ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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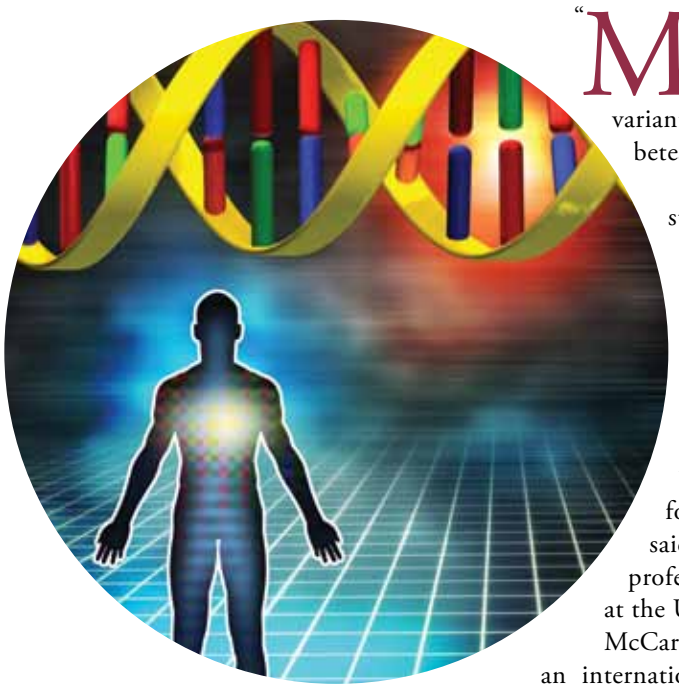
Search is on for Rarely Occurring Genetic Variants for Type 2 Diabetes

Findings from studies of five ancestry groups may aid diabetes knowledge

By Cathy Yarbrough



"Missing heritability" has become the holy grail in the search for genetic variants underlying type 2 diabetes.

Genome-wide association studies have linked over 60 commonly occurring susceptibility loci to type 2 diabetes, but the impact of each of these variations is modest. These commonly occurring variants represent only about 10 percent of overall risk for developing the disease, said Mark McCarthy, MD, professor of diabetic medicine at the University of Oxford.

McCarthy is one of the leaders of an international research consortium with a unique approach to identifying missing heritability, that is, the genetic variants that rarely occur in the population but that may have much stronger effects on type 2 diabetes disease risk than do the common variants thus far identified.

The consortium's approach is to sequence and analyze the whole exomes—or coding portions of genes—of 10,000 individuals of five major ancestry groups: African American, East Asian, European, Hispanic, and South Asian.

The search for the variants that influence an individual's genetic predisposition for developing type 2 diabetes and renal disease requires such large population studies and often many years of work, said Arlene Chapman,

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Losartan Fails to Prevent Allograft Fibrosis and Loss in Transplant Recipients

Trial Results Attest to the Safety of Angiotensin II Blockade

By Tracy Hampton

Angiotensin II blockade can slow the progression of chronic kidney disease, but how effective is it in kidney transplant recipients? Investigators recently completed a large, randomized placebo-controlled clinical trial that looked at this very question.

"Contrary to what has been observed in native kidney disease, angiotensin II blockade did not demonstrate a statistically significant benefit in lessening fibrosis or terminal kidney failure from severe fibrosis," said first author Hassan Ibrahim, MD, professor in the division of renal diseases and hypertension at the University of Minnesota, Twin Cities campus. "Nevertheless, angiotensin II blockade was safe and well tolerated."

The study, which is published in the *Journal of the American Society of Nephrology*, provides valuable information that can be used to design future interventional trials to treat kidney transplant recipients.

Trial design and results

Immunosuppressants help prolong the function of transplanted organs, but thera-

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Inside

Losartan

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pies that target non-immunological damage to these organs—such as elevated blood pressure and tissue fibrosis—have not been studied. Because angiotensin II blockade, which causes blood vessels to dilate, can slow the progression of kidney disease in the nontransplant setting, Ibrahim and his colleagues reasoned that the strategy should also be tested in transplant recipients.

"To our knowledge this is the first randomized placebo-controlled trial of angiotensin II blockade in these patients," Ibrahim said.

The rationale for the trial rested on the hypothesis that blocking the fibrogenic effects of angiotensin II and ameliorating the hemodynamic consequences of reduced nephron number would reduce structural damage in transplanted kidneys.

The trial included 153 kidney transplant recipients who received either 100 mg of losartan per day or placebo within 3 months of transplantation. Treatment continued for 5 years. Losartan blocks the receptor for angiotensin II, an important factor involved in the renin-angiotensin-aldosterone system, which is a complex hormone system that regulates blood pressure and fluid balance.

A key premise of the trial was that losartan would exert a beneficial effect independently of its blood pressure–lowering properties, so every effort was made to keep blood pressure levels similar in the two treatment groups. This involved treating patients with calcium-channel blockers, followed by diuretics as second-line therapy and β-blockers as third-line therapy.

The primary outcome of the trial was a composite of doubling of the cortical interstitial compartment (a precursor of fibrosis) from baseline to 5 years or end stage renal disease from interstitial fibrosis and tubular atrophy, previously termed chronic allograft nephropathy. In the intention-to-treat analysis of patients with adequate structural data, the primary end point occurred in six of 47 patients who received losartan and 12 of 44 patients who received placebo, but the investigators found no significant effect of losartan on time to a composite of end stage renal disease, death, or doubling of creatinine level. In a secondary analysis, losartan seemed to reduce the risk of a composite of doubling of interstitial volume or all-cause end stage renal disease by 64 percent, but this finding requires validation.

Additional studies warranted

Although losartan was not associated with a statistically significant benefit in the primary outcome, it was well tolerated. Despite a higher level of serum potassium, only one case of severe hyperkalemia (potassium level greater than 6 mEq/L) occurred. Serum potassium levels were consistently 0.1 to 0.3 mEq/L higher in the losartan group, and hyperkalemia was observed intermittently in 17 of 77 (22.1 percent) patients in the losartan group and 5 of 76 (6.6 percent) patients in the placebo group. A total of 291 adverse events were reported, averaging 1.71 per participant in the losartan group and 2.09 in the placebo group.

According to the authors, a possible explanation for the lack of a clear and robust benefit of losartan, which has been observed in relatively advanced native kidney disease, is that this study was a primary prevention trial that included many relatively low-risk patients, mostly white recipients of live-donor kidney transplants who had low immunologic risk.

They also noted that the degree of interstitial expansion in the patients in this study was less than what has been described in the literature. The study's original sample size estimate and power calculations predicted that 60 percent of placebo-treated patients would double their cortical interstitial fractional volume or develop end stage renal disease from interstitial fibrosis and tubular atrophy, but at the end of the trial, fewer patients than expected reached that end point.

"The event rate in the trial was much lower than what was expected, which affected the statistical power of our findings," Ibrahim said.

The investigators concluded that the trend toward a treatment benefit from losartan and the lack of clear harm supports the performance of a larger clinical trial. In this regard, the findings

provide valuable information for future studies of non-immunological therapies for kidney transplant recipients.

Consensus among experts

"Although the study had a negative result on the primary prevention of interstitial fibrosis and tubular atrophy, it showed the excellent tolerance of losartan in these patients with a good control of blood pressure," said Joseph Campistol, MD, director of the Clinical Institute of Nephrology and Urology at the Hospital Clinic in Barcelona. "With these results in mind, the antihypertensive treatment in transplant patients could be re-evaluated."

Ibrahim noted that results from a similar ongoing trial in Canada should provide additional information on the potential role of angiotensin II blockade in these patients.

Study co-authors include Scott Jackson, MS, Jeffrey Connaire, MD, Arthur Matas, MD, Arthur Ney, MD, Ann West, RN, Nicole Lentsch, RN, Jensina Ericksen, Jenny Bodner, RN, Bertram Kasiske, MD, FACP (Hennepin County Medical Center); Behzad Najafian, MD (University of Washington); and Michael Mauer, MD (University of Minnesota).

Disclosures: The study was sponsored by NIDDK (grant #U01 DK060706-09). The drug and placebo were provided by Merck Pharmaceuticals.

The article, entitled "Angiotensin II Blockade in Kidney Transplant Recipients," is available at http://jasn.asn-journals.org/, doi: 10.1681/2012080777.

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Genetic Variant

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MD, professor of medicine at Emory University. "This research has to be conducted in various stages and must be replicated," she said.

Including patients and controls representing the major ancestry groups strengthens the likelihood that variants may be discovered that either characterize all ancestries or just one group, said Chapman. Variants may include those that reduce risk and thereby are protective as well as those that increase risk for developing the disease, she said.

Genomics studies in the past have focused on individuals of Northern European ancestry, said leading genomics researcher Nicholas Katsanis, PhD. However, the variants identified in any one group "may be invisible in other populations," he said. Katsanis is the Jean and George Brumley Jr., MD, professor of developmental biology, and professor of pediatrics and cell biology at Duke University.

Because each ancestry group in the whole-exome studies includes equal numbers of controls and patients with type 2 diabetes, the researchers should be able to determine whether there are variants that increase or reduce an individual's predisposition for developing diabetes, said Tanya M. Teslovich, PhD, who spoke about the research at a recent meeting of the American Society of Human Genetics in San Francisco.

Teslovich, a research fellow in statistical genetics at the University of Michigan, and McCarthy are among the 75 scientists at 27 universities and other institutions participating in the Type 2 Diabetes—GENES (Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples) collaboration.

Although the commonly occurring loci already identified by genome-wide sequencing confer only a moderate risk, Teslovich and the other researchers regard them as beacons.

"We hypothesize that genes underlying the common signals identified in genome-wide sequencing also harbor low-frequency and rare variants," she said.

