ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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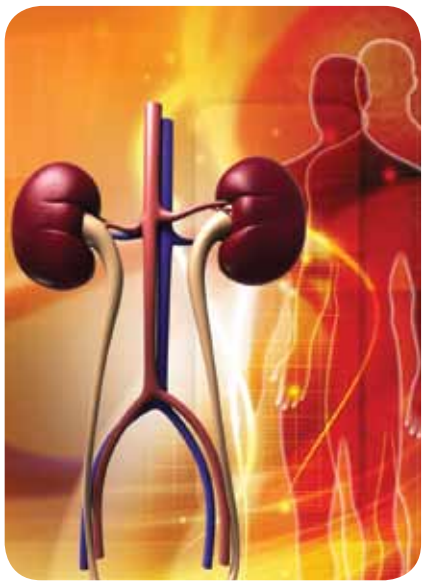
Even Low Levels of Donor-Specific Antibodies Adversely Affect Kidney Allograft Outcomes



The presence of donor-specific antibodies in kidney recipients is a significant hurdle to successful organ transplantation with good long-term outcomes. Although this is a well-accepted fact, the clinical significance of different levels of these antibodies has been unclear. Now, new research indicates that recipients who have even very low levels of preformed antibodies directed against a donated kidney have a significantly increased risk of acute rejection and graft failure. The findings, which are published in the *Journal of the American Society of Nephrology*, could help physicians determine better donor-recipient matches and tailor recipients' immunosuppressive therapy after transplantation.

"Our study reviews disparate findings across different patient cohorts of varying levels of immunological risk and for the first time demonstrates a universally applicable risk stratification using the results of the various currently available immunological testing," said first author Sumit Mohan, MD, of Columbia University.

Detecting antibodies

Transplant recipients who have had previous transplants, blood transfusions, and other sensitizing events often have antibodies directed against a particular donor's kidney. Many studies have examined the risks associated with the presence of such donor-specific antibodies in transplant recipients, and there are conflicting reports of the clinical significance of antibodies detected by newer, more sensitive solid-phase assays, especially when the results of more traditional tests such as flow cytometry crossmatching are negative.

"This has been confusing and has limited our ability to understand and develop standard clinical management for patients with donor-specific antibodies at the time of transplantation while at the same time potentially preventing transplantation of certain donor-recipient pairs," said Mohan. Understanding the true level of risk in patients with antibodies detected by different techniques is essential to optimizing outcomes after transplantation.

Continued on page 4

GAO Report on ESA Utilization Stirs Controversy, Uncertainty

By Rachel Shaffer

The recently released Government Accountability Office (GAO) report, "End-Stage Renal Disease: Reduction in Drug Utilization Suggests Bundled Payment is Too High," has generated controversy within the kidney community.

Focused on erythropoiesis-stimulating agent (ESA) utilization, the report comes at a time when a potential rebasing of the bundled payment rate is already creating uncertainty and concern. The report introduces additional controversy by recommending reducing that payment rate quickly and dramatically.

As the Medicare ESRD Prospective Payment System—more commonly known as "the bundle"—and the Quality Incentive Program (QIP) enter their third year of operation, rebasing the bundle is a front-and-center issue for the nephrology community. At press time, it was not entirely clear which part of the federal government—Congress or the Centers for Medicare & Medicaid Services (CMS)—will drive that process, or when. It remains to be seen to what extent CMS's slated 2014 addition of oral-only drugs to the bundle, recommendations from government entities such as the GAO and the

Continued on page 3

Inside

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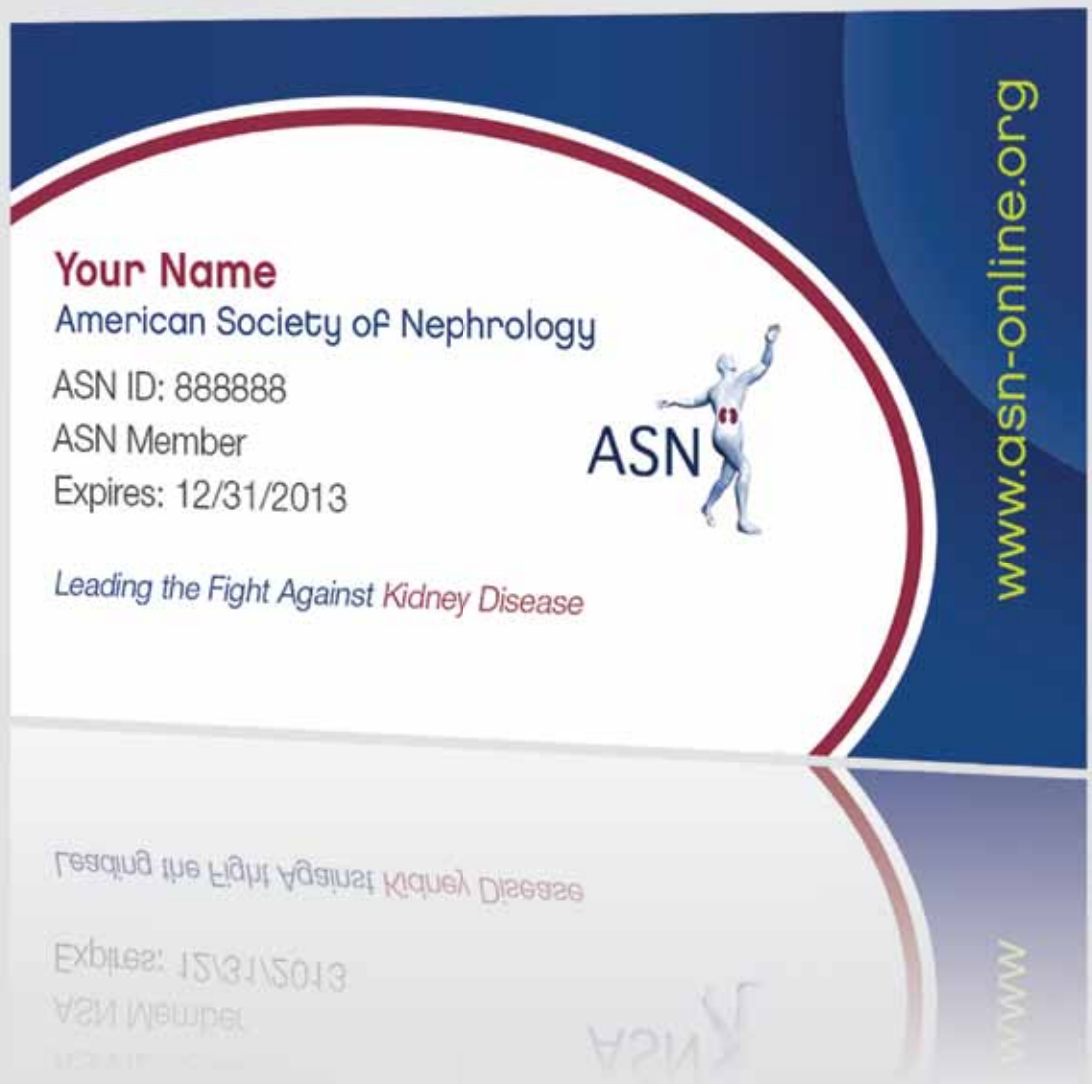

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GAO Report

Continued from page 1

Medicare Payment Advisory Commission (MedPAC), or congressional efforts to find big-ticket savings, or some combination thereof, could influence a potential rebasing in 2013.

CMS implemented the new bundled payment system and the QIP—the first-ever mandatory value-based purchasing program in Medicare—in 2011. The transition to the new system will be completed on January 1, 2014, when the bundle will be expanded to include payment for certain "oral-only" drugs that do not have injectable equivalents, which are currently covered under Medicare Part D. In theory, next January's deadline means that the methodology for calculating the base payment rate should be adjusted and a new bundled payment value set to account for these additional drugs before 2014 begins.

