ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KIDNEY WEEK EDITION

KidneyNews

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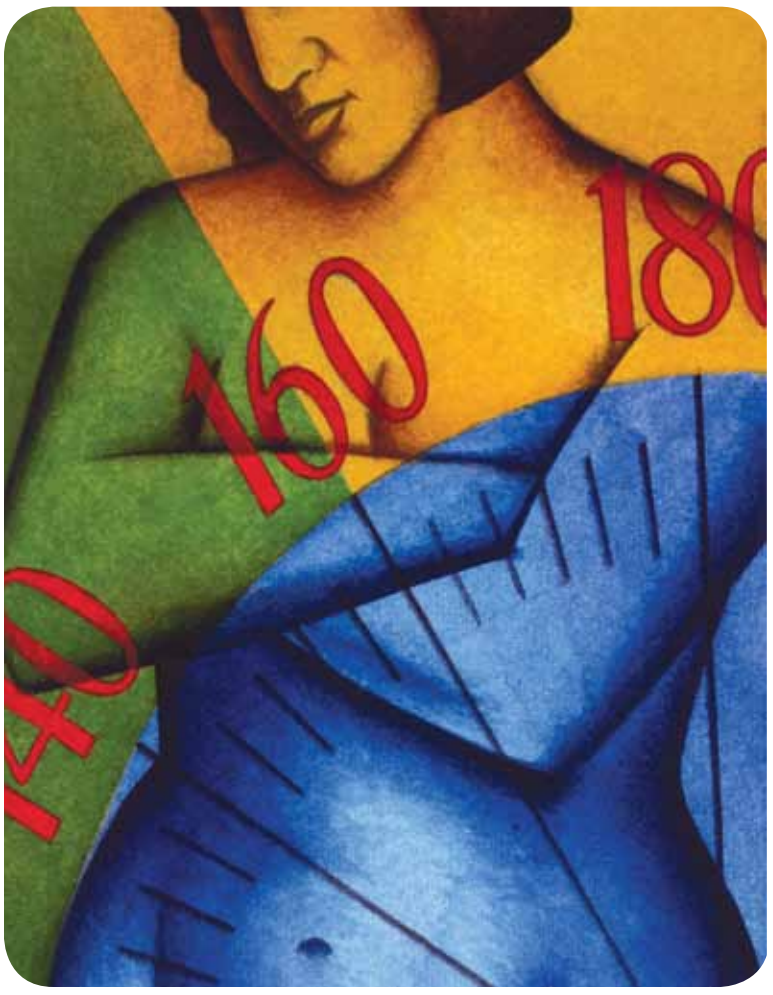
Obesity and Kidney Damage: Key Cell Process Likely Involved



It is well known that obesity is an important risk factor for kidney dysfunction in patients with diseases such as diabetic nephropathy, but the mechanism underlying this connection has remained unclear. Now researchers have found that suppression of a critical cellular process called autophagy, which is important for preventing kidney damage, may be involved. The findings are published in a recent *Journal of the American Society of Nephrology* article.

"This study is the first to clarify one of the mechanisms by which obesity induces kidney dysfunction," said first author Kosuke Yamahara, of the Department of Medicine at Shiga University of Medical Science, in Japan.

Mechanism found in mice

Yamahara, along with senior author Takashi Uzu, MD, PhD, and others, looked at the potential role of autophagy in obesity's effects on kidney function because authophagy insufficiency is common in obese individuals and is involved in the pathogenesis of obesity-related metabolic diseases. Autophagy is a degradation system within cells that removes damaged proteins and other defective cellular components to maintain intracellular homeostasis during stress conditions, including starvation, hypoxia, and endoplasmic reticulum stress.

In the kidneys, autophagy appears to play a protective role against normal aging and acute kidney injury. Previous work by Uzu and colleagues revealed that calorie restriction in mice promotes increased expression of a protein called NAD-dependent deacetylase sirtuin 1 (Sirt1) in aged kidneys and attenuates kidney damage by restoring autophagy activity (Kume S, et al. *J Clin Invest* 2010; 120:1043–1055).

In their latest work, when the investigators conducted a variety of additional experiments in mice, they found that in normal-weight animals with proteinuria, autophagy was active in kidney cells. However, in obese mice with proteinuria, autophagy was suppressed and kidney cells—specifically, proximal tubular epithelial cells—became damaged. In addition, when normal-weight mice with proteinuria were genetically altered so that autophagy was defective (by deletion of the *Atg5* gene), the animals also experienced damage to proximal tubular epithelial cells.

During the course of evolution, the researchers noted, organisms have developed

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KIDNEY WEEK SCIENTIFIC SESSIONS

THURSDAY

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The Role of FGF23 and Klotho in Endothelial Dysfunction and Vascular Calcification
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SATURDAY

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New Insights into Mechanisms and Consequences of Fibrogenesis: An Avenue to Novel Therapeutics for Kidney Disease
Young Investigator Award: Jeremy S. Duffield

Obesity Causes Kidney Damage

Continued from page 1

mechanisms by which autophagy can be induced by calorie restriction and various intracellular stresses to overcome stress conditions during prolonged starvation. It makes sense that a "hypernutrient" state would suppress fasting-induced autophagy in the tissues of obese mice.

Relevance to humans

With more thorough experiments, the researchers discovered that a potent suppressor of autophagy (called mTOR) was hyperactivated in the kidneys of obese mice. Treatment with an mTOR inhibitor ameliorated autophagy insufficiency.

Next, the investigators conducted experiments to assess the potential application of their findings in humans. By examining human renal biopsy specimens from two nonobese patients with IgA nephropathy, an obese patient with IgA nephropathy, and an obese patient with type 2 diabetes with overt proteinuria, the scientists found that both mTOR hyperactivation and autophagy suppression were present in specimens from obese, but not nonobese, patients with kidney disease.