"Screening the exomes in a range of diverse ethnic groups increases the range of variants of each gene surveyed, and thereby improves our ability to detect genes showing differences in the patterns of the DNA codes for proteins between individuals with type 2 diabetes and controls," Teslovich said.

Initial analysis of the sequence data of 3500 African American, East Asian, and South Asian individuals identified about 1.6 million single nucleotide variants (SNVs), 71.5 percent of which were previously unknown.

"Only about 89,000, or 5.6 percent, of these 1.6 million variants are present in all three ancestry groups," she said.

About 35.4 percent of the SNVs are unique to African Americans, while 35.4 percent and 30.6 percent, respectively, occur only in East Asians and South Asians. The analysis is too preliminary to state that these population-specific variants are associated with type 2 diabetes and contribute to disease risk in a single population, Teslovich said.

During the analysis of the sequence data on the participants with East Asian ancestry, Teslovich and her colleagues found that a variant in the *PAX4* gene is associated with type 2 diabetes. Previous studies have shown that the gene is involved in pancreatic islet development and is linked to early diabetes onset.

In early 2013, the researchers will complete the exome sequencing of the 10,000 individuals in the study population. About 5300 individuals, half with type 2 diabetes and half controls, have been sequenced thus far, Teslovich said.

The study's design should yield a catalog of variations, including alleles that are common in the general population as well as those that are observed in only a small number of individuals.

"We will then examine each of the variants to determine which ones may affect an individual's risk of developing type 2 diabetes," she said.

Even if the Type 2 Diabetes—GENES collaboration does not identify any rarely occurring variants with a strong effect on risk for type 2 diabetes, the group's findings will add to researchers' and clinicians' knowledge of diabetes.

"To some extent that doesn't matter because we can still learn a lot about the biology of diabetes from such variants, and that has always been our primary motivation," McCarthy said.

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Journal View

Teen Overweight and Obesity Increase Long-Term ESRD Risk

Very-long-term follow-up shows elevated rates of ESRD for overweight and obese adolescents, according to a report in the *Archives of Internal Medicine*.

The study included approximately 1.2 million adolescents undergoing examination for compulsory military service in Israel from 1967 through 1997. Linkage to a national ESRD registry was performed to identify incident cases of ESRD between 1980 and 2010, at a mean follow-up time of 25 years. Body mass index at age 17 was evaluated as a predictor of ESRD developing in adulthood.

Treated ESRD was recorded during follow-up in 874 individuals, for an incidence rate of 2.87 per 100,000 person-years. The risk was significantly elevated for participants with overweight or obesity in adolescence. The incidence rates per 100,000 person-years were 6.08 for those in the 85th to 95th percentile of body mass index and 13.40 for those in the 95th percentile or higher.

With adjustment for blood pressure and other variables, the risk for the development of ESRD during follow-up was increased threefold for the overweight group and sevenfold for the obese group: hazard ratio 3.00 and 6.89, respectively. The risk was especially high for diabetic ESRD, HR 5.96 for overweight and 19.37 for obese adolescents, but was also elevated for nondiabetic ESRD, HR 2.17 and 3.41, respectively.

With rising rates of pediatric overweight and obesity, it is important to evaluate the implications for future risk of chronic diseases, including ESRD. The new study shows that overweight and obese adolescents are at increased risk of ESRD, including nondiabetic ESRD, at 25 years' follow-up. The authors call for further investigation of possible mechanisms, especially because the risk is increased for causes of ESRD apparently unrelated to obesity [Vivante A, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. *Arch Intern Med* 2012; 172:1644–1650].

In Canada, Similar Outcomes with HD and PD

Nationwide data on Canadian patients with ESRD show similar outcomes for those given peritoneal dialysis (PD) versus hemodialysis (HD), reports a study in *Nephrology Dialysis Transplantation*.

Using the Canadian Organ Replacement Register, the researchers identified 46,839 patients who started renal replacement therapy from 1991 through 2004. Of these, 69.5 percent were incident on HD and 30.5 percent on PD. Patients were followed up for survival through 2007, with outcomes compared for patients starting dialysis in 1991–1995, 1996–2000, and 2001–2004.

On intention-to-treat analysis across the study period, overall survival was better with PD through the first 18 months but was better with HD after 36 months. For the 2001–2004 cohort, survival was better with PD for the first 2 years, after which there was no significant difference between PD and HD. Peritoneal dialysis was associated with a 27 percent increase in mortality for elderly women (older than 65) with diabetes. As expected, technique survival was lower with PD than with HD, although it improved slightly from the 1991–1995 cohort to the 2001–2004 cohort.

In Canada, the use of PD as the initial dialysis modality has remained relatively stable over time but has decreased in recent years: from 37 percent in 1991 to 18 percent in 2007. The authors used newer statistical models to compare PD and HD survival in a contemporary cohort of incident dialysis patients in Canada.

The results show overall similar survival for ESRD patients receiving PD versus HD. Survival is higher with PD for the first 2 years but is similar thereafter. The authors conclude that "PD and HD should be seen as complementary modalities" offering a choice of treatment approaches for the individual patient [Yeates K, et al. Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. *Nephrol Dial Transplant* 2012; 27:3568–3575].

Decreased Kidney Function Increases Bleeding Risk with Enoxaparin

Patients with moderate renal impairment have a sharply increased risk of major bleeding during treatment with enoxaparin, suggests a report in the *Archives of Internal Medicine*.

From June through November 2009, 164 patients at the authors' Veterans Administration medical center were treated with enoxaparin sodium (1 mg/kg every 12 hours or 1.5 mg/kg once daily). On the basis of a creatinine clearance of 30–50 mL/min, 59 patients were classified as having moderate renal impairment. Episodes of major bleeding—causing death, hospitalization, longer hospital stay, or emergency department visit—were compared for patients with moderate renal impairment versus normal renal function (creatinine clearance over 80 mL/min).

Twenty-two percent of patients with moderate renal impairment had major bleeding episodes while taking enoxaparin, compared with 5.7 percent of those with normal renal function. The odds ratio for major bleeding in the moderate renal impairment group was 4.7, decreasing to 3.9 on multivariable adjustment for other risk factors. Independently of renal function, the risk of major bleeding was higher in patients receiving enoxaparin as bridge therapy: 13.7 percent, compared with 8.1 percent for those receiving new anticoagulation. Thromboembolism, evaluated as a secondary outcome, was similar between groups.

Enoxaparin, a low-molecular-weight heparin, allows simplified dosing without the need for laboratory monitoring. Even though enoxaparin is excreted by the kidneys, there is no recommended dose adjustment for patients with moderate renal impairment.

This study finds a fourfold increase in major bleeding with enoxaparin in patients with moderate renal impairment. More research is needed to establish appropriate dosing of this important and widely used anticoagulant in patients with reduced kidney function [DeCarolis DD, et al. Enoxaparin outcomes in patients with moderate renal impairment. *Arch Intern Med* 2012; 172:1713–1718].

CCB plus ARB Improves Outcomes in Hypertension and CKD

In high-risk older adults with hypertension and chronic kidney disease (CKD), adding a calcium channel blocker (CCB) to high-dose angiotensin II receptor blockade (ARB) yields further reductions in cardiovascular events, reports a trial in *Kidney International*.

The multicenter "OlmeSartan and Calcium Antagonists Randomized" (OSCAR) trial included 1078 older Japanese adults with hypertension and baseline cardiovascular disease and/or diabetes. In the main trial, patients were randomly assigned to upward titration of ARB or to the addition of a CCB to ARB therapy. The current study was a prespecified subgroup analysis assessing treatment responses according to baseline estimated GFR (eGFR).

On the basis of an eGFR of less than 60 mL/min/1.73 m^2, 353 patients had CKD; in almost all, eGFR was 30–59 mL/min/1.73 m^2. In patients with or without CKD, blood pressure was lower with CCB plus ARB than with high-dose ARB.

Among CKD patients, the primary composite outcome of cardiovascular events and noncardiovascular death was about twice as high in the high-dose ARB group: 30 versus 16 events, hazard ratio 2.25. In particular, the rates of cerebrovascular and heart failure events were higher in CKD patients receiving high-dose ARB, compared with CCB plus ARB. By contrast, for patients without CKD, the primary event rate was similar between treatment groups. The subgroup interaction was significant, with high-dose ARB being an independent prognostic factor for primary events among

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Journal View

CCB plus ARB

Continued from page 7

patients with CKD.

High-dose ARB therapy lowers the rate of cardiovascular and renal events in certain high-risk groups of patients with hypertension. The combination of an ARB with a CCB is a recommended treatment for the general hypertensive population.

This OSCAR subgroup analysis suggests that ARB plus CCB is more effective than high-dose ARB for elderly high-risk patients with CKD. In this group, the combination yields a lower risk of cardiovascular events, particularly stroke and heart failure. The results lend new insights for decisions about antihypertensive therapy for older adults with CKD [Kim-Matsuyama S, et al. An angiotensin II receptor blocker–calcium channel blocker combination prevents cardiovascular events in elderly high-risk hypertensive patients with chronic kidney disease better than high-dose angiotensin II receptor blockade alone in hypertensive patients with diabetic nephropathy. *Kidney Int* 2013; 83:167–176].

ACEIs Linked to Increased Angioedema Risk

The risk of angioedema appears higher for patients taking angiotensin-converting enzyme inhibitors (ACEIs) compared with other drugs targeting the renin-angiotensin-aldosterone system, according to a study in the *Archives of Internal Medicine*.

The retrospective analysis included adult patients from 17 health plans contributing data to the Mini-Sentinel program. From 2001 through 2010, more than 1.8 million patients started treatment with an ACEI, 467,313 with an angiotensin receptor blocker (ARB), and 4867 with the direct renin inhibitor aliskiren. A propensity score approach was used to compare the risk of angioedema between these three groups and with 1.6 million patients starting treatment with a β-blocker.