To date, however, CMS has not determined the methodology it will use to incorporate oral-only drugs into the bundled payment, and it is unclear whether the agency has the legal authority to do so. The December GAO report highlighted CMS's statement that they "did not have immediate plans to rebase the rate and that the statute does not provide CMS with explicit authority to do so." Although the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA) did not explicitly authorize CMS to rebase the payment rate to account for changes over time in the utilization of dialysis and related items and services, such as ESRD drugs, it did not explicitly prohibit CMS from doing so.

MIPPA does require CMS to update the payment amount to account for changes in the prices of items and services already included in the bundle and for changes in productivity. CMS increased the rate by 2.1 percent in 2012 and recently announced its intention to increase it by 2.3 percent in 2013.

Who actually has the authority to order a rebasing of the bundle is not the only debatable issue. Generating considerable controversy are GAO's finding that ESRD drug utilization in 2011 was about 23 percent lower than in 2007, and its recommendation that Congress should "consider requiring the Secretary of HHS [Department of Health and Human Services, which includes CMS] to rebase the ESRD bundled payment rate as soon as possible and on a periodic basis thereafter, using the most current available data."

GAO posited that Medicare payments for dialysis services would have been about $650 million lower in 2011 if the bundled payment amount reflected average ESRD drug utilization in that year (rather than utilization in 2007, the year used for calculating the current bundled payment rate). GAO stated "our findings suggest that the current bundled payment rate is excessive given recent changes in ESRD drug utilization."

The GAO report was narrowly focused, examining just one aspect of care—anemia management—rather than the complete scope of products and services that go into providing dialysis that the bundle encompasses.

"By examining only one component of care, the GAO report completely ignored the many other components that are necessary to deliver the highest quality care for dialysis patients," said Robert Sepucha, senior vice president for policy and business development at Fresenius Medical Care North America. He added the report "also failed to take into account that the true cost of a given component has two variables: price and utilization. In focusing solely on declining utilization without any regard to the rising costs of ESAs, the report provided an incomplete and ultimately inaccurate view of the bundle."

The finding that ESRD drug utilization has declined in the past 5 years is not new. Several studies—including those from the Dialysis Outpatient Practice Monitor System (DOPPS) and the United States Renal Data Service (USRDS)—have recently found that ESRD drug utilization, particularly ESA use, has declined since 2007. MedPAC also reported in December 2012 that ESA use had declined in recent years. Nonetheless, MedPAC, which assessed ESAs as well as many other components of dialysis care, concluded that the payment system is too new to consider rebasing at this time.

"MedPAC actually reviewed a more complete set of data for dialysis facilities than the GAO and is not recommending any of the dramatic cuts GAO is proposing," said Katrina Russell, president of the National Renal Administrators Association (NRAA).

The reasons behind the decline in ESA use are complex and still not fully understood. "The cause of reduced ESA use is undoubtedly multifactorial," observed ASN Public Policy Board Chair Thomas H. Hostetter, MD.

"In 2011, the Food and Drug Administration changed the ESA label, eliminating a safe lower target dose, and it appears that nephrologists acted accordingly by reducing ESA use," Hostetter said. "Several studies showing the risk of targeting high hemoglobins in recent years also likely contributed to a decline in ESA use, and then you do have the bundled payment and the QIP. So it is very challenging, at least at the present time, to conclusively draw out what is really driving this reduction. Most important, it is still unclear what effect the reduction may have on long-term patient outcomes—beneficial, neutral, or harmful."

Dialysis Patient Citizens (DPC) is urging caution in implementing the report's conclusions, according to DPC Executive Director Hrant Jamgochian.

"As noted in the report, the patient impact of this decline is unclear," Jamgochian said. "While early evidence suggests that the incidence of stroke and heart attacks has declined with decreasing ESA use, there has been an increase in blood transfusion rates, which can have adverse health effects on patients and can limit access to successful kidney transplants. Before knowing the full patient impact of these changes, we caution policymakers not to ask too hastily to reinforce this decreased utilization by adjusting reimbursement rates downward."

NRAA's Russell added that "making cuts of the magnitude GAO is recommending would impose great financial strain on small dialysis organizations and could lead to fewer choices and access to care problems for patients."

While the nephrology community is in agreement that the exact causes of the decrease in ESA use and its effect on patients remain unknown, the notion that CMS may be paying for more ESRD drugs than are being used attracted the attention of some members of Congress, even ahead of the GAO report. The report's release has likely increased the possibility that Congress would consider rebasing the bundle and claim any savings to help cover the cost of a year-end legislative package.

Given the vulnerable patient population the Medicare ESRD Program serves, there is considerable concern that legislative rebasing of the bundle—earlier than anticipated in the life cycle of the new payment system—could create serious unintended consequences for patients.

"The ESRD bundled payment system is new, complex, and still in the implementation phase, with many changes, including adding oral medications into the bundle in 2014, making it even more complex," said Allen Nissenson, MD, chief medical officer at DaVita. "Complete, rigorous, and valid data are required to ensure that any adjustments to the payment system that are made in the future are justifiable, appropriate, and are in the best interests of patient clinical outcomes. Data meeting these requirements are not yet available."

At press time, it remained possible that Congress could legislate a rebasing of the bundle and use the savings it prescribes as a budgetary offset as it attempts to address the fiscal cliff, the Sustainable Growth Rate, and other costly issues. Congress asked the Congressional Budget Office (CBO) to estimate how much savings could be obtained by rebasing the bundle at this time. CBO's estimate will play a significant role in determining Congress' appetite for pursuing rebasing, because the legislative branch is likely to focus on "big" savings rather than squander time and political capital negotiating smaller-ticket provisions.

"There is no question that Medicare's reimbursement rate needs to accurately reflect the total cost of care," said Fresenius' Sepucha. "Should a rebasing occur, we believe the experts at CMS should lead the process so it is done thoughtfully and comprehensively. But that process should not be undertaken hastily, nor should it be done in a vacuum."

Said Hostetter: "Any rebasing of the bundle needs to be thoughtful and transparent, examine every component of high-quality care, and provide opportunities for input from patients, health professionals, and other experts. ASN will continue to collaborate with other stakeholders in the nephrology community to advocate that any future rebasing be conducted through a CMS rulemaking process that meets these criteria. Rebasing the bundle in search of savings is not something that Congress should attempt based on one report that largely examined just one of the many, many components of care for our complex patients."

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Donor-Specific Antibodies

Continued from page 1

To determine this risk, Mohan and his colleagues sifted through the medical literature to find studies that assessed donor-specific antibodies and health outcomes in kidney transplant recipients. Their search identified seven retrospective cohort studies that included 1119 patients. These studies included patients who were shown to be negative for donor-specific antibodies by flow cytometry crossmatching. They compared patients with and without donor-specific antibodies detected by solid-phase assays at the time of transplantation. The analysis allowed the investigators to define the level of risk of acute antibody-mediated rejection and allograft failure in patients with donor-specific antibodies relative to patients without.

Determining risk

After analyzing the results of these studies, the investigators determined that the detection of donor-specific antibodies by newer solid-phase assays—despite negative results from older tests—nearly doubles the risk for acute antibody-mediated rejection and increases the risk of graft failure by 76 percent. (The absolute risk of failure in the first year in the United States is currently about 8.2 percent for first-time recipients and about 10.7 percent for recipients of repeated transplants.)

