reported.

For those striving to make sense of the marketplace for therapies for RCC patients, especially those with advanced cancer, Motley Fool has published an informative story that guides readers through the most promising competitors, including those mentioned above, Bristol-Myers Squibb with its combination of Opdivo and Yervoy, as well as Exelixis with Cabometyx and Novartis with Afinitor.

Says Motley Fool, "The highest sales in the kidney-cancer market will go to the drug—or, at this point, drug combination—used by the most first-line patients. But that treatment will fail for many patients, offering plenty of opportunity for good drugs to be used as second-line treatments."

In other cancer news, Hoffmann–La Roche (Basel, Switzerland) and Genentech, (South San Francisco, CA) have published results of their drug atezolizumab (Hoffman-LaRoche brand name Tecentriq) in combination with bevacizumab (Genentech's Avastin) versus sunitinib as a first-line therapy for metastatic renal cell carcinoma.

The study, published recently in the *Lancet*, showed that the combination of drugs prolonged progression-free survival compared with sunitinib and had a favorable safety profile. Further research is needed to demonstrate a survival benefit to the combination, the authors wrote.

A New Kind of Home Dialysis

Simergent announced plans to use a new round of seed money, $2.835 million, to further development of a cheaper, quieter home dialysis machine. The company, with offices in Okla-

homa City and Chicago, said in a media release that its Archimedes dialysis system "aims to reduce healthcare expenditures, improve patient health, and make it easier for patients to perform dialysis at home."

The majority of funding for this innovation comes from the Oklahoma-based company i2E. The funding will support Simergent as it continues to design the system, manufacture the device, and perform regulatory testing needed for FDA approval.

Website ChicagoInno.com interviewed co-founder and CEO Steve Lindo and learned that the company will be selling the product directly to dialysis clinics and providers. In this way, the cost would "be paid for using Medicare budgets allocated to dialysis providers," Lindo said. The federal healthcare program would be able to save money on dialysis by shifting more patients to the home setting, Lindo noted.

While patients would still interface with the machines at night through implanted catheters, the device features a way to prevent peritonitis (inflamed abdominal tissue). The machine would be quieter compared with current home dialysis machines, which can disrupt sleep, the company notes.

Simergent has its eye on foreign sales, too, in countries such as Mexico, China, and India, that would be attracted to a lower-cost option. In a 2015 *Lancet* article, investigators noted that at least 23 million people may have died prematurely from kidney failure because they could not access life-saving treatment. Most deaths occurred in China, India, Indonesia, Pakistan, and Nigeria.

Nephrologists may welcome such a new device, as well as other innovations in dialysis. A recent survey of 202 nephrologists by Spherix Global Insights showed that 41% of nephrologists agreed that "There is less opportunity for innovation in my specialty compared to other specialties." Overall, 48% of nephrologists responded that more innovation exists within the non-dialysis setting than in the dialysis setting. Nephrologists' highest priority was for new agents that could slow the progression of CKD, the survey found.

Anemia News

Rockwell Medical, Inc. (Wixom, MI) announced that the United States has approved commercial sales of Dialysate Triferic.

The company is developing multiple formulations of Triferic for treating anemia in adult hemodialysis patients. Dialysate Triferic is the first formulation to be sold. Rockwell expects to file a New Drug Application (NDA) with the FDA for its next formulation, I.V. Triferic, within the second quarter of 2019, the company said in a media release.

Rockwell received a preliminary recommendation from the Centers for Medicare & Medicaid Services (CMS) on April 26, 2019. Receipt of final approval would result in a unique J-code for the powder packet formulation of Dialysate Triferic (J-codes are created and used for non-orally administered medications and chemotherapy drugs; the code would be J1444).

"Dialysate Triferic is an innovative physiological alternative to existing IV iron formulations," said Marcos Rothstein, MD, professor of medicine in the Division of Nephrology at Washington University School of Medicine. He said the new product does not increase iron stores and has no ties to any cases of anaphylaxis. "Additionally, in patients with reticuloendothelial (RE) block, it overcomes functional iron deficiency," Rothstein said.

Fibrogen, based in San Francisco, has announced results from a safety analysis of its Roxadustat Global Phase 3 program and data reports focused on major adverse cardiovascular events. The phase 3 trials were conducted by FibroGen, as well as partners Astellas Pharma (Tokyo) and AstraZeneca (Cambridge, UK) to learn more about its ability to treat anemia in CKD patients. Patients who participated fell into three groups: non-dialysis dependent (NDD), patients new to dialysis, and dialysis-dependent (DD) CKD populations. In dialysis patients, roxadustat was compared with Epogen (epoetin alfa). For predialysis patients, the study drug was compared with a placebo.