The "real-world" study showed an overall low rate of angioedema, with a total of 4511 events during follow-up. However, risk was elevated with ACEIs or aliskiren. The cumulative incidence per 1000 patients was 1.79 with ACEIs and 1.44 with aliskiren, compared with 0.62 with ARBs and 0.58 with β-blockers. The incidence rates per 1000 person-years were 4.38 for ACEIs and 4.67 for aliskiren, compared with 1.66 for ARBs and 1.67 for β-blockers.

The adjusted hazard ratio for angioedema (compared with β-blockers) was 3.04 with ACEIs and 2.85 for aliskiren. The risk of serious angioedema causing airway obstruction was low, but higher with ACEIs.

Some reports have linked drugs targeting the renin-angiotensin-aldosterone system to an increased risk of angioedema, but few have addressed the magnitude of this risk or the differences in risk between drug classes. The new study suggests that angioedema risk, though low overall, is elevated threefold in patients taking ACEIs compared with β-blockers. Aliskiren may also increase risk, according to studies based on a small number of cases; risk may differ for individual ARBs as well [Toh S, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012; 172:1582–1589].

Vaccines Improve Survival in Dialysis Patients

Influenza and pneumococcal vaccination are associated with improved survival for patients receiving dialysis, concludes a report in the *American Journal of Kidney Diseases*.

The study included data from 903 of 1033 dialysis facilities in ESRD Networks 6, 11, and 15. The centers provided information on health status at the start of dialysis, receipt of influenza and pneumococcal vaccination, and mortality associated with the 2005–2006 influenza season. The analysis included data on 36,966 patients who had been receiving dialysis for at least 1 year as of the end of 2005. All-cause mortality was compared for vaccinated versus unvaccinated patients.

During the 2005–2006 season, 41.8 percent of patients were vaccinated against influenza and pneumococcal disease. Vaccinated patients were older, in worse health, more likely not to be black, and more likely to be receiving hemodialysis. The 1-year mortality was 17.1 percent overall, 15.9 percent for patients receiving both vaccinations, and 20.3 percent for those receiving neither vaccination. Mortality was even higher for patients who refused vaccination for "other reasons" or whose vaccination status was unknown.

Both vaccinations, alone and together, were associated with lower mortality. In adjusted models, the odds ratios for death were 0.71 for patients with influenza vaccination alone, 0.76 for those with pneumococcal vaccination alone, and 0.61 for those with both vaccinations. These patterns were supported on survival analysis.

Dialysis patients are a high-priority group for vaccination against influenza and other vaccine-preventable diseases. Because of their frequent interactions with health professionals, they have repeated opportunities for vaccinations and other preventive care.

This large analysis demonstrates "significant, strong, and independent" improvement in survival among dialysis patients who receive influenza and/or pneumococcal vaccination. The investigators conclude, "Every dialysis visit can be a preventive health opportunity for those not yet immunized." [Bond TC, et al. Mortality of dialysis patients according to influenza and pneumococcal vaccination status. *Am J Kidney Dis* 2012; 60:959–965].

CKD Prediction Models Are "In Their Infancy"

Although much more work is needed in development and clinical application, risk models to predict chronic kidney disease (CKD) and its progression show "acceptable" discrimination, concludes a systematic review in *PLOS Medicine*.

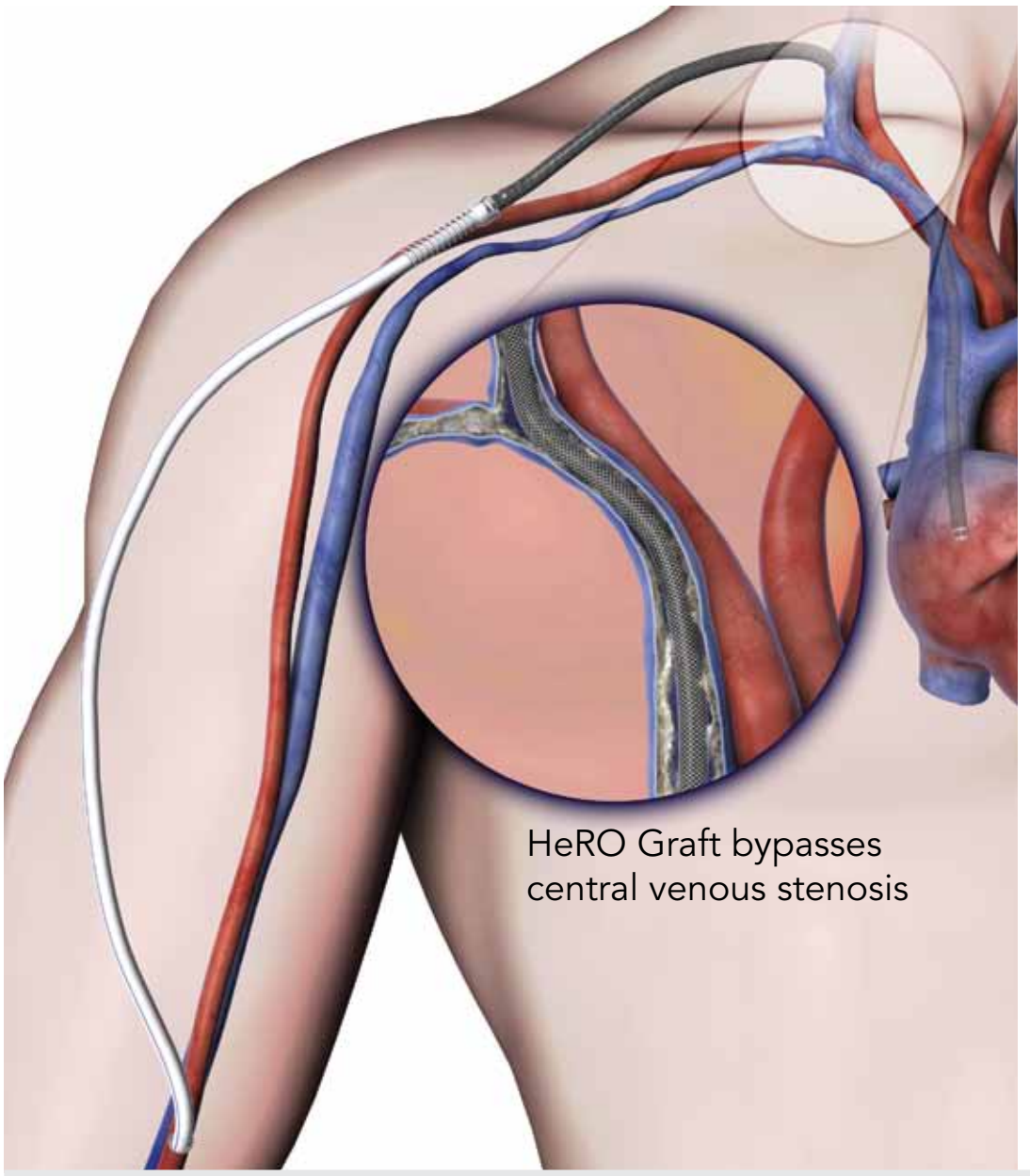
The investigators performed a critical assessment of CKD risk models. A literature search identified 26 publications reporting on the development, validation, or impact assessment of models to predict the risk of CKD occurrence or progression. Discrimination, recalibration, and reclassification performance were assessed, along with validation and impact assessment.

In derivation samples, most of the CKD risk models showed acceptable to good discriminatory performance, with area under the receiver operating characteristics curve values greater than 0.70. Calibration was generally acceptable, although less frequently evaluated. External validation was performed for only eight out of 30 occurrence models and five out of 17 progression models, with modest-to-acceptable discrimination.

The studies provided little information on the predictive value of newer circulatory or genetic CKD biomarkers, or on the clinical impact of the prediction models. In addition to a lack of validation studies, the derivation samples were limited by a lack of ethnic diversity. Limitations of the review included the lack of a consensus approach to rating prediction models and the difficulty of assessing publication bias.

Risk assessment of CKD has important implications for prevention and early detection. Although risk factors for CKD development and progression have been identified, their value in CKD risk stratification through clinical prediction models has yet to be established.

"These findings suggest that the development and clinical application of CKD risk models is still in its infancy," the investigators conclude. Although published models show acceptable discriminatory performance, their value in clinical practice remains to be demonstrated. More work on calibration and external validation is needed before the models are incorporated into clinical guidelines [Echouffo-Tcheugui JB, Kengne AP. Risk models to predict chronic kidney disease and its progression: a systematic review. *PLOS Med* 2012; 9(11):e1001344; doi:10.1371/journal.pmed.1001344].



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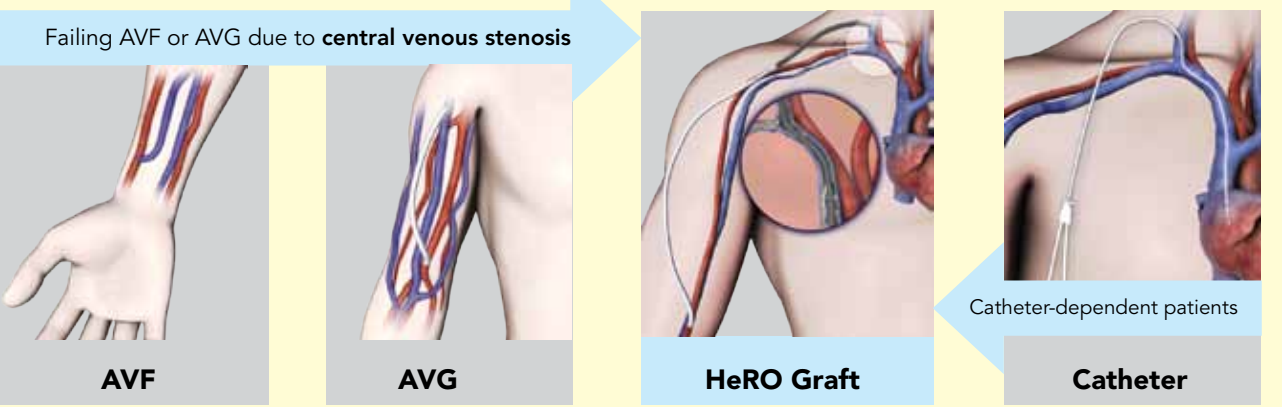

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1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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Policy Update

Fiscal Cliff Deal a Mixed Bag

By Rachel Shaffer and Grant Olan

The worst outcomes of the "fiscal cliff" were averted for now with President Barack Obama's signing into law the American Taxpayer Relief Act (ATRA) on January 2. In addition to permanently extending most of the 2001 and 2003 temporary tax cuts, the new law includes spending cuts to prevent a nearly $27 billion cut to Medicare physician reimbursement rates in 2013, and delays sequestration—automatic across-the-board spending cuts to federal discretionary spending and a 2 percent cut to other Medicare services initially scheduled to take effect January 2, 2013—for 2 months until March 2013.