Previously reported cohorts of patients who were tested only with the most recent solid-phase assays were more heterogeneous than previously thought, the authors found. These cohorts included patients who would have been identified as being at risk by flow cytometry; as a result, these cohorts tended to have a much higher risk of acute antibody-mediated rejection (odds ratio of 7.8) and similar graft failure (odds ratio of 1.7). The researchers were also able to demonstrate differences in relative risk in patients with and without donor-specific antibodies by solid-phase assays when the cohorts were defined by flow cytometry results.

"Our findings allow clinicians to use the results of various tests available to measure the presence of antibodies in recipients for both prognostication and potential identification of those patients who would benefit from more aggressive immunosuppression at the time of transplantation," said Mohan. The findings also suggest the need for increased vigilance in patients with donor-specific antibodies detected by solid-phase assay with a negative crossmatch—and perhaps more so in patients with donor-specific antibodies detected by solid-phase assays at centers that have foregone flow crossmatching tests.

Mohan noted that the study was limited by the quality of the current literature; the included studies tended to have very different immunosuppression treatment protocols, and they reported outcomes after different lengths of follow-up. Nonetheless, the results were consistent and confirmed differences of patient outcomes based on differences in the measurement of immunological risk by flow cytometry and solid-phase assays regardless of the immunosuppression protocol used.

"This article is an important reminder that donor-specific antibodies are clinically relevant, the treatment protocols are heterogeneous, and the available evidence is limited," said Dorry Segev, MD, PhD, who was not involved with the research and is a transplant surgeon at the Johns Hopkins School of Medicine. Segev is an expert in issues related to incompatible kidney transplantation and organ allocation. "The problem of sensitization to donor-specific antibodies is not going away, but rather is getting worse, and will not be solved by paired donation alone. The findings provide strong motivation for the creation of large multicenter cohorts to better study treatment protocols and center-specific effects in kidney transplantation across donor-specific antibody barriers," he added.

Nearly 17,000 kidney transplantations take place each year in the United States.

Study coauthors include Demetra Tsapepas, PharmD, Bekir Tanriover, MD, R. John Crew, MD, Geoffrey Dube, MD, Lloyd E. Ratner, MD, David Cohen, MD, and Jai Radhakrishnan, MD.

Disclosures: The authors reported no financial disclosures.

The article, entitled "Donor-Specific Antibodies Adversely Impact Kidney Allograft Outcomes," is online at http://jasn.asnjournals.org/, doi: 10.1681/2012070664.

Something to Say?

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2013: The Year Ahead

The new year promises to be filled with change. As the Affordable Care Act unfolds, healthcare will move toward accountable care organizations and medical homes. The Food and Drug Administration considers new endpoints for kidney drugs, perhaps facilitating entry into the market.

Scientific advances suggest that bioengineered and artificial kidneys may not be far in the future.

Falling prices for genetic sequencing may bring a brave new world of individualized medical care sooner than we thought.

From policy to practice, nephrology is changing. Here are some of the things we will be watching in 2013.

Regenerative Medicine and Bioartificial Kidneys Could Aid Shortage of Donor Kidneys

For Guiseppe Orlando, MD, and Shuro Roy, PhD, 2012 was a year of milestones for their respective research programs that ultimately will help combat the critical shortage of donor organs for kidney transplantation. The year 2013 promises to bring their work to further fruition.

Orlando, a transplant surgeon and scientist, headed the Wake Forest Institute for Regenerative Medicine research team that succeeded in creating acellular renal extracellular matrix (ECM) scaffolds through decellularization–recellularization technology. The scaffolds were applied to whole porcine kidneys.

"These kidneys maintained their innate three-dimensional architecture as well as their vascular system and may represent the ideal platform for kidney engineering," said Orlando, who reported the research in the journal *Annals of Surgery*.

His goal is a bioengineered kidney that could be manufactured from the patient's own cells.

For Roy, a bioengineer in the University of California at San Francisco's (UCSF) Department of Bioengineering and Therapeutic Sciences, the goal is not to generate new renal tissue but to design reliable implantable renal assist devices—bioartificial kidneys —for end stage renal disease (ESRD) patients.

Last year, the U.S. Food and Drug Administration (FDA) selected the UCSF bioartificial kidney for its Innovation Pathway 2.0, because of the device's "transformative potential" in ESRD and "its potential to benefit from early interactions with the FDA in the approval process," according to the university.

Roy and the project's medical director, William H. Fissell, MD, associate professor of clinical medicine, Vanderbilt University Medical Center, have been working for about 10 years with a multidisciplinary team of 40 researchers in nine U.S. laboratories to develop the bioartificial kidney, aiming for clinical trials by 2017.

Could donated kidneys produce scaffolds for populating ESRD patients' own cells?

Orlando, who was an invited lecturer in the "Bioengineering and Informatics: Curing Renal Disease with Cells and Devices" session at Kidney Week 2012, implanted the acellular scaffolds in pigs and one

month later removed them.

Pathological examination showed that the renal ultrastructure had not changed, but a nonspecific inflammatory response, which is normally triggered following any surgical trauma, had occurred, Orlando said.

Orlando and his colleagues next will evaluate the scaffolds in pigs after the structures have been seeded with kidney-specific cells and possibly other cell types, such as those that pave the blood vessels of organs to allow implantation.

If the research succeeds, Orlando said he envisions using donated human kidneys to produce the acellular scaffolds, which would be repopulated with the ESRD patient's own cells.

Bioartificial kidney

To design the bioartificial kidney, Roy and colleagues took advantage of technological advances in microelectromechanical systems and nanotechnology. These technologies enabled the researchers to miniaturize the large-size extracorporeal renal assist device developed at the University of Michigan through the use of high-efficiency ultrafiltration membranes that can be mass produced.

The ideal bioartificial kidney would perform the kidney's filtration functions as well as maintain water and salt balance, produce vitamin D, and regulate blood pressure and pH.

"We try to mimic a number of those functions through a combination of mechanical components—silicon filters that we have developed—with cells that we've harvested from human kidneys," Roy said.

The current prototype can provide stable differentiated functions of renal tubule cells harvested from human kidneys in an engineered construct, the cell bioreactor, Roy said.

The team continues to build and test increasingly complex prototypes with improved silicon membranes. They also are experimenting with a combined hemofilter and cell bioreactor and are packaging the device for preclinical testing.

Roy also spoke at Kidney Week 2012.

New Endpoints for Chronic Kidney Disease?

How do we decide if a therapy slows the progression of chronic kidney disease? In the past, doubling of serum creatinine has been accepted by the Food and Drug Administration (FDA). Recent studies have used smaller changes in estimated glomerular filtration rate as endpoints, and the FDA has convened a group to formally address the issue. New endpoints could facilitate clinical trials of new treatments, getting drugs tested and on the market sooner.

Accountable Care Organizations and Nephrology-Specific Care Remain Key Issues For 2013

With the successful launch of several Accountable Care Organization (ACO) programs—including the Pioneer ACO model, the Advance Payment model, and the Medicare Shared Savings Program—the Center for Medicare and Medicaid Innovation (CMMI) is looking toward implementing similar strategies to coordinate care and improve outcomes for groups of patients with specific diseases. All signs suggest that the Centers for Medicare & Medicaid Service's Innovation Center is interested in launching a nephrology-specific integrated nephrology care delivery model pilot project or demonstration—which would make it the first-ever disease-specific integrated care delivery model.

Once again, the nephrology community is poised to pioneer innovations in patient care delivery and payment ahead of other areas of medicine.