The pooled findings from the global trials showed that roxadustat in some instances did not perform better than the comparison drug/placebo in the area of cardiac event data. Only in the "incident dialysis" (new to dialysis) group was the study drug "superior" to epoetin alfa in the results for "time to first Major Adverse Cardiac Events (MACE), plus heart failure requiring hospitalization and unstable angina requiring hospitalization" (MACE+), according to a media release.

FierceBiotech noted that "After talking to management at FibroGen to unpack 'a very complex dataset,' analysts at Jefferies think the readout is far better than investors feared initially and ultimately a positive for the biotech company and its partners, AstraZeneca and Astellas." Jeffries is an investment banking firm.

The European Medicines Agency (EMA) noted that the primary safety assessment should be for the MACE+ category before approval. For a planned NDA submission to the FDA, one of the key safety endpoints is MACE.

Detective Nephron

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

Henle A case for you, sir!

The detective sits facing the window, awaiting the arrival of his new students.

Nephron What do you have for us today, my dear apprentice?

Henle A 60-year-old man with proteinuria, microscopic hematuria, and an acute rise in creatinine level.

Nephron I see that you have taken a break from the electrolyte disorders and moved to the world of acute kidney injury (AKI). This is why nephrology is so much fun. It has so much variety to offer to us diagnosticians.

Henle Hmmm… getting back to the case, the patient was in his usual state of health until a few weeks ago when he was seeing his primary care physician; a creatinine level of 2.2 mg/dL was noted. It was 1.6 mg/dL several months earlier.

Nephron What was his creatinine level 1 year ago?

Henle It was 0.7 mg/dL 1 year ago

Nephron (*angrily*): OK; did you examine his urine?

Henle Yes, of course I did. There are a few red blood cells, none dysmorphic, and many white blood cells. I noticed several white cell casts but no red cell casts, and no signs of any granular casts.

Nephron Is there any proteinuria?

Henle Yes, 2.2 grams in a 24-hour urine collection.

Nephron I am sure they did serologies before they called you.

Henle Here are the results: antinuclear antibodies, anti–double-stranded DNA, myeloperoxidase, and proteinase 3—all negative results. His HIV test result is negative. Hepatitis B and C results are negative.

Nephron Stop right there. Before we go any further, let's think if this is truly an injury to the glomerulus.

Henle (*wondering to himself about quick decision by Nephron)*: Hmmm. I am not too sure whether this is a glomerular process.

Nephron Why is this not a rapidly progressive glomerular process?

Henle In this case, antineutrophil cytoplasmic antibodies and antiglomerular basement membrane antibodies are negative … and I suppose he could have an immune complex glomerular process.

Nephron My dear apprentice, you have a lot to learn still. First and foremost, can you give me this individual's medication list? Please go get that while I drink my coffee.

Henle leaves to get the information, and Nephron gets a cup of warm coffee. Henle returns after a few hours.

Nephron Please read out all his medications to me.

Henle He is receiving only two medications: insulin for his type 2 diabetes mellitus and loperamide for chronic diarrhea because of his episodes of chronic pancreatitis.

Nephron (*shocked*): Interesting! And boring. It's likely diabetic nephropathy. Go on to the next case.

Henle (*jumps in*): Can we go back to his laboratory results? Did I mention that he had a serum immunoglobulin free light chain ratio of 2.2 and a mild IgG κ spike in the serum immunofixation?

Nephron (*eyes light up*): Of course there is. So you're telling me there is potentially a monoclonal gammopathy of renal significance (MGRS)? I suppose there are more reports on MGRS than there are cases in nephrology. But a free light chain ratio of 2.2 is not concerning for someone with a creatinine in the range of 2 to 3 g/dL. Remember, both free light chains are cleared by the kidney. I would still continue the workup and not just stop at this immunofixation. Two-thirds of patients with MGRS have non–paraprotein-related findings in the kidney biopsy specimens, but the other third do have MGRS. What is his ethnicity?

Henle White.

Nephron Hmmm… if we still think this is a glomerular process, could it be MGRS? Or just diabetic nephropathy?

Henle (*confused*): Hmmm…. so is that the connection? How about we start from a more basic approach? Why are we jumping into the glomerulus without a systematic approach?

Nephron (*interrupting*): Is there anything on his physical examination?

Henle Nothing specific except some trace edema bilaterally in the lower extremities. There was some concern for potential lymph nodes felt in the axillary regions. I think we are jumping around too much. It's as if I am getting power texts of multiple information.