The new March deadline enacted for dealing with sequestration also coincides with two other major deadlines. The U.S. government faces a possible government shutdown in March (when current appropriations for government expire) unless Congress approves appropriations for the remainder of Fiscal Year (FY) 2013. Moreover, the United States government will default on its debt soon unless Congress raises the "debt ceiling," the legal limit of how much debt the United States can assume.

Dialysis-specific provisions bring challenges, opportunities for 2013

For patients with kidney disease and the nephrologists who treat them, the fiscal cliff deal Congress brokered was a mixed bag. To pay for the tax cut extension, Medicare physician payments in 2013 (see box, page 12), and other costly components of the deal, Congress had to identify savings from government operations to "offset" those costs.

A Government Accountability Office (GAO) report released in December 2012 described significant potential savings in the Medicare End-Stage Renal Disease (ESRD) Program and caught Congress' attention. In a nutshell, the GAO report suggested that Medicare had been paying for more erythropoiesis-stimulating agents (ESAs) than were being administered. GAO concluded that by "rebasing" the base bundled payment rate, the Centers for Medicare & Medicaid Services (CMS) would reduce its ESA costs considerably. As described in the January issue of *ASN Kidney News*, many in the kidney community—including ASN—expressed concerns about a congressionally-mandated rebasing based on a report that focused on just one element of ESRD care.

Despite these concerns, when the Congressional Budget Office estimated that rebasing could save nearly $5 billion over 10 years, Congress moved forward with using it as an "offset" in the fiscal cliff deal. However, it is critical to note that this figure is an estimate only: Medicare is not legally mandated to actually achieve that level of savings. Thus far, some estimates floating around Washington have "guesstimated" rebasing could result in an approximately $10 reduction in the base rate (about 4 percent) of each payment.

While it remains to be seen how much savings CMS will ultimately wrest through rebasing, five key components that will affect the kidney community in the shorter term emerged from the dialysis-related provisions of the fiscal cliff deal. Specifically, the deal:

1. **Granted CMS authority to rebase the bundled payment rate.** Prior to the passage of ATRA, CMS did not actually believe that it had the legal authority to rebase the bundle—an important detail the GAO report clarified. Through ATRA, Congress specified that CMS not only has the authority to rebase, but also now has a mandate to do so. It is likely that CMS will begin the rebasing process in the 2013 rulemaking cycle.
2. **Specified data years to inform rebasing calculations.** ATRA instructs the secretary of the Department of Health and Human Services (HHS) to compare base biologic rates in the 2007 rule with 2012 utilization rates, and to use data from the most recent year available—2012—in rebasing calculations. Importantly, the Secretary must also use the most recently available Average Sales Prices (ASP) and examine other changes in prices for drugs and biologics.
3. **Mandated an analysis of case-mix adjustments by 2016.** ATRA further instructs the HHS secretary to conduct an analysis of the current case-mix adjustors to the bundled payment system and make necessary revisions by 2016. Given that case-mix adjustors—established in 2010—have been viewed as a particularly flawed element of the bundled payment system by some, the possibility for improvement is now on the table.
4. **Delayed addition of oral-only drugs to the bundled payment system.** Oral-only drugs with no injectable equivalents were slated to be added to the bundled payment system beginning in 2014—a date that ATRA delayed by 2 years to January 1, 2016. While the reasons for that delay were not immediately clear from a financial perspective, it may come as welcome news to units that were not entirely prepared to make the transition.
5. **Asked GAO to submit a report on oral-only drug addition.** ATRA requires GAO to submit a report to Congress regarding the HHS secretary's plans to add oral-only drugs to the bundle no later than December 31, 2015. Because ATRA also mandated that the oral-only drugs be added to the bundle no later than the following day—January 1, 2016—it remains somewhat unclear how the timing of GAO's and HHS's activities will play out.

To summarize, nephrologists have seen Medicare physician payments sustained through 2013, but are not out of the woods yet, as the effects of ATRA on the patients they care for and on the dialysis units they see patients in remain murky. Moreover, it remains unclear what will happen to the Medicare budget during March negotiations that revisit sequestration and the slated 2 percent cut to Medicare. ASN plans to work with the kidney care community to ensure that Congress makes the best possible decisions for patients and the ESRD program in the coming months, recognizing the vulnerability of patients on dialysis and the cuts that the program has already sustained in recent years.

Big decisions delayed until March

The Budget Control Act, signed during the summer of 2011, raised the federal debt ceiling and enacted $2.1 trillion in cuts to federal spending in several stages. Phase one cut $21 billion from several discretionary programs in the FY 2012 budget, and cuts budget levels for FY 2013–2021 by about $900 billion (Table I).

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Table I
2011 Budget Control Act Cuts

FY 2012:	**$21 billion** cut from several discretionary programs
FY 2013–2021:	**$908 billion** of budget level cuts
FY 2013–2021:	**$1.2 trillion** in automatic across-the-board cuts to all discretionary programs if Congress does nothing to avert sequestration

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Fiscal Cliff

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During phase two, Budget Control Act provisions empowered a Joint Committee on Deficit Reduction to present a plan for making the remaining $1.2 trillion in cuts, but the committee failed to come up with a plan. That failure would have triggered $1.2 trillion in automatic across-the-board cuts to all federal discretionary spending beginning January 2, 2013. But Congress and the president delayed sequestration by 2 months, thereby delaying the "fiscal cliff" to March 2013.

In response to the threat of sequestration, ASN in July joined a new coalition of 3000 national, state, and local organizations—including other medical specialty societies and research organizations—and has been advocating for a balanced approach to deficit reduction that does not rely on further cuts to non-defense discretionary (NDD) spending, which includes funding for medical research, transportation, education, public safety, public health, and other important government services.

ASN's collaborations with the NDD community include:

- A "Rally to Restore Balance and Protect America's Families" on Capitol Hill to launch the NDD campaign with key members of Congress.
- NDD community-wide national days of action, congressional briefings, and Capitol Hill meetings during the fall of 2012.
- An ASN member campaign targeting members of Congress with nearly 450 emails, letters, calls, and meetings.

These activities built support for NDD programs that in part helped delay the implementation of sequestration until March 1, 2013, and give Congress and the president more time to avert it. Otherwise, $1.2 trillion in cuts will come on top of the more than $900 billion already cut. That would equate to a cut of about 6.5 percent for federal medical research and other NDD programs in FY 2013.

The current outlook for a deal to

Sustainable Growth Rate 101

Since 1997, CMS has calculated Medicare physician reimbursement rates for the following year based on a formula called the Sustainable Growth Rate (SGR). Originally enacted by Congress to ensure that yearly increases in Medicare beneficiary expenses do not exceed growth in gross domestic product, the SGR formula is now widely recognized as flawed. It would cut Medicare payments every year, leaving physicians responsible for shouldering growing health care costs. Instead of replacing the flawed formula, Congress temporarily postpones the called-for cuts every year, known as the "doc fix." ASN and countless other organizations in the medical community have called on Congress to collaborate with our organizations to replace the old formula and start over with a new, stable formula that accurately reflects the cost of care. In the fiscal cliff deal, Congress extended current Medicare physician payment rates through December 31, 2013, avoiding the 26.5 percent cut scheduled by the SGR.

avert sequestration in March is grim. Congress has thus far proven incapable of agreeing on how to apply the remaining $1.2 trillion of cuts mandated by the 2011 Budget Control Act, and Senate Minority Leader Mitch McConnell (R-KY) says additional revenue as an offset is off the table. It is hard to imagine how a deal can come together to avert sequestration without revenue offsets or a complete repeal. And having delayed sequestration once, it is unlikely Congress would kick the can down the road again.

"ASN shares concerns about the growing national debt and supports responsible federal deficit reduction measures. But federal NDD programs like medical research are not the main drivers of our nation's debt and have already done a fair share for deficit reduction," said ASN Research Advocacy Committee Chair John R. Sedor, MD. "I urge everyone to join ASN's campaign in support of medical research and other NDD programs. Visit http://www.asn-online.org/policy/ to learn how."

U.S. Preventive Services Task Force Supports Kidney Disease Screening Research

By Ian H. de Boer, Grant Olan, and Uptal D. Patel, on behalf of the American Society of Nephrology Chronic Kidney Disease Advisory Group

In 2012, the Agency for Healthcare Research and Quality (AHRQ) comprehensively summarized the available evidence evaluating the risks and benefits of screening for chronic kidney disease (CKD) in the general population. Utilizing these data, the U.S. Preventive Services Task Force (USPSTF) determined that existing evidence was insufficient to balance the benefits and harms of routine screening for CKD in asymptomatic adults. Subsequently, the USPSTF identified screening for CKD as its top priority in a report to Congress on high-priority evidence gaps for clinical preventive services. USPSTF also identified screening for CKD in African Americans as the most important evidence gap related to specific populations.