Here's what to watch as the year progresses:

- The Innovation Center's announcement of a request for proposals (RPF) to participate in a pilot project or demonstration. Although there was some speculation that an RFP would be released in the fall of 2012, and later that it might be released following the presidential election, as of press time no announcement had been made.
- Details on the scope of CMMI pilot or demonstration projects—and whether there might be multiple models. Multiple models could help facilitate the participation of a diverse range of provider types and locations as well as enable patients in different care environments to benefit. ASN and other patient and health professional organizations have also advocated that at least one pilot or demonstration project should include "upstream" patients with late-stage chronic kidney disease (CKD) in addition to patients with end stage renal disease (ESRD). Also unknown is how "prescriptive" an RFP might be; would CMMI specifically delineate the components it wants to see in a pilot or demo, or will applicants be encouraged to innovate independently, proposing a diversity of care delivery strategies?
- How many entities respond to the RFP and, ultimately, how many patients have the opportunity to receive care in these cutting-edge new care delivery pilots or demos.

Regardless of what a final pilot or demonstration project will look like, there is considerable excitement within the nephrology community as well as within the Innovation Center that a nephrology-specific integrated nephrology care delivery model could foster transformative improvements in patient care and produce valuable lessons for other areas of medicine—such as oncology—that may look to develop integrated care delivery models in the future.

Genomic Medicine: the Trek Toward the Clinic

Significant advances will occur in applying genomics to medicine over the next few years, predicts Eric D. Green, MD, PhD, director of the National Institutes of Health's National Human Genome Research Institute (NHRGI). After 2020, those advances will have an impact on improving the effectiveness of health care, but it will be a "long, hard process," Green said.

"We have a long way to go to fully understand the human genome," Green said. "The Human Genome Project was the starting line and by no means the end."

Unraveling the genetic risk factors for common complex diseases like diabetes, heart disease, and cancer will continue to be a priority because these diseases represent a major health care burden. "The lowest hanging fruit is cancer genomics," Green said.

Green gave a state-of-the-art lecture, "Entering the Era of Genomic Medicine: Research Opportunities and Challenges," at Kidney Week 2012 in San Diego.

The scientific community currently has only a Cliff Notes view of the functional landscape of the human genome. To change the view from Cliff Notes to encyclopedic, NHGRI sponsors the ENCODE (ENCyclopedia Of DNA Elements) project to compile a comprehensive catalog of functional elements that control the expression of genetic information in a cell.

ENCODE was launched just a few months after the 2003 completion of the Human Genome Project. During the post-Human Genome Project era, scientists have learned that the "whole story" cannot be told by the primary DNA sequence alone, Green said. Epigenetic factors that "decorate the DNA sequence," to modify the expression, or activity, of specific genes are another major player in the genome.

Less than 2 percent of the human genome contains the 20,000 genes that encode proteins. The remaining 98 percent encode transcription factors and other elements, not all of which are known.

The "non-protein parts" are not as well understood as the protein-coding genes, Green said. But they will continue to attract more attention because mutations in the non-protein parts, not the protein-coding genes, are the main DNA contributors to risk for developing commonly occurring, non-Mendelian, multi-genetic diseases such as kidney disease, diabetes, hypertension, cardiovascular disorders, and cancer.

In contrast, the rare, single-gene Mendelian disorders such as cystic fibrosis are caused by mutations in the protein-coding genes, Green said.

To jumpstart the discovery of risk variants for commonly occurring diseases, NHGRI has sponsored several major research programs, including the Genome Wide Association Study (GWAS), the HapMap Project, and the 1,000 Genomes Project.

Yet scientists' ability to store, analyze, and interpret data has not advanced as quickly as the sequencing technologies that can decipher exomes, the protein-coding genes, and whole genomes.

"The numerous DNA sequences that have been deciphered since 2003 combined with new information about the genomic architecture of disease is massive," Green said, and "is the largest current bottleneck" in genomic medicine.

"We have a big data problem," he said. "We are victims of our own success." Less than a decade ago it took 3 to 4 months and $10 million to $50 million to decipher the human genome. Today an individual's genome can be sequenced in three to four days for $4000 to $8000. Soon it will cost $1000, Green said, enabling the widespread application of DNA sequencing in the clinic as well as the lab.

A second bottleneck likely to be addressed in coming years is information dissemination. Including clinical genomics information systems in electronic health records systems may be one approach.

"Physicians are still a long way from submitting their patients' full genomes for sequencing, not because the price is high, but because the data are difficult to interpret," wrote Nobel laureate Harold Varmus, MD, a former Director of NIH and now head of the National Cancer Institute in *Genome Medicine*..

The 2013 Outlook for Research Funding

By Grant Olan

Current federal deficit reduction efforts could lead to more cuts to U.S. medical research funding. Since the November 2012 election, Congress has been consumed with averting the "fiscal cliff" on January 2, 2013.

As of press time, Congress and President Obama had not reached a deal, but most experts agree that one would be made either before or after the January deadline. If before, the agreement would most likely employ a two-step process whereby Congress would agree with the president to allow the 2003 tax cuts to expire for the top 2 percent of wage earners and postpone the automatic $1.2 trillion across-the-board cuts to federal discretionary programs for the first 6 or 9 months in 2013 to allow time to identify areas in the federal budget for savings or cuts and to revise the tax code.

If the United States goes over the fiscal cliff before Congress and the president reach a deal, other issues will come to the forefront that must be dealt with: principally, funding the remainder of the Fiscal Year (FY) 2013 budget that expires on September 30, 2013, and raising the "debt ceiling" before the United States reaches the legal limit of how much debt the federal government can assume. Congress will also take up FY 2014 budget and appropriations bills in the spring.

As Congress and the president deal with all of these issues, ASN will be on the front lines to remind lawmakers that medical research has already done its part and that more cuts to research funding will not balance the budget.

"ASN is greatly concerned that more cuts are on the horizon for the National Institutes of Health (NIH) and medical research at other federal agencies as talks intensify on the U.S. budget and debt ceiling," said ASN Research Advocacy Committee Chair John Sedor, MD.

The White House Office of Management and Budget (OMB) projected NIH would see another cut of $2.5 billion, or 8.2 percent, and the loss of up to 2300 research grants if there is no deal to avert the fiscal cliff. National Cancer Institute Director Harold Varmus, MD, claims cancer research would actually sustain cuts closer to 40 percent since NIH has decided to fund administrative costs and current obligations before new grants in the event the United States goes over the fiscal cliff.

Whether 8.2 percent or 40 percent, NIH Director Francis Collins, MD, PhD, declared that the cuts "would be devastating for many investigators who are seeking to continue programs that they have had funded in the past and are back for their competing renewal, or who are starting things that are entirely new; and I think the burden would hit particularly heavily upon first-time investigators who are seeking to get their programs up and going."

Today, only one in six applications (18 percent) are approved for NIH research funding—an all-time low—and the average age of a scientist receiving their first grant is 40 years. More cuts to medical research would not only mean the loss of promising research, they could jeopardize the position of the United States as the global leader in research, with countries such as China doubling down on investment in this area. For these reasons, ASN has been aggressively advocating for a balanced approach to deficit reduction that does not rely on further cuts to research.

Funding for patient outcomes at risk?

Cuts would also hamper other research agencies like the Patient-Centered Outcomes Research Institute (PCORI) established by the 2010 Affordable Care Act (ACA). PCORI's mission is to help "fund research that will provide patients, their caregivers, and clinicians with the evidence-based information needed to make better-informed health care decisions."

Although the Supreme Court upheld the constitutionality of the ACA last June, funding for PCORI would still be subject to sequestration (the technical term for the fiscal cliff). The White House OMB estimated in September that the Patient-Centered Outcomes Research Trust Fund, which funds PCORI, would be subject to a 7.6 percent cut, amounting to $30 million from the $390 million fund in FY 2013. Despite the uncertainty, PCORI continues to forge ahead. After laying infrastructure groundwork and selecting research priorities in 2011 and 2012, PCORI is poised to begin tackling its mission in earnest in 2013 if its funding is not decimated by sequestration.