Nephron Haha! As you say, laughing out loud. The social media generation shouldn't have a problem with overproduction of information. You can handle it. I am assuming you want to go over a systematic approach to rule in and rule out other causes of AKI?

Henle Yes. I don't think it is a prerenal condition, because his urine sodium is high, and I don't think it's a postrenal condition, because I personally inserted a Foley catheter, and a bladder sonogram shows no significant residual volume. He is not oliguric.

That leaves us with intrarenal causes. A tubular cause is still possible, regardless of the hematuria and proteinuria. This could be garden-variety tubular necrosis, but I can't find any source of low BP or any toxic medications, and the urinalysis showed no granular casts. An interstitial cause still bothers me. He has a lot of white blood cells and casts in his urine, and the result of his urine culture is negative, which suggests a sterile pyuria. He might have an acute interstitial nephritis, and the proteinuria could be of tubular origin.

I don't think he has a vascular disease process, although his platelets are low and he has anemia. Perhaps we should check his lactate dehydrogenase and haptoglobin levels, and do a peripheral smear to make sure there is no thrombotic microangiopathy, or

perhaps a bone marrow evaluation (which might rule out MGRS and make sure we are not missing other infiltrative process such as a lymphoma)? You already discussed the glomerular causes. I might get complement levels as well.

Nephron Amazing thought process, Henle. I am proud of you! Regardless, go ahead, and let's get some answers with the tests you ordered. Also, do you think a renal sonogram or a CT scan might help, given you have a concern for lymphoma? Also, why is this not diabetic nephropathy? And why do I keep asking that question?

Henle I suppose. Why not? The size of the kidney might give us a clue regarding a differential diagnosis. Alas, diabetic nephropathy is a default diagnosis here. His hemoglobin A1c has been 6% for years, and he has no diabetic retinopathy. In addition, the kidney size might help rule out diabetic nephropathy.

Nephron Sure, if you say so. Well, how sudden is the rise in proteinuria? That might be a clue if this is not diabetic nephropathy. Go find out more information, my friend.

Henle exits.

Nephron Fine work by Henle.

A day later

Henle He is not doing well. His renal function and anemia are worse. His complements are normal. His renal sonogram shows massively enlarged hyperechoic kidneys that are rather large: 17.5 cm bilaterally in the longitudinal axis. To me, the large size suggests HIV-associated nephropathy, amyloidosis, obstruction, or some combination—but he does not have an obstruction. Another possibility is diabetic kidney disease, but a size over 15 cm sounds rather large to me, and sudden proteinuria in just a few months does not fit the picture. A CT scan shows multiple diffuse large areas of patchy decreased enhancement on both kidneys. Differential diagnosis includes vasculitis, with metastases or lymphoma less likely but not entirely excluded. His lactate dehydrogenase was not that elevated at 400 U/L, and this is surprising. His proteinuria is also new—it was normal 1 year ago, and a few months ago it was 1 gram over 24 hours. I think we have to rule out a lymphoma, given the axillary lymph nodes, large kidneys, positive immunofixation, and worsening creatinine level. I think there might be infiltrative disease in the kidney.

Nephron Please also obtain a bone marrow biopsy and a lymph node biopsy.

Henle, puzzled, leaves the room but returns quickly.

Nephron And?

Henle Bone marrow biopsy result is negative. I scheduled him for a kidney biopsy and lymph node biopsy.

Nephron Henle, your initial hunch was correct. You were thinking of causes of sterile pyuria and came up with interstitial nephritis. What else can cause leaking of white blood cells into the urine and interstitial nephritis and large kidneys or masses around the kidney?

Henle Infiltrative disease? Or some other systemic process?

Nephron Does this patient have any other "itis" in the past besides pancreatitis?

Henle (*surprised*): Yes, pancreatitis, and prostatitis as well. Why?

Nephron Yes, please get a kidney biopsy as soon as possible. Also, please make sure to look in the lymph node and kidney biopsy specimens for all subtypes of IgG.

Henle leaves the room in a rush and returns a day later.

Nephron And?

Henle More puzzling than I thought. No lymphoma. The lymph node biopsy specimen showed IgG4-positive plasma cells with fibrosis, consistent with IgG4-related disease. The kidney biopsy specimen also showed IgG4-related interstitial nephritis with significant chronic changes.

Nephron (*with confidence*): Infiltrating lymphoma in the kidney can lead to large kidneys, sterile pyuria, and AKI, but IgG4 disease is a mimicking disease and often missed, as in this case. In addition, the proteinuria might have been tubular in origin, given that the glomeruli appear normal in many cases.