ASN commended the USPSTF for its recommendation to Congress for further research on CKD screening to fill evidence gaps and also urged ongoing CKD screening among high-risk populations.

"The USPSTF recommendation shows the task force recognizes that CKD is a serious and growing public health threat," said ASN CKD Advisory Group Chair Uptal D. Patel, MD. "More than 26 million Americans are estimated to have kidney disease today, and only 1 in 10 are aware they have the disease," Patel said. "When identified by health professionals early, however, the progression of kidney disease to kidney failure can be slowed or halted, thus reducing the high morbidity and costs associated with dialysis and transplantation."

The initial USPSTF determination specifically excluded people diagnosed with diabetes mellitus and hypertension. Diabetes and hypertension are the most common risk factors for CKD. The prevalence of CKD is approximately 27.5 percent among the 30.6 percent of adults 20 years of age or older in the United States with hypertension, and approximately 34.5 percent among the 10.6 percent of adults

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20 years of age or older in the United States with diabetes. Clinical trials in these populations demonstrate that antihypertensive interventions reduce the risk of both CKD progression and cardiovascular complications.

For these reasons, ASN recommended to the USPSTF continued screening of patients with hypertension and diabetes for CKD. Existing guidelines from a number of professional organizations, including the American Diabetes Association, the National Kidney Foundation, and the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, also recommend screening these high-risk populations for CKD.

In addition to screening patients who have comorbid conditions that cause CKD, ASN's response to the USPSTF highlighted other patient characteristics that confer increased risk and may also warrant screening, including family history of kidney failure as a strong risk factor for kidney disease. The National Kidney Disease Education Program (NKDEP) at the National Institutes of Health has advocated for screening patients who have a family history of kidney disease.

Moreover, ASN noted that screening individuals with a family history of kidney disease may also help address disparities among racial and ethnic minority populations in the United States. African Americans and Native Americans are up to four times more likely than Caucasians to progress to kidney failure, while Hispanics are twice as likely. The elevated risk of developing CKD and kidney failure in these groups is not well explained by the higher prevalence of diabetes and hypertension. (African Americans, for example, are at disproportionate risk for developing focal segmental glomerulosclerosis and primary glomerulopathy, due in part to a high prevalence of high-risk polymorphisms in the *Apolipoprotein L1* gene.) However, recent findings indicate that CKD screening and treatment of African Americans may be more cost-effective than CKD screening and treatment of non–African Americans.

ASN also pointed out that NKDEP and the American Heart Association also recommend CKD screening for patients with a clinical diagnosis of cardiovascular disease, who are also at high risk of kidney disease. CKD is common among patients with cardiovascular disease and is a strong independent risk factor for cardiovascular events and death. As such, screening for CKD has been recommended for all adult patients with cardiovascular disease, including those with coronary artery disease or congestive heart failure.

The thorough evaluation of CKD screening among asymptomatic adults without diabetes or hypertension completed by AHRQ and USPSTF raises important unanswered questions for public health. ASN recommends ongoing screening of high-risk groups for CKD, both good for patients and good economic sense, and applauds the USPSTF recommendation to Congress for further research on CKD screening to fill evidence gaps.

Ian H. de Boer, MD, is affiliated with the division of nephrology at the Kidney Research Institute, University of Washington, Seattle.

Grant Olan, is a policy associate with ASN. Uptal Patel, MD, is an associate professor of medicine and pediatrics, an investigator in the Health Services Research and Development Unit at the Durham Veterans Affairs Medical Center, and core faculty at the Duke Clinical Research Institute.

Kidney TREKS: ASN's New Initiative to Increase Interest in Nephrology Careers

By Lauren Stern and Mark Parker

KIdney Treks begins with a one-week, fully funded lab-based course in June 2013 at Mount Desert Island Biologic Laboratories in Bar Harbor, Maine. Med students may apply online at www.asn-online.org/education/training/students/kidney-treks.aspx until May 15.

In recent years much attention has been focused on medical students' and residents' declining interest in nephrology careers (1,2). The numbers of candidates, especially U.S. medical graduates (USMGs), applying to nephrology fellowship programs have dwindled over the past decade. In the 2012 fellowship appointment year there were only 1.1 applicants for each nephrology position in the National Residency Matching Program and only 24.2% of matched applicants were USMGs (3). This decline seems unjustified since nephrology remains an intellectually challenging and rewarding field. Some of the reasons being reported for this shift include minimal nephrology exposure during medical school and internal medicine residency, unstimulating renal pathophysiology introductory coursework, and a lack of mentorship. In addition, there is great concern that the supply of international medical graduates, who have composed a large portion of the nephrology fellowship applicant pool for many years, may dwindle because of increasing difficulties in obtaining visas to train and work in the United States or improved opportunities to return to their countries of origin.

Innovation and discovery in nephrology are also in jeopardy. Fewer students are choosing career paths as physician-scientists, especially in internal medicine and its subspecialties (4). Contraction of funding sources for young investigators, lack of mentorship and research opportunities in medical school, diminished remuneration, and an increased debt burden paired with protracted length of research training are among the cited culprits (5).

In response to these concerns, the ASN Workforce Committee has devised an innovative way to attract USMGs to nephrology and research at an early stage in their training. ASN's new Kidney TREKS (Tutored Research and Education for Kidney Scholars) program is aimed at trainees at the medical school level. It begins with a unique laboratory experience at Mount Desert Island Biologic Laboratories (MDIBL) in Bar Harbor, Maine. This 1-week, fully funded, lab-based hands-on course will take place June 8–14, 2013. Modeled on the highly successful "Origins of Renal Physiology" course for fellows and junior faculty at MDIBL, and directed by Mark Zeidel, MD, FASN, Chair of the Department of Medicine at Beth Israel Deaconess Hospital in Boston, the week will feature renowned investigators in the field. Students will participate in modules that allow them to perform experiments and discuss and present results that help them understand key concepts in nephrology, including water and salt homeostasis, acid-base homeostasis, glomerular function, personalized medicine, and genetics. Both classical experiments and modern molecular

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Information for Patients
See Medication Guide in the full prescribing information

- Inform females of reproductive potential that use of Myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, and advise them as to the appropriate steps to manage these risks including that they must use acceptable contraception (**see WARNINGS: Embryofetal Toxicity, PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).
- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential. In the event of a positive pregnancy test, the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.
- Females of reproductive potential must use acceptable birth control during entire Myfortic therapy and for 6 weeks after stopping Myfortic, unless the patient chooses to avoid heterosexual sexual intercourse completely (abstinence) (**see PRECAUTIONS: Pregnancy Exposure Prevention and Planning, Table 4**).
- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.
- It is recommended that Myfortic be administered on an empty stomach, one hour before or two hours after food intake (**see DOSAGE AND ADMINISTRATION in the full prescribing information**).
- In order to maintain the integrity of the enteric coating of the tablet, patients should be instructed not to crush, chew, or cut Myfortic tablets and to swallow the tablets whole.
- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
- Inform patients that they need repeated appropriate laboratory tests while they are taking Myfortic.
- Advise patients that they should not breastfeed during Myfortic therapy.

Laboratory Tests
Complete blood count should be performed weekly during the first month, twice monthly for the second and the third month of treatment, then monthly through the first year. If neutropenia develops (ANC <1.3×10^3/µL), dosing with Myfortic should be interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly (**see WARNINGS**).

Drug Interactions
The following drug interaction studies have been conducted with Myfortic:

Gastroprotective agents
Antacids with magnesium and aluminum hydroxides:
Absorption of a single dose of Myfortic was decreased when administered to 12 stable renal transplant patients also taking magnesium-aluminum-containing antacids (30 mL): the mean C_{max} and $AUC_{(0-t)}$ values for MPA were 25% and 37% lower, respectively, than when Myfortic was administered alone under fasting conditions. It is recommended that Myfortic and antacids not be administered simultaneously.

Proton Pump inhibitors:
In a study conducted in 12 healthy volunteers, the pharmacokinetics of MPA were observed to be similar when a single dose of 720 mg Myfortic was administered alone and following concomitant administration of Myfortic and pantoprazole, which was administered at a dose of 40 mg BID for 4 days.

Cyclosporine: When studied in stable renal transplant patients, cyclosporine, USP (MODIFIED) pharmacokinetics were unaffected by steady-state dosing of Myfortic.

The following recommendations are derived from drug interaction studies conducted following the administration of mycophenolate mofetil:

Acyclovir/Ganciclovir: May be taken with Myfortic; however, during the period of treatment, physicians should monitor blood cell counts. Both acyclovir/ganciclovir and MPAG concentrations are increased in the presence of renal impairment, their coexistence may compete for tubular secretion and further increase in the concentrations of the two.

Azathioprine/Mycophenolate Mofetil: Given that azathioprine and mycophenolate mofetil inhibit purine metabolism, it is recommended that Myfortic not be administered concomitantly with azathioprine or mycophenolate mofetil.

Cholestyramine and Drugs that Bind Bile Acids: These drugs interrupt enterohepatic recirculation and reduce MPA exposure when coadministered with mycophenolate mofetil. Therefore, do not administer Myfortic with cholestyramine or other agents that may interfere with enterohepatic recirculation or drugs that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to reduce the efficacy of Myfortic.

Oral Contraceptives: In a drug-drug interaction study, mean levonorgesterol AUC was decreased by 15% when coadministered with mycophenolate mofetil. Although Myfortic may not have any influence on the ovulation-suppressing action of oral contraceptives it is recommended to co-administer Myfortic with hormonal contraceptives, (e.g. birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used. (**see PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).

Live Vaccines: During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination (**see PRECAUTIONS, Immunizations**).