In May of 2012, PCORI adopted a revised "National Priorities for Research and Research Agenda" after considerable public input from many different stakeholders during a 54-day comment period. ASN recommended that PCORI consider kidney disease as a model for chronic disease research because kidney disease affects individuals throughout the human lifespan, as well as racial and ethnic minority populations. The care of pediatric and adult patients with CKD provides a model for care of patients with common diseases who have complex medical histories, multiple comorbidities, and are cared for in a variety of settings at a high cost. The full letter is available at http://www.asn-online.org/policy/.

PCORI adopted several of ASN's suggestions, including a recommendation to make disparities in the development and progression of chronic illnesses, including CKD, a core research priority. In addition to addressing disparities, PCORI's five national priorities include assessment of prevention, diagnosis, and treatment options; improving health care systems; communication and dissemination research; and accelerating patient-centered outcomes research and methodological research. The complete PCORI report is available at http://www.pcori.org/news-room/.

In November 2012, PCORI adopted 47 revised methodology standards to guide the conduct of patient-centered outcomes research. A full report, providing context for the revised methodology standards, will be available in the spring. Researchers conducting PCORI-funded studies will be required to adhere to the methodology outlined in this report.

Signaling a shift from planning-related activities to more research-oriented activities, PCORI also authorized the development of three research funding announcements in November. PCORI will support studying treatment options for uterine fibroids, the safety and benefits of treatment options for severe asthma, and fall prevention in the elderly. The agency is also currently considering input from the public on two additional topics for funding that it will announce in early 2013. More information about funding opportunities is available at http://www.pcori.org/funding-opportunities/.

As PCORI moves ahead with or without a fully funded budget, ASN will continue to advocate the importance of investments in research by all federal agencies that improve the health of kidney patients.

ASN and FDA Form the Kidney Health Initiative

KIDNEY HEALTH INITIATIVE

ASN and the U.S. Food and Drug Administration (FDA) have joined forces to form the Kidney Health Initiative (KHI). Established through a memorandum of understanding signed in September 2012, KHI's mission is to "advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products."

"KHI represents an exciting undertaking by ASN and FDA to bring about long-needed interactions between all of the different health care stakeholders responsible for developing, delivering, and monitoring care for patients with kidney disease," said ASN President Bruce Molitoris, MD, FASN. "Bringing together the different, often fractured, components of the health care industry into interdisciplinary interactions will promote innovation, hasten translation, and improve the quality of patient care through new diagnostic and therapeutic advances. By catalyzing these developments, KHI will benefit stakeholders, including payers, but most importantly our patients."

KHI has attracted attention from a diverse range of stakeholders in the kidney community, and at press time comprised nearly 20 member organizations. As KHI begins operations in 2013, how do stakeholders view its potential and what impact could KHI have on kidney research and patient safety?

KHI structure and scope

With up to 26 million Americans living with kidney disease, and given the disease's serious health implications and economic burdens, KHI's creation is timely. During his President's Address at ASN Kidney Week 2012, Ronald Falk, MD, FASN, introduced KHI to the kidney community by stating that the ASN-FDA partnership would "help write a new and exciting chapter in our fight against kidney disease." KHI seeks to address the lack of new medications for kidney disease and improve patient safety by facilitating dialogue, developing efficient trial designs, drafting white papers, and creating a transparent infrastructure to facilitate communication and collaboration among the greater kidney community and the FDA. To learn more about KHI's mission and objectives, please visit http://www.asn-online.org/khi/KHI_Mission.pdf.

KHI is open to a wide variety of stakeholders, including patient and health professional organizations, pharmaceutical and biotechnology companies, device manufacturers, dialysis providers, foundations, research institutes, and U.S. and international government agencies. And because nephrologists collaborate with many other medical specialties, organizations representing these professionals (such as cardiovascular disease or diabetes) are eligible for KHI membership.

KHI's public-private framework is a byproduct of FDA's Critical Path Initiative (CPI), a blueprint to foster innovation in the development and evaluation of medical products. Other CPI partnerships include the Clinical Trials Transformation Initiative, the Medicare Device Innovation Consortium, and the Cardiac Safety Research Consortium (CSRC), which served as the template for KHI. A partnership between FDA and the Duke Clinical Research Institute, CSRC evaluates the cardiac safety profiles of new drugs and devices. Since 2006, CSRC has authored nine white papers, convened several think tanks, and created the CSRC ECG Warehouse—a database of electrocardiogram data that is an important resource for cardiac researchers.

Although similar to CSRC, KHI differs in its structure and scope. ASN will serve as an equal partner with FDA on the KHI board of directors, which is headed by two co-chairs—one each from ASN and FDA. The board will also include voting members from each branch of FDA, as well as non-voting members from other federal agencies, including the National Institutes of Health, Centers for Disease Control and Prevention, and the Centers for Medicare & Medicaid Services.

The inaugural KHI co-chairs are Prabir Roy-Chaudhury, MD, PhD, FASN, of the division of nephrology at the University of Cincinnati College of Medicine, and Patrick Archdeacon, MD, of the FDA's Center for Drug Evaluation and Research.

Roy-Chaudhury views KHI as an opportunity to improve nephrology's "orphan status" in the areas of randomized controlled clinical trials and bringing new therapeutics to market. "This requires having all of the stakeholders—physicians, patient advocacy groups, industry, and, critically, FDA—at the same table working together to open pathways for getting the right drug, biologic, or device to the right patient in the right way," he said.

"KHI is a forum where FDA can be more responsive to the nephrology community," said Archdeacon, "and we're looking forward to hearing from KHI members about what they perceive are the important issues and priorities."

KHI's focus on bringing patients to the table distinguishes it from other CPI partnerships. "Having patients involved is absolutely critical," said ASN co-chair Roy-Chaudhury. "They give KHI a different and much-needed perspective, because patients and patient advocacy groups often have the ability to quickly focus down on the key obstacles to better care, in a way that health care professionals may not be able to," he added. The FDA co-chair Archdeacon agrees, noting "FDA, industry, and the entire nephrology community need to better understand the issues facing kidney patients, as experienced by the patients themselves. KHI will allow us to hear from the patients directly."

In launching KHI, ASN and FDA personnel worked proactively to develop a strong and transparent policy regarding conflict of interest (COI) management and disclosure. KHI board members and working group participants are required to disclose and update COI disclosures for the duration of their involvement. Because some members will possess competitive interests, KHI has a clearly delineated plan for disclosing and managing COIs in the selection of, and participation in, KHI projects and activities, which is available at http://www.asn-online.org/khi/coi.aspx.

Stakeholder perspectives

Reaction among stakeholders in the kidney space to KHI's creation has been uniformly positive. "I'm really excited to see this true collaboration between industry, practitioners, FDA, and patients—the end users who have the most important voice," said Karen E. Ryals, executive director of the American Association of Kidney Patients. She views KHI as an opportunity to address patient safety issues, explore new avenues in treatment, and most important to improve communication not only between patients and kidney professionals but within care settings. "The kidney community can become segmented, but if we work in a collaborative spirit I believe a lot more will get done, which will benefit patients tremendously," Ryals said.

"I believe those of us in industry are quite excited about KHI," said Mark T. Houser, MD, of Abbott Laboratories. "From a drug development perspective, anything that improves dialogue and communication between the renal community, regulatory agencies, and industry is highly desirable, and should lead to advancements in the number of new therapeutics to treat patients with CKD. These interactions should help identify areas where the needs for new therapies are the greatest, and also provide additional clarity to industry regarding a regulatory path which always reduces risk in drug development. However, given that drug development is a global process it will clearly be important to include other global regulatory agencies as KHI matures."