Henle is stunned.

Nephron There were subtle clues here, but clearly this was not diabetic nephropathy. This was not MGRS, either. You went through a systematic process, and a kidney biopsy was essential here.

Henle (*puzzled*): But presenting only in the kidneys and in no other place? Is that possible?

Nephron This is a systemic process and has been in this man's body for years. Pancreatitis might have been the first "itis" that this presented with. This disease causes inflammation and formation of fibrosis at several sites. Autoimmune pancreatitis was one of the first states in which IgG4 disease was discovered in 2003. IgG4-related kidney disease can have any pattern of renal involvement: the glomeruli, tubules, and interstitial vessels, and also the renal pelvis, may all be affected. The most frequent renal manifestations are IgG4-related tubulointerstitial disease (most common), membranous GN, obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis, prostatitis, or ureteral inflammation. The role of IgG4 in the pathophysiology of IgG4-related kidney disease is still controversial. Cellular immunity, particularly T cell–mediated immunity, might be playing a major role.

Henle Can't you just diagnose using IgG4 levels in the serum?

Nephron (*angrily*): Life is always not that simple, Henle. A diagnosis should not be made solely on the basis of serum IgG4 levels because there are both false positives and false negatives in serum IgG4 testing. Elevated IgG4 does not equate to IgG4-related kidney disease. A serum IgG4 level >1350 mg/L is a suggested cutoff value for the diagnosis of IgG4-related kidney disease; however, that is to be used as a useful screening tool, not a standalone diagnostic marker. A tissue diagnosis is indeed important as a differential diagnosis in lymphoma or a paraprotein disorder.

Nephron In addition, often in this disease the complements might be low. In your case, they were normal.

Henle I am still confused regarding this disease. Is this a precancerous condition, an autoimmune disease, or an allergic reaction?

Nephron (*smiling*): Glad you asked, my friend. Always ask! The current hypothesis is that this is a combination of autoimmune and allergic diseases. CD4+ cytotoxic T cells orchestrating the disease are sustained by continuous antigen presentation by B cells and plasmablasts. And if you are an onconephrologist, think of the patient being on a checkpoint inhibitor. The immune system is constantly activated and causing all forms of "itis." In IgG4 disease, there is also a lot of "itis" and inflammation of similar sorts. A T-follicular helper cell response that is separate from the CD4+ cytotoxic T lymphocytes is likely to be responsible for the development of germinal centers within lymph nodes (and involved organs) and the production of cytokines that drive the IgG4 class-switch, culminating in the creation of IgG4-secreting plasmablasts and long-lived plasma cells. B cell depletion often does not lead to the complete normalization of serum IgG4 concentrations even after clinical remission, implying that long-lived plasma cells continue

Continued on page 16 >

Detective Nephron Continued from page 17

to make this immunoglobulin.

Henle I assume treatment with steroids or immunosuppression will help this process?

Nephron High-dose prednisone can help with tapering over weeks and then maintenance over 1 to 4 years. In refractory or frequently recurrent cases, immunosuppressive medications including mycophenolate, cyclophosphamide, and azathioprine can be combined with steroids. I am sure "Vitamin R," or rituximab, has been used in many tough cases. Seems like the renal world is in love with that agent. Regardless, in IgG4 disease, with appropriate immunosuppressive treatment, kidney function can be preserved in most patients.

Nephron What are you waiting for?

Henle leaves to discuss the case with his hematology colleagues.

A few weeks later

Henle What a dramatic response. After steroids were initiated, the patient's renal function improved, and his proteinuria resolved. In addition, I repeated a sonogram, and the kidneys are now 10 cm bilaterally. This is amazing!

Nephron Well done, apprentice. Keep an open mind. Again, with a renal disorder you diagnosed a systemic disease that saved this patient's life. This was a complex disease and a complex case—although I recently read that nephrologists treat the most complex patients. That is a true statement. Complexity creates curiosity, and for a detective, it creates a venue for solving tough cases! Henle, let's get a cup of my favorite coffee.

Detective Nephron was developed by Kenar D. Jhaveri, MD, professor of medicine at Zucker School of Medicine at Hofstra/Northwell. Special thanks to Dr. Rimda Wanchoo, associate professor of medicine at Zucker School of Medicine at Hofstra/Northwell, for her editorial assistance. This case was provided by Smitha Anam, MD, fellow, and Enrica Fung, MD, assistant professor, both from Loma Linda University, Southern California. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.

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Index to Advertisers

Baxter . . . . . Page 2
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