Drugs that alter the gastrointestinal flora may interact with Myfortic by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 104-week oral carcinogenicity study in rats, mycophenolate sodium was not tumorigenic at daily doses up to 9 mg/kg, the highest dose tested. This dose resulted in approximately 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6 times the proposed mycophenolate sodium therapeutic dose based upon body surface area).

The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells, and the *in-vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay (*Salmonella typhimurium* TA 1535, 97a, 98, 100, & 102) or the chromosomal aberration assay in human lymphocytes. Mycophenolate mofetil generated similar genotoxic activity. The genotoxic activity of MPA is probably due to the depletion of the nucleotide pool required for DNA synthesis as a result of the pharmacodynamic mode of action of MPA (inhibition of nucleotide synthesis).

Mycophenolate sodium had no effect on male rat fertility at daily oral doses as high as 18 mg/kg and exhibited no testicular or spermatogenic effects at daily oral doses of 20 mg/kg for 13 weeks (approximately two-fold the therapeutic systemic exposure of MPA). No effects on female fertility were seen up to a daily dose of 20 mg/kg, which was approximately three-fold higher than the recommended therapeutic dose based upon systemic exposure.

Pregnancy
Pregnancy Category D (See WARNINGS)
Following oral or IV administration, MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Risks and benefits of Myfortic should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. For those females using Myfortic at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the Health Care Community to better understand the effects of mycophenolate in pregnancy.

In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected from 1995 to 2007) on 77 women exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs. There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day Myfortic. In teratology studies in rabbits, fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to about 0.8 times the recommended clinical dose, corrected for BSA).

Nursing Mothers
It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from MPA, a decision should be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy, taking into account the importance of the drug to the mother.

Pediatric Use
De novo Renal Transplant
The safety and effectiveness of Myfortic in *de novo* pediatric renal transplant patients have not been established.

Stable Renal Transplant
There are no pharmacokinetic data available for pediatric patients <5 years. The safety and effectiveness of Myfortic have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic in this age group is supported by evidence from adequate and well-controlled studies of Myfortic in stable adult renal transplant patients. Limited pharmacokinetic data are available for stable pediatric renal transplant patients in the age group 5-16 years. Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic tablets (**see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION in the full prescribing information**).

Geriatric Use
Patients ≥65 years may generally be at increased risk of adverse drug reactions due to immunosuppression. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
The incidence of adverse events for Myfortic® (mycophenolic acid) was determined in randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in *de novo* and maintenance kidney transplant patients.

The principal adverse reactions associated with the administration of Myfortic include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea and nasopharyngitis in maintenance patients.

Adverse events reported in ≥20% of patients receiving Myfortic or mycophenolate mofetil in the 12-month *de novo* renal study and maintenance renal study, when used in combination with cyclosporine, USP (MODIFIED) and corticosteroids, are listed in Table 5. Adverse event rates were similar between Myfortic and mycophenolate mofetil in both *de novo* and maintenance patients.

Table 5 Adverse Events (%) in Controlled de novo and Maintenance Renal Studies Reported in ≥20% of Patients

	***de novo* Renal Study**		**Maintenance Renal Study**	
	Myfortic® 1.44 g/day (n=213)	**mycophenolate mofetil 2 g/day (n=210)**	**Myfortic® 1.44 g/day (n=159)**	**mycophenolate mofetil 2 g/day (n=163)**
Blood and Lymphatic System Disorders				
Anemia	21.6	21.9	–	–
Leukopenia	19.2	20.5	–	–
Gastrointestinal System Disorders				
Constipation	38.0	39.5	–	–
Nausea	29.1	27.1	24.5	19.0
Diarrhea	23.5	24.8	21.4	24.5
Vomiting	23.0	20.0	–	–
Dyspepsia	22.5	19.0	–	–

(continued)

Kidney TREKS

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techniques will be explored.

Participants will then enter a longitudinal mentorship component of the program and will be paired with a nephrologist at their home institution. This mentor will serve to guide them through nephrology electives and additional research opportunities, such as application to the ASN Student Scholars Grants program. Finally, participants will be invited to attend ASN Kidney Week during their third or fourth years in medical school through the ASN Program for Medical Students and Residents. This successful initiative includes guided learning pathways and exposes trainees to the full spectrum of nephrology discovery at Kidney Week.

Applications for the Kidney TREKS program can be found online at http://www.asn-online.org/education/training/students/kidney-treks.aspx. Medical students of all levels are encouraged to apply and acceptance will be on a rolling basis with a final deadline of May 15, 2013.

Lauren Stern, MD, is affiliated wtih Boston Medical Center and Boston University School of Medicine, and Mark Parker, MD, is director of the division of nephrology and transplantation, Maine Medical Center, and associate clinical professor of Medicine, Tufts University School of Medicine.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Industry Spotlight

Prepping for the Next Wave of Managed Care?

A health care industry analyst has made a prediction for 2013 that American companies like Denver-based DaVita, the second largest provider of dialysis services in the United States, may be best positioned to "benefit from changes in the health care market stemming from Obamacare."

In early January, Martin Brunninger, head of the medical technology sector at Nomura Securities, told a CNBC cable audience that because 70 percent of the dialysis care market is dominated by two big players (DaVita and Germany's Fresenius), "we have efficiency gains and there's not much more earnings power in the U.S. sector."

Brunninger said that if one company moves away strictly from dialysis care, however, that company likely would enjoy an advantage. "DaVita has diversified away and they have a broader approach now in saving managed dollars for broader patient populations," he added. "I think that is the future."

On November 1, 2012, HealthCare Partners merged into a subsidiary of DaVita's parent company. The parent company changed its name to DaVita HealthCare Partners Inc. HealthCare Partners, now one of the two main operating divisions of DaVita HealthCare Partners, with operations in southern California, central Florida, southern Nevada, and northern New Mexico, assumes clinical and economic accountability and management responsibility for nearly all of the health care needs of a patient population. This includes offering professional services provided by primary care and specialty physicians as well as coordinating hospital and other services, the company noted.

In addition, the DaVita subsidiary runs the first and largest pharmacy dedicated to serving the unique needs of kidney patients. In 2012, DaVita Rx expanded its services to help manage patient medications and clinical outcomes. DaVita recently agreed to provide certain pharmacy services to Fresenius Medical Care, which will use DaVita Rx prescription drug services for its Medicare patients in the United States.

DaVita also announced in an unrelated transaction that it will extend its supply agreement with Fresenius Medical Care for certain dialysis supplies including hemodialysis machines and disposable products.

DaVita Rx also focuses on patient compliance by providing refill reminders, reviews for possible drug interactions, and other services, with the aim of healthier patients who have an improved quality of life.

With provisions of the Affordable Care Act slated to take effect within the coming year, DaVita's move toward serving broader populations may help the firm capitalize on moves toward managed care, Brunninger said.

As health care systems around the world keep moving toward lower spending on increasing numbers of patients, "it doesn't necessarily mean the quality needs to be diminished," Brunninger said. "It's about management and where the profits are going."

Companies Collaborate to Produce Wearable Dialysis Technology

AWAK Technologies has signed an agreement with Baxter International Inc. to develop wearable dialysis technology. The agreement lets AWAK continue developing its investigational peritoneal dialysis-based automated wearable artificial kidney, the company said.

AWAK Technologies is a research-focused, medical technology company dedicated to the development and commercialization of sorbent-based dialysis regeneration technology.

"Our agreement with Baxter is part of our overall strategy to bring innovative technologies for dialysis treatment to market that include collaborations and licensing agreements with academia including the University of California, Los Angeles (UCLA) and Temasek Polytechnic, Singapore, as well as working cooperatively with government agencies in the United States and Singapore; such as the U.S. Veteran Affairs Innovation Initiative (VAi2), SPRING Singapore and International Enterprise (IE) Singapore," said NEO Kok-Beng, President & CEO of AWAK Technologies.

The agreement will provide Baxter with exclusive global manufacturing and a distribution license for AWAK's investigational peritoneal dialysis-based automated wearable artificial kidney, a minority ownership stake in the company, and the option to purchase additional equity in the company.

Fresenius Dialyzes in Wee Hours, Offloads Biotech Biz

Dialysis takes numerous hours of patients' time per week, which can greatly interfere with family, work, and recreational schedules. Now Fresenius Medical Care North America (FMCNA), the largest provider of dialysis services in the United States, has established more than 140 nighttime dialysis center sites.

FMCNA, the nation's leading network of dialysis facilities, established programs across the country, including recently opened programs in Weymouth, Massachusetts; Waco, Texas; Coeur d'Alene, Idaho; and Santa Fe, California. More are scheduled to open this year.

FMCNA's nighttime dialysis option offers the same level of supervised care as traditional daytime, in-center treatments, but patients receive their dialysis at night, usually over a longer time, the company reported.

Night-ime dialysis is a more gradual process, and at night, patients typically receive treatments three times a week but over an 8-hour period (versus a typical 3- to 4-hour period for daytime dialysis). When dialysis is provided over a longer time, fluids are removed more slowly, which results in a more gentle treatment for most patients, the company reported.

"In-center, nocturnal dialysis is a viable alternative to standard in-center dialysis for patients who require greater fluid and phosphorus removal and who are amenable to spending 3 nights a week in the dialysis facility," said Eduardo Lacson, Jr., MD, FMCNA's vice president for clinical science, epidemiology, and research. He recently published a study that demonstrated the health benefits of nighttime dialysis, among them improved clearance of phosphorus and fluid, in nearly 750 FMCNA patients who switched from daytime to nighttime dialysis. Studies also suggest that nighttime dialysis patients may be able to better control their blood pressure and mineral levels, allowing them to eat a wider variety of foods, according to Fresenius.