Archdeacon added there needs to be a perception that ideas developed at KHI can apply worldwide. "KHI has received a fair amount of interest from outside the United States, and I'm optimistic that KHI's influence can extend beyond our borders," he said.

Sharon A. Perlman, MD, of the American Society of Pediatric Nephrology (ASPN), said she is delighted with the mission and broad focus of KHI, adding that ASPN is especially interested in advocating for improved development of drugs and devices for treatment of children and adolescents with kidney disease. "Given the relatively small number of pediatric nephrology patients with any specific disorder, KHI's objective to develop approaches to the systematic collection

Continued on page 12

Kidney Health Initiative

Continued from page 17

of retrospective or prospective data, as well as to establish data standards, offers an opportunity to maximize the information available from clinical trials conducted on these relatively small patient populations," she said.

"As a KHI pioneer member, the American Society of Diagnostic and Interventional Nephrology (ASDIN) has an opportunity to collaborate with ASN and FDA to nurture novel therapeutics that meet patient care goals that all three entities share," said Alexander S. Yevzlin, MD, ASDIN president-elect. Interventional nephrology focuses primarily on vascular access, and ASDIN would like to see improvements in the delivery of access care via novel therapeutic solutions and increased knowledge of vascular disease processes, he said.

Could KHI benefit FDA as well, in facilitating cross-talk among FDA's different branches? Absolutely, said Archdeacon. Because of the wide range of products and breadth of diseases that impact the kidney, there are numerous FDA review divisions that regulate products affecting kidney health that may not regularly interact with one another. "Having a single forum where we're able to talk about nephrology and ways to facilitate innovation and renal safety also provides a good opportunity for the FDA to facilitate intramural interaction," he said.

Moving research forward

What will KHI's role be in the promotion and advancement of kidney research? Molitoris believes "KHI represents an opportunity to delineate the clinical aspects and quality measures that will be used to evaluate drugs, devices, biologics, and food products. This will help researchers—whether academics or industry, basic or clinical—target specific undertakings thereby facilitating development and delivery of new diagnostic and therapeutic advances. Once a specific disease aspect is identified as being a therapeutic end point, then efforts to hasten and approve diagnostic capabilities will ensue so as to provide the best possible mechanism of quantifying the clinical end point, which will also help define therapeutic strategies," he added.

One of the challenges of developing new therapies for kidney disease hinges on the difficulty in designing a trial in nephrology, said Archdeacon. "Compared to other therapeutic areas, the time required for kidney disease to manifest and have a clinical impact in the patient can be extremely long, which makes it more challenging to study."

"KHI also levels the playing fields for smaller companies and therefore will be an engine of innovation as it brings together the entire health care industry, including the FDA, to unite behind specific ideas, targets, and quality measures," said Molitoris. "Hopefully everyone in the 'room' will understand and appreciate that we all have a stake in the process, and will keep patient health and well-being at the forefront of all decision-making processes."

One of KHI's objectives is the systematic collection of retrospective or prospective data, such as registries and/or global databases, and establishment of data standards, which could be of great benefit to researchers.

"The development of databases and registries are expensive undertakings, and the cost-value relationship has been debated within the kidney community, especially at NIH, for quite some time," said Molitoris. "However, I think it is safe to say that if KHI can help facilitate the development of these two processes it will be an important step forward in helping to delineate the natural history of the disease processes, successful therapies, and how to individualize therapy so as to achieve the best outcomes while minimizing adverse effects."

Arriving at a challenging fiscal time for medical research, how could KHI influence the environment for kidney research funding?

"If KHI can help create consensus among all the stakeholders on the best practices for studying kidney disease, I think we can expect that whatever resources that are put into that sphere will produce more output," said Archdeacon, adding "if we can make it more feasible and more attractive to study kidney health then it's reasonable to expect that we may see an increase in the resources dedicated to it."

A focus on safety

KHI's focus on patient safety should be of great value to the kidney community, said Abbott's Houser. "Active surveillance of adverse drug reactions, maintenance of patient registries, studies of biomarkers that might predict adverse outcomes and/or response to therapeutics are all areas that can be explored as part of KHI."

Roy-Chaudhury adds that KHI can establish standard guidelines for the assessment of renal toxicity of new products across the entire spectrum of disease. "It's critically important that nephrologists be involved, whether with industry or FDA, and if the correct steps to rule out renal toxicity are identified, the review process can be accelerated because compounds could be vetted beforehand. In the area of patient safety, the scope and impact of KHI can extend well beyond the renal space."

The next steps for KHI

KHI will appoint board members in 2013 who will be charged with reviewing candidate projects and activities, with the eye toward selecting one or two key projects that could be completed in a short timeframe, said Archdeacon. Roy-Chaudhury believes that the initial project(s) should be enablers of future, larger projects, for example, endpoints for clinical trials. "It would be wonderful to have one set of endpoints for clinical trials in a particular area of nephrology (vascular access or transplantation for example) that everybody—physician groups, FDA, and industry—all agree on."

How can ASN members become involved in KHI? "ASN members will play an important role in setting the course for the near term with regard to important undertakings for KHI," said Molitoris. "In addition to serving on the board of directors, ASN members will be involved in subcommittees and working subgroups developing the informational material and approaches necessary to answer specific project questions."

Roy-Chaudhury also sees KHI as a venue for ASN members to "channel their wealth of knowledge to facilitate the bench-to-bedside development of novel drugs, devices, and biologics, and also to provide direction, substance, and prestige to KHI."

To learn more about KHI and how your organization can join, please visit http://www.asn-online.org/khi/, or contact the project director for KHI, Melissa West, at mwest@asn-online.org.

KHI Objectives

1. Facilitate dialog and research that informs regulatory processes with regard to the kidney health of patients being treated for kidney-related as well as other diseases.
2. Assess current medical therapies and diagnostics to identify areas in need of greater innovation and/or better defined regulatory pathways.
3. Develop innovative and efficient trial designs appropriate to answer the most important questions related to kidney health.
4. Establish expert consensus around common terminology and key definitions related to kidney health.
5. Develop approaches to the systematic collection of retrospective or prospective data, such as registries and/or global databases, and establishment of data standards.
6. Coordinate "think tanks," public forums, educational exchanges, and other events to promote discussion and updates on topics in kidney health pertaining to drug, device, biologics, and food product development and evaluation.
7. Create transparent infrastructure and processes that facilitate collaboration and communication among the greater nephrology community and the FDA, including:
   - Seeking input from all stakeholders (including the FDA, industry, nephrologists and other health professionals, the public or patient groups, the National Institutes of Health, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, and other federal agencies).
   - Leveraging previously conducted and ongoing clinical studies, research infrastructure, and databases.
   - Creating an open and efficient mechanism for encouraging and evaluating potential projects submitted to KHI and ensuring objective evaluation.
   - Involving consortium members in the selection and execution of projects.
8. Establish systems to optimize postmarket surveillance of products that affect kidney health, either intentionally or via adverse drug reactions.
9. Draft white papers regarding key issues, describing opportunities and challenges and proposing solutions, as well as promoting execution of these solutions.

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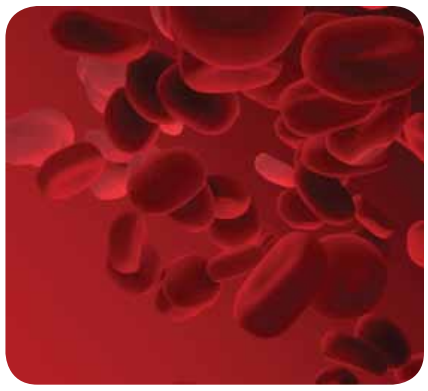
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Journal View

Increased Complications with Preoperative Hyponatremia



Surgical patients with hyponatremia have an elevated risk of death and complications in the 30 days postoperatively, according to a report in the *Archives of Internal Medicine*.