Overall, parent company Fresenius Medical Care is focusing on its core strengths of delivering dialysis and transfusion services, as seen recently when Fresenius floated its biotech arm for sale, Reuters reported. Fresenius reported in December 2012 that it planned to discontinue the Fresenius Biotech subsidiary, which posted sales of about 26 million Euros (about $34 million) in the first 9 months of 2012. Fresenius may retain some dialysis-related drugs.

At the same time, Fresenius said that it had "successfully closed the acquisition of blood-transfusion-technology company Fenwal Holdings, Inc.…as part of the company's strategy to expand in the medical-devices/transfusion-technology segment," Fox Business News reported.

Dialysis Businesses Attractive Targets

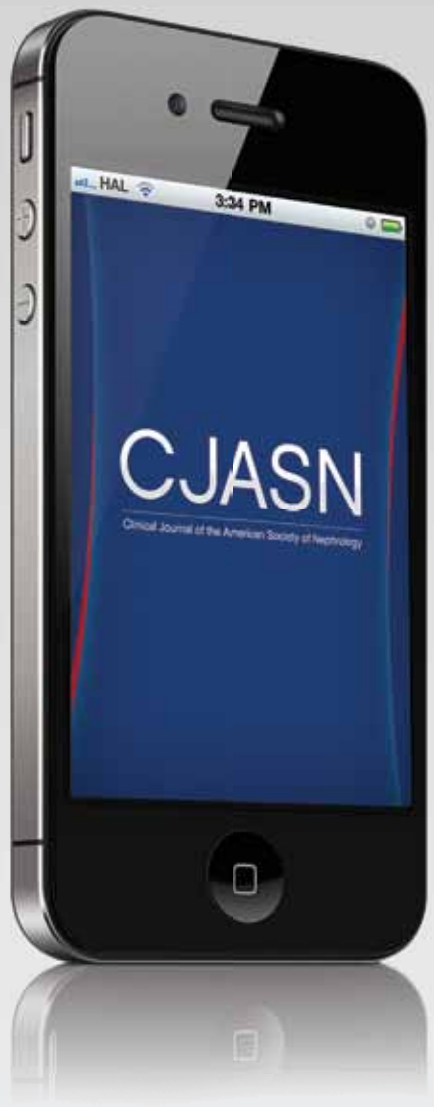
Just after Baxter bid $4 billion to purchase Gambro, a maker of dialysis-related products, in the hope of being a dominant force in the dialysis marketplace, there is another news item out of Gambro's Brentwood, Tennessee home base. Ambulatory Services of America (ASA), of Brentwood, has bought a majority interest in six dialysis centers and an acute dialysis program in the Los Angeles area.

The terms of the purchase were not disclosed, but the facilities were purchased from Kidney Centers Inc. (KCI), and the six dialysis centers currently serve 700 patients. The acute dialysis program serves eight hospitals.

"Given the strong presence of Innovative Dialysis in the Los Angeles area, we had long known of KCI, and we appreciated its physician joint venture model, which is much like ours," said Timothy Martin, the chief executive officer of ASA and its subsidiary, Innovative Dialysis. "At Innovative Dialysis, we prefer to operate in joint ventures with physicians where our nephrologist-partners can take the lead in providing high-quality care to patients with ESRD, and we can support them by taking care of the business aspects of running dialysis facilities. We look forward to working with the staff at these facilities as well as their physician partners."

Through this acquisition, ASA now provides care to 7000 patients through 85 dialysis programs, ASA announced in December 2012.

The ASA vision is to become the first national clinical enterprise to consolidate ambulatory services from multiple medical specialties. The company plans to do this through deals with differing specialties that provide high-quality, evidence-based services that help demonstrate improved clinical outcomes. The initial focus is on both radiation oncology and renal dialysis.



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ALEXION

Time out.

Let’s take a moment to look at the current state of the lab industry.

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NIH Glomerular Disease Conference Leads to New Opportunities for Advancing Knowledge and Treatments

By Charles E. Alpers

Major research advances in the past 2 decades have provided a greatly enhanced understanding of mechanisms underlying glomerular disease. These include the identification of proteins specific to podocytes and the slit diaphragm, and the diseases that may develop as a consequence of mutation or dysfunction of these proteins. Research has also demonstrated the pathogenic contribution of abnormally galactosylated immunoglobulin A (IgA) to the development of IgA nephropathy; pinpointed SpeB as the major inciting antigen of acute poststreptococcal glomerulonephritis; and identified the phospholipase A2 receptor (PLA_2R) as the principal antigen in most cases of idiopathic membranous nephropathy.

Other studies have provided evidence that a specific circulating factor (soluble urokinase receptor [suPAR]) is implicated in the pathogenesis of focal and segmental glomerulosclerosis (FSGS), and that another factor (the hyposialylated form of angiopoietin-like-protein 4 [ANGPTL4]) may be involved in the pathogenesis of minimal change disease (MCD). However, the extent to which these factors may be causative remains to be established. Despite these and other major accomplishments in understanding their pathogenesis, there has been a lack of corresponding advances in therapeutics for these diseases.

Given this background, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in conjunction with the ASN Glomerular Disease Advisory Group, organized the "Glomerular Disease Pathophysiology, Biomarkers, and Registries for Facilitating Translational Research" conference, which was held at the National Institutes of Health (NIH) campus in Bethesda, MD, on April 17 and 18, 2012. The conference goals were to identify approaches to build upon this body of knowledge; develop an infrastructure that would facilitate implementation of clinical trials of new therapeutics in glomerular disease; and foster a dialogue between academic researchers, private-sector entities (including biotechnology companies and major pharmaceutical companies), and the U.S. Food and Drug Administration (FDA) that would ultimately serve to reduce the obstacles in bringing new agents for treatment of glomerular diseases to clinical trials.

The conference began with presentations by leaders of clinical trial networks from outside the glomerular disease field, including Frank Accurso, MD, of the University of Colorado on behalf of the Cystic Fibrosis Foundation Therapeutics Development Network, which now supports phase III trials conducted at 77 sites, and Neil Solomons, MD, of Vifor Pharma, speaking on behalf of the Aspreva Lupus Management Study (ALMS).

Discussion subsequently focused on specific disease entities and the potential for therapeutic interventions in each category. The keynote overview speaker, former ASN President William Couser, MD, reviewed both areas of progress made in the past 4 decades—including the identification of key pathogenic molecules described above—and the residual critical gaps in our understanding. The latter include insufficient knowledge of the initiating events in most glomerular diseases and of the best targets for therapeutic intervention. A major problem in the care of patients with glomerular diseases is that most therapeutics in current use were developed for application in other medical fields, such as transplantation and rheumatology, that require systemic therapy and do not target specific glomerular processes. An advantage of more tightly targeted therapeutics is that they offer the possibility of reduced toxicities and off-target effects.

Other presentations, followed by breakout discussion groups, focused specifically on the MCD/FSGS spectrum of diseases, IgA nephropathy, membranous nephropathy, vasculitis, and the recently emerging entity C3 glomerulopathy. Discussion centered on clinical trial assessment, and the need for a durable multi-institutional clinical trials infrastructure with the necessary bioinformatics and biorepository support akin to what has been accomplished with the cystic fibrosis network and the large oncology group study networks, such as the Southwest Oncology Group (SWOG). Such an infrastructure would enable the recruitment of a sufficient number of patients for meaningful trial results and would obviate the need to create a trial network anew for each potential clinical study of a glomerular disease therapeutic.

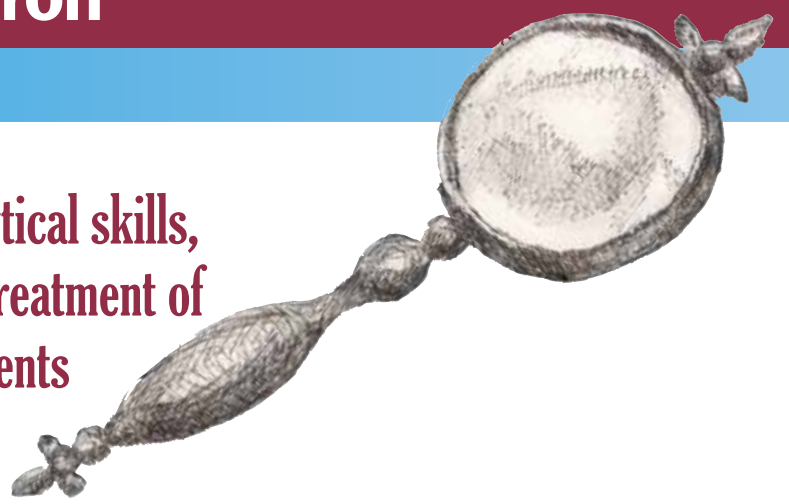
A topic discussed at length, but not resolved at this meeting, was achieving agreement with representatives of the FDA on acceptable surrogate biomarkers for progressive glomerular disease. This has been a particularly challenging issue because end points, such as development of ESRD or death, are neither inevitable nor necessarily early events in the evolution of glomerular disease. The most obvious surrogate marker for glomerular disease—proteinuria—has too many vagaries to be currently acceptable to the FDA as a biomarker across different glomerular disease categories. The identification of specific pathogenic moieties, such as anti-PLA_2R antibodies in membranous nephropathy and circulating suPAR in FSGS, may allow development of future assays that could be disease specific and fulfill a biomarker function for monitoring disease progress in future clinical trials.

There were several important outcomes from this conference. First was the issuance of a request for applications from the NIDDK (RFA-DK-12-014, application due date February 27, 2013) to fund consortium sites that will establish and longitudinally follow cohorts of patients with common glomerular diseases (MCD, FSGS, IgA nephropathy, and idiopathic membranous nephropathy) who can then be entered into clinical trials and studies that validate biomarkers of disease progression and other relevant clinical and translational studies. Second, as highlighted in the ASN President's Address by Ronald Falk, MD, FASN, at Kidney Week 2012, this conference furthered a dialogue that contributed to the development of the Kidney Health Initiative (KHI), a partnership of ASN and the FDA.

The mission of KHI is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products. For more information about KHI, please visit http://www.asn-online.org/khi/.

Charles E. Alpers, MD, is a member of the ASN Glomerular Diseases Advisory Group. Alpers is associated with the department of pathology at the University of Washington Medical Center in Seattle.

Detective Nephron



Detective Nephron, world-renowned for expertise in analytical 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 consultant.

Nephron What do we have today, my dear apprentice?

Henle A 65-year-old woman with hematuria and a subacute rise in creatinine.

Nephron I see that you have taken a break from the electrolyte disorders and moved to the glomerular disease world. This is why nephrology is so much fun: it has so much variety to offer diagnosticians.

Henle Hmmm… getting back to the case, she was in her usual state of health until a few weeks ago, when she started noticing foamy urine and fatigue.

Nephron What is her creatinine level now?

Henle It was 0.7 mg/dL 1 year ago and 1.2 mg/dL 2 months ago. Now it is 1.9 mg/dL.

Nephron Did you look at her urine?

Henle Yes, of course I did. There are many red blood cells and a few white blood cells. The red cells are dysmorphic, but no red cell casts that I could notice, and no signs of any granular casts.

Nephron Is there any proteinuria?

Henle Yes, there is: 3.5 grams in a 24-hour urine collection.

A knock on the door is heard.

Nephron Come on in, Dr. Slit Podocyte. You are just in the nick of time again.

Henle looks at Dr. Nephron as Dr. Podocyte enters the room.

Nephron Dr. Podocyte helped us solve our last case in glomerular disease. Let's take this one together. Does that sound good, Slit?

Podocyte Good morning, Henle. I am Dr. Slit Podocyte. Nice to meet you.

Nephron Henle has a case here of an elderly lady with hematuria, a subacute decline in renal function, and nonspecific complaint of fatigue.

Henle Her anti nuclear antibody, anti–double–stranded DNA, and anti neutrophil cytoplasmic antibody titers are negative as well. Her C3 is slightly depressed, and she has a normal C4 value.

Nephron Stop right there. So you are telling me you already have a diagnosis? Why are you presenting this case, then?

Podocyte Sounds as if you have a glomerular disease with low complements. Very few would present in this manner.

Henle Given the low C3, I would consider postinfectious glomerular process, membranoproliferative glomerulonephritis (MPGN) pattern of injury, or a proliferative pattern such as in lupus nephritis.

Podocyte You are doing a great job. Given the negative serologic results, lupus nephritis is less likely but is always a possibility. Can you expand on the MPGN pattern of injury and perhaps think more in terms of C3 glomerulopathy?

Nephron My dear apprentice, you still have a lot to learn.

Henle Well, historically, MPGN has been classified as type I, II, or III on the basis of electron microscope (EM) findings. A more useful classification is based on immunofluorescence (IF), which is clinically more useful. And sometimes a persistent postinfectious glomerular nephritis (GN) will also present with low C3 levels. The term "atypical postinfectious GN" is used for such cases.

Nephron Please continue as I drink my coffee.

Podocyte The EM approach should likely be replaced by the IF approach.

Henle But in this patient, we don't even know that it's MPGN. It could be postinfectious GN for all you know. The biopsy was done only this morning.

Podocyte Excellent. Let's discuss after the biopsy findings what to do next.

Nephron Interesting! Not the approach I usually take.

Henle returns a few hours later. Slit and Nephron enjoy their warm coffee.

Podocyte What's so interesting? Just because it's not an electrolyte case. This is actually fascinating! In glomerular diseases, we need biopsies to make a diagnosis.

Henle Is there a connection of this to the presentation?

Podocyte What did it show?

Henle Yes—and the biopsy confirmed an MPGN pattern of injury on light microscopy.

Podocyte Just as we suspected. Now IF is the next important part of the biopsy. Also, I am glad you use the term "MPGN pattern of injury" rather than "MPGN" because this is truly a pattern of injury with most causes being secondary in nature.

Henle Hmm… IF showed immunoglobulin (Ig) G (3+), kappa (3+), and C3(3+); the other results were all negative. EM showed subendothelial deposits, as one would expect in an MPGN pattern.

Nephron I am assuming she has MPGN type 1.

Podocyte Let's discuss this in more detail. Not so soon—and I don't agree with Dr. Nephron. How about staining for lambda?

Henle Negative for lambda.

Podocyte She has monoclonal deposits in the IF findings. Isn't that the case?

Henle Yes, IgG kappa and C3.

Nephron Ahh! She has myeloma!

Henle Where does MPGN fit in all this?

Podocyte Good question. Think of MPGN again as a pattern of injury that results from capillary wall injury. If there is no staining in IF (which also can happen), then such a pattern might be seen in chronic thrombotic microangiopathies from medications, from radiation, after stem cell transplantation, and so forth. If there is IF staining, you move to diseases resulting from deposition of immune complexes or complement factors or both. Now here is the major breakdown: if there is C3 and immunoglobulin staining, one has to consider many secondary causes such as infections, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus), and paraprotein-mediated diseases. The paraprotein-mediated diseases usually have a monoclonal component seen at biopsy. Classically, monoclonal gammopathy of undetermined significance (MGUS) has been noted to be a major cause of the MPGN pattern of injury. The old classification of MPGN type I would fit under this category if no secondary cause is found and would be labeled idiopathic MPGN.

Henle Then how do you define C3 glomerulopathy?

Nephron Good question. Now, as we already noted, IF was positive for C3 and immunoglobulins, so we should be thinking infections, autoimmune diseases, and paraprotein deposition. If the IF is positive only for C3 strongly, you get an MPGN pattern resulting from deposition of complement factors. This is defined as C3 glomerulopathy. What the C3 glomerulopathy is trying to tell us is that the injury is due to a problem in the alternative pathway complement cascade and hence leads to deposition of complement factors that ultimately might lead to double contouring and MPGN-like lesions. One needs to keep in mind that other patterns such as mesangial proliferative, diffuse proliferative, and even crescentic GN can result from all these causes of MPGN.

What constitutes C3 glomerulopathy is glomerular deposits of complement C3 (and other complement factors of the alternative and terminal pathway) and absence of immunoglobulin within the glomeruli or just pauci immunoglobin deposition. C3 glomerulopathy is further classified into dense deposit disease and C3 glomerulonephritis, both of which result from alternative pathway abnormalities. Why one results in dense deposit disease and another in C3 glomerulonephritis is not known. However, this may have to do with where the alternative pathway is disrupted, allele variants, and severity of disruption.

Henle Why is this classification important?

Nephron Perhaps we can look for these causes in specific cases and tailor the treatment accordingly. Medications affecting the complement system such as eczulimab might be of benefit in some of these disease entities in the near future. With regard to Ig-positive MPGN, for example, MPGN associated with monoclonal gammopathy is likely to recur after transplantation, whereas MPGN due to infections is less likely to recur. There are few data about recurrent MPGN causes by alternative pathway abnormalities, although early studies suggest that these also recur. If one suspects C3 glomerulopathies, it's worth checking the complement cascade function: C3 and C4 levels. Check also for C3 nephritic factor, factor H antibodies, and serum membrane attack complex levels. Tests of genetic mutations for CFH, CFI, and allele variants are also available.

Podocyte Good work, Dr. Nephron. You have done well!

Henle This is very revealing. In other words, in this case, she likely has MGUS that hasn't been diagnosed.

Henle leaves, and returns a few days later.

Nephron Fine work, Detective!

Podocyte It's always nice to drop in and discuss a good case of glomerular disease.

Henle Her serum free light chains suggested an elevated free kappa-to-lambda ratio of 5. Her bone marrow biopsy specimen showed 5 percent plasma cells, which is consistent with MGUS. Greater than 10 percent and she would have a myeloma. So now we are left with MGUS and MPGN. Do we treat or not? And what do we treat with?

Nephron This is a tough question you are asking, Henle.

Podocyte To me it seems that if damage is happening in an organ, particularly in the kidney, because of the monoclonal nature of this light chain kappa, how can we call this "undetermined significance"? It is clear to me that it is significant. Unfortunately, the hematology community needs to learn more about this entity and perhaps not call it MGUS when there is end-organ damage. Some cases of this have been successfully treated with anti–B cell agents such as rituximab. However, it makes more sense to treat this entity as a paraprotein, targeting agents such as those used in multiple myeloma. But, until we have more data, we might not be able to do anything.

Nephron We prescribe medications all the time, and we have to be careful regarding the potential drastic effects they can have on the body. My dear apprentice, MGUS is a chronic entity, and so is MPGN, and it is possible that she might not need treatment for now. Conservative management is reasonable, given the lack of data.

Podocyte I disagree. I would give her rituximab if B lymphocytes were responsible for the monoclonal gammopathy. Rituximab would not be effective if plasma cells were responsible for the monoclonal gammopathy. This raises the question whether drugs such as bortezomib would be of benefit in such cases.

Henle watches them argue.

Nephron Henle, as you can see, we don't have a final answer for you. That is perfectly reasonable and the main reason why ongoing research in nephrology is critical. The current status of nephrology research is grim. It needs more energy and enthusiasm from residents, students, and fellows to move the field forward. Nevertheless, from a single entity of MPGN, you diagnosed a potential premalignancy state in this patient. Never underestimate the power of the nephrologist.

Detective Nephron was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra Medical School and an attending nephrologist at North Shore University and Long Island Jewish Medical Center in Great Neck, New York. Thanks to Dr. Rimda Wanchoo of the Weill Cornell Medical Center, New York, and Dr. Sanjeev Sethi of the Mayo Clinic, Minnesota, for their editorial assistance. Send correspondence regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com.

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