A national quality improvement database was used to identify more than 940,000 patients undergoing major surgery at U.S. hospitals from 2005 through 2010. Based on a sodium level less than 135 mEq/L, 7.8 percent of patients had preoperative hyponatremia. Adverse outcomes in the 30-day perioperative period—including death, major coronary events, wound infections, and pneumonia—were compared for patients with hyponatremia versus normal serum sodium levels.

Thirty-day mortality was 5.2 percent for patients with hyponatremia versus 1.3 percent for those with normal baseline sodium: adjusted odds ratio (OR) 1.44. Hyponatremia was associated with increased mortality across a wide range of patient subgroups. The increase in mortality was more pronounced for hyponatremic patients undergoing nonemergency surgery, OR 1.59; and those in American Society of Anesthesiologists class 1 and 2, OR 1.93.

Several morbidity outcomes were also increased among patients with preoperative hyponatremia, including major coronary events, OR 1.21; pneumonia, OR 1.24; and wound infections, OR 1.17. For most procedures, patients with hyponatremia had approximately a one-day increase in median length of stay.

Hyponatremia is a known, potentially reversible risk factor for adverse outcomes in medically ill inpatients. This large database study links preoperative hyponatremia to an increased risk of perioperative morbidity and mortality after major surgery. Discussing the clinical implications, the researchers write, "[O]ne reasonable approach is to monitor for perioperative complications in all patients at risk and to selectively treat hyponatremia before nonemergency surgical procedures when a reversible cause is found" [Leung AA, et al: Preoperative hyponatremia and perioperative complications. *Arch Intern Med*. 2012; 172: 1–8].

Lower Blood Pressure Doesn't Reduce Mortality in Type 2 Diabetes

Aggressive blood pressure reduction in the year after diagnosis of type 2 diabetes does not lead to a reduced risk of death, according to a study of primary care data in the *British Medical Journal*.

The researchers analyzed data from nearly 127,000 adult patients with type 2 diabetes newly diagnosed at U.K. general practices between 1990 and 2005. Systolic and diastolic blood pressures during the subsequent year were analyzed for association with mortality. Comparisons were made for patients with and without established cardiovascular disease—present in 9.8 percent of patients at baseline. Median follow-up was 3.5 years.

With adjustment for a wide range of baseline characteristics, "tight" control of blood pressure to less than 130/80 mm Hg was not associated with increased survival in patients with cardiovascular disease. For patients with systolic blood pressure of 110 mm Hg, the hazard ratio

for death was 2.79, compared to those with "usual control"—systolic blood pressure 130 to 139 mm Hg. For diastolic blood pressure, hazard ratios for death were 1.32 at 70 to 74 mm Hg and 1.89 at less than 70 mm Hg, compared to usual control of 80 to 84 mm Hg.

Lower blood pressure targets were also associated with increased mortality among patients without cardiovascular disease. Similar patterns were found on analysis of patients receiving treatment for diagnosed hypertension.

Aggressive blood pressure reduction has been recommended for high-risk patients with diabetes, cardiovascular disease, or kidney disease. The new data suggest that lowering blood pressure to less than 130/80 mm Hg may be associated with increased, rather than decreased, all-cause mortality. The risk may be greatest at blood pressures less than 110/75 mm Hg [Vamos EP, et al: Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study. *BMJ* 2012; 345: e5567].

Can ICU Chloride Restriction Lower AKI Risk?

A "chloride-restrictive" approach to fluid management may reduce the risk of acute kidney injury (AKI) in critically ill patients, according to a preliminary communication in *The Journal of the American Medical Association*.

In two sequential six-month periods, the researchers compared a chloride-restrictive versus a standard, "chloride-liberal" strategy to intravenous fluid management. In the first treatment period, adults in a university ICU received standard intravenous fluids. This was followed by a six-month phase-out period. Then in the second treatment period, chloride-rich fluids were given only with approval of the attending specialist, with alternative fluids specified. Cases of AKI were defined by the injury and failure class of the risk, injury, failure, loss, end-stage (RIFLE) classification.

The standard strategy was used in 760 patients and the chloride-restrictive strategy in 773. Total chloride administration decreased from 694 to 496 mmoL per patient. The mean increase in serum creatinine was 22.6 µmol/L during the control period versus 14.8 µmol/L during the intervention period.

The incidence of RIFLE-defined AKI decreased from 14.0 percent during the control period to 8.4 percent during the intervention period. Use of renal replacement therapy (RRT) decreased from 10.0 to 6.3 percent. These effects remained significant on covariate adjustment: odds ratio 0.52 for both AKI and RRT. In-hospital death, lengths of stay, and need for RRT after discharge were similar between groups.

Administration of chloride-containing intravenous fluids might contribute to the risk of AKI in critically ill patients. The new trial suggests that the use of a chloride-restrictive strategy might decrease this risk. While emphasizing the need for further study, the authors believe their results "suggest the need to exert prudence in the administration of fluids with supraphysiological concentrations of chloride, especially in critically ill patients with evidence of early acute renal dysfunction or at risk of acute dysfunction" [Yunos NM, et al: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012; 308: 1556–1572].

Journal View

Tacrolimus for Steroid-Resistant Nephrotic Syndrome in Children

For children with nephrotic syndrome that does not respond to steroids, the combination of tacrolimus and prednisolone is preferable to cyclophosphamide, concludes a trial in *Kidney International*.

The randomized trial included 131 consecutive children with idiopathic steroid-resistant nephrotic syndrome at five pediatric nephrology units. Diagnoses included minimal change disease, focal segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis. Patients were stratified for initial or late steroid resistance. They were then assigned to tacrolimus, 0.1 to 0.15 mg/kg/day for 12 months; or cyclophosphamide. The two groups received equal doses of alternate-day prednisolone.

Defined according to spot urine protein-to-creatinine ratios, the rate of complete or partial remission at 6 months was 82.5 percent with tacrolimus versus 45.9 percent with cyclophosphamide: hazard ratio 2.64. Complete remission rates were 52.4 percent versus 14.8 percent, respectively. The tacrolimus group also had a higher 12-month rate of sustained remission or steroid-sensitive relapse.

More children withdrew in the cyclophosphamide group, mainly because of infections. To achieve one additional remission, the number needed to treat with tacrolimus was three.

There is no agreed-upon approach to the management of idiopathic steroid-resistant nephrotic syndrome in children. This multicenter trial strongly supports the combination of tacrolimus and prednisolone over cyclophosphamide. The authors note that tacrolimus may cause acute nephrotoxicity, but this usually responds to dose reduction [Gulati A, et al: Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. *Kidney Int* 2012: 82; 1130–1135].

Industry Spotlight

Kidney Cancer Drug Approved in U.S. Faces Scrutiny in Europe

Questions are being raised about the effectiveness of axitinib as a life-prolonging second-line treatment for patients with advanced renal cancer.

Manufactured by Pfizer and marketed as Inlyta, Axitinib was approved in the United States in January 2012 and in Europe in September 2012. The U.K.'s National Institute for Health and Clinical Excellence (NICE), which provides guidance to the National Health Service (NHS), recently released a preliminary report recommending against the use of axitinib as a second-line therapy for the treatment of advanced kidney cancer because of how comparisons with other treatments were conducted.

The preliminary decision by the independent Appraisal Committee of NICE was that axitinib should not be recommended for kidney cancer treatment after first-line treatment failure with sunitinib (another kidney cancer drug from Pfizer marketed as Sutent) or a cytokine drug.

However, the committee questioned the comparison information: trial data provided by Pfizer included a direct comparison of axitinib to sofafenib, a drug that NICE had previously recommended against.

The trial also failed to persuasively compare axitinib to the "best supportive care"—the current standard of treatment for patients in the United Kingdom using NHS services—because it used simulated and possibly uncertain results from a different study. Because of validity uncertainties, NICE decided not to recommend the drug (for more information about the NICE decision, please visit http://www.nice.org.uk/newsroom/pressreleases/NICEConsultsNewKidneyCancerDrug.jsp.)

The simulated treatment comparison resulted in an estimated median progression-free survival of 4.6 months in the group taking axitinib after first-line treatment with sunitinib compared with best supportive care and 8.3 months for median overall survival in favor of axitinib, but the committee preliminarily rejected the comparison.

"Before we recommend any new treatment we have to be sure the evidence on how well it works is robust and that it is cost effective," said Andrew Dillon, the NICE's CEO. "We do not want to divert NHS funds to a treatment that costs more but doesn't help people live longer."

In response, Pfizer noted its disappointment with the preliminary guidance, and said that NICE does not currently recommend any targeted therapies for advanced kidney cancer following failure of first-line drugs, just "best supportive care."

Pfizer's U.K. head of oncology, Ben Osborn, said that "we believe that in this disease area where there is still a high level of unmet need, axitinib represents good value to the NHS. To this end, we are committed to working through the NICE consultation process to address the uncertainties within this preliminary recommendation."

Pfizer has high hopes for axitinib worldwide, as it is one of the products that the drug manufacturer is hoping will offset losses. The company's successful drug Lipitor (atorvastatin) faces competition from generic drugs.

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 m² 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)

Baxter Launches Bid to Dominate Dialysis Market

Baxter International, one of the largest health care suppliers in the world, is in discussions with Swedish dialysis product maker Gambro in a bid to buy the company for $4 billion. The acquisition would be a long-sought addition to Baxter's dialysis holdings, according to the *Wall Street Journal* (WSJ).

Based in Deerfield, IL, Baxter manufactures peritoneal dialysis machines for home dialysis, and Gambro would give Baxter access to the hospital market for hemodialysis and other products. If Baxter is able to complete the deal, the company could dominate the kidney dialysis market, *Forbes* reported.

"This is a market that is going to grow for a long time," Baxter chairman and CEO Bob Parkinson said during a conference call in early December with Wall Street investors and analysts, according to *Forbes*.

Under Parkinson's leadership, Baxter's financial situation has improved, allowing the company to attempt a deal of this magnitude, *Forbes* reported. S&P Capital IQ added that if Baxter were successful in buying Gambro it would be Baxter's biggest acquisition ever.

The synergies between the two companies would benefit Baxter's current portfolio of products. Baxter's bioscience division produces such products as plasma-based proteins to treat hemophilia, and its medical products

Continued on page 18

Industry Spotlight

Baxter

Continued from page 17

unit manufactures equipment for injecting various fluids and drugs, according to the *WSJ*.

Gambro, a company held by two Scandinavian private-equity firms, positions itself as "the leader in blood purification therapies in the hospital setting." Sales of its products—including hemodialysis devices such as advanced monitors, dialyzers, bloodlines, cyclers, and dialysis solutions—totaled $1.6 billion in 2011, *Forbes* reported.

Baxter's Parkinson said the Gambro deal is a good fit for Baxter overall, and would provide a platform for additional deals and growth in developing regions.

Reuters reported that Baxter posted sales of $13.89 billion in 2011.

At the end of the third quarter of 2012 Baxter had $3.19 billion in cash, and announced it would spend $1 million in cash from overseas operations and accrue an additional $3 billion in debt to complete the deal. Baxter had about $3 billion in cash flow in 2011, according to *WSJ*.

ASN Introduces Video Series on Improving Dialysis Rounds for Geriatric Patients

ASN recently released a five-part video series, "Improving Dialysis Rounds for Geriatric Patients," produced by the ASN Geriatric Nephrology Advisory Group and made possible with support from the Association of Specialty Professors.

The publicly available, free video series, accessible online at http://www.asnrounds.org, reflects ASN's dedication to providing resources related to geriatric care in response to increasing interest in individualizing care for geriatric patients. Each video covers critical aspects of care for aging patients, including patient assessment, dialysis care, recognition of physical and mental decline, quality-of-life issues, and sharing crucial decision-making information with patients and caretakers.

"The ASN Geriatric Nephrology Advisory Group and I believe these exceptional videos go a long way to providing the most optimal care for kidney patients," said ASN President Bruce Molitoris, MD, FASN. ASN encourages all nephrology health professionals to watch the videos and share them with their networks of peers and trainees.

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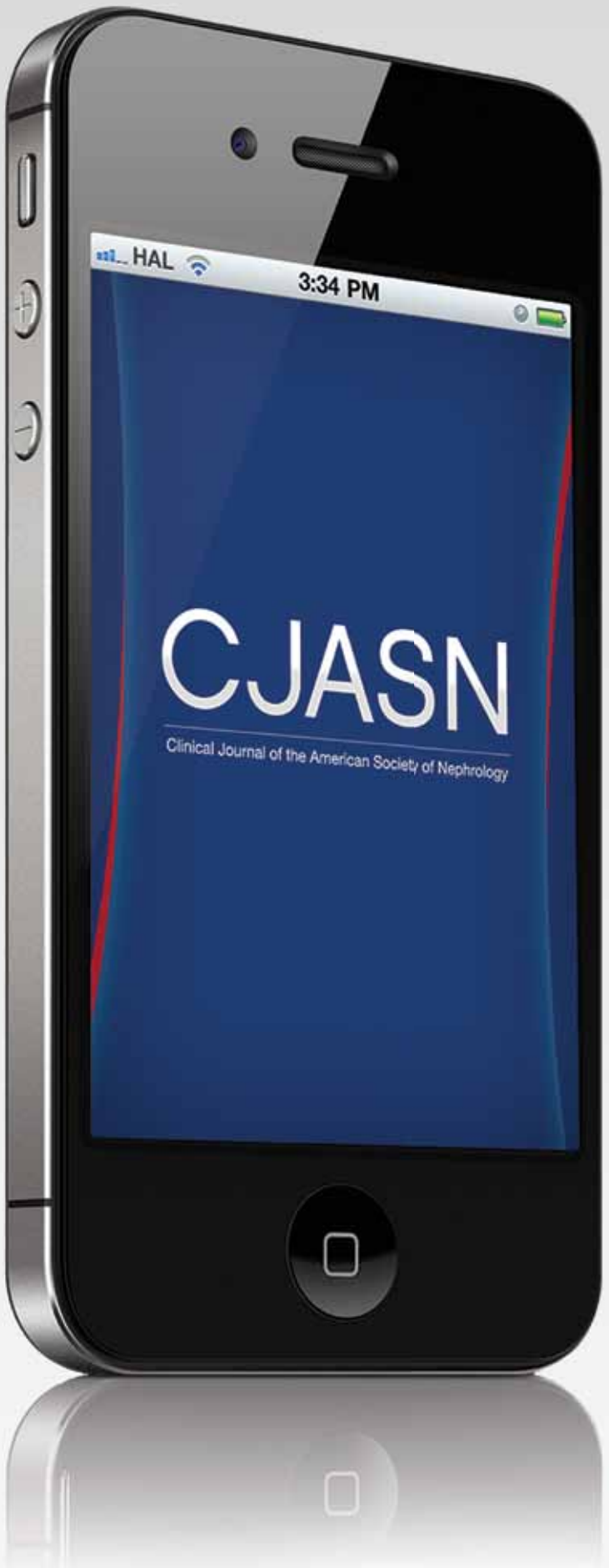

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