"Obesity suppresses autophagy via an abnormal activation of nutrition sensing signals in the kidney," said Yamahara. "Our results suggest that restoring the kidney-protective action of autophagy may improve the kidney health of obese patients."

While the results are preliminary, they offer new avenues of research for protecting the kidney health of obese individuals.

According to Ken Inoki, PhD, of the University of Michigan in Ann Arbor, the study indicates that induction or restoration of the "self-eating" process in the proximal tubules plays an important renoprotective role in acute kidney injury as well as in chronic glomerulopathy with proteinuria. In an accompanying editorial (*Proximal Tubules Forget "Self-Eating" When They Meet Western Meal*), he stated that in order to study the molecular mechanisms involved, it may be important to examine the activity of mTOR in the proximal tubules of newborn mice whose tubular cells are exposed to physiologic proteinuria, and to determine whether reversible alteration or damage of proximal tubules occurs in autophagy-deficient newborn mice.

Yamahara and his team also note that because obesity-related exacerbation of proteinuria-induced kidney damage may involve molecular mechanisms besides impaired autophagy, efforts to identify these mechanisms may lead to better renal outcomes and increased healthy life expectancy in obese patients with proteinuria.

The findings may also have relevance to wider health topics because autophagy is currently the focus of research in various fields, including aging, metabolic diseases, and immune diseases. The results from this study and the researchers' earlier work should help in the design of future studies aiming to further explore autophagy-related diseases. The findings and methods used might also help in the development of new therapies to delay the progression of tissue damage that occurs when autophagy is suppressed.

Study co-authors include Shinji Kume, Daisuke Koya, Yuki Tanaka, Yoshikata Morita, Masami Chin-Kanasaki, Hisazumi Araki, Keiji Isshiki, Shin-ichi Araki, Masakazu Haneda, Taiji Matsusaka, Atsunori Kashiwagi, and Hiroshi Maegawa.

Disclosures: The authors reported no financial disclosures.

The article, entitled "Obesity-mediated Autophagy Insufficiency Exacerbates Proteinuria-induced Tubulointerstitial Lesions," is available online at http://jasn.asnjournals.org/, doi: 10.1681/ASN.2012111080.

Brief Summary: Consult full package insert for complete Prescribing Information.

INDICATIONS AND USAGE: Phoslyra® (calcium acetate oral solution 667 mg per 5 mL) is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD). Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders.

DOSAGE AND ADMINISTRATION: The recommended initial dose of Phoslyra for the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS AND PRECAUTIONS:

Hypercalcemia. Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (Phoslyra). Avoid the concurrent use of calcium supplements, including calcium-based nonprescription antacids, with Phoslyra. An overdose of Phoslyra may lead to progressive hypercalcemia, which may require emergency measures. Therefore, early in the treatment phase during the dosage adjustment period, monitor serum calcium levels twice weekly. Should hypercalcemia develop, reduce the Phoslyra dosage or discontinue the treatment, depending on the severity of hypercalcemia.

More severe hypercalcemia (Ca >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing Phoslyra therapy. Mild hypercalcemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcemia is usually controlled by reducing the Phoslyra dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well.

Chronic hypercalcemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification.

The long-term effect of Phoslyra on the progression of vascular or soft tissue calcification has not been determined.

Hypercalcemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment.

Maintain the serum calcium-phosphorus product (Ca X P) below 55 mg^2/dL^2.

Concomitant Use with Medications. Hypercalcemia may aggravate digitalis toxicity. Phoslyra contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

ADVERSE REACTIONS: No clinical trials have been performed with Phoslyra in the intended population. Because the dose and active ingredients of Phoslyra are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar.

Hypercalcemia is discussed elsewhere *[see Warnings and Precautions]*.

Clinical Trial Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical studies, calcium acetate has been generally well tolerated.

The solid dose formulation of calcium acetate was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and in a two week double-blind, placebo-controlled, cross-over study with 69 enrolled ESRD hemodialysis patients. Adverse reactions (>2% on treatment) from these trials are presented in Table 1.

Table 1: Adverse Reactions in Patients with End-Stage Renal Disease Undergoing Hemodialysis

	Total adverse reactions reported for calcium acetate n=167	3-mo, open-label study of calcium acetate n=98	Double-blind, placebo-controlled, cross-over study of calcium acetate n=69	
			Calcium acetate	Placebo
Preferred Term	n (%)	n (%)	n (%)	n (%)
Nausea	6 (3.6)	6 (6.1)	0 (0.0)	0 (0.0)
Vomiting	4 (2.4)	4 (4.1)	0 (0.0)	0 (0.0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	0 (0.0)

Calcium acetate oral solution was studied in a randomized, controlled, 3-arm, open label, cross-over, single-dose study comparing calcium acetate oral solution to a solid formulation in healthy volunteers on a controlled diet. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with the oral solution.

Postmarketing Experience. The following additional adverse reactions have been identified during post-approval of calcium acetate: dizziness, edema, and weakness.

DRUG INTERACTIONS: The drug interaction profile of Phoslyra is characterized by the potential of calcium to bind to drugs with anionic functions (e.g., carboxyl, carbonyl, and hydroxyl groups). Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials with all forms of calcium acetate.

Ciprofloxacin. In a study of 15 healthy subjects, a co-administered single dose of 4 calcium acetate tablets (approximately 2.7 g) decreased the bioavailability of ciprofloxacin by approximately 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C. Phoslyra contains calcium acetate. Animal reproduction studies have not been conducted with Phoslyra, and there are no adequate and well controlled studies of Phoslyra use in pregnant women. Patients with end stage renal disease may develop hypercalcemia with calcium acetate treatment *[see Warnings and Precautions]*. Maintenance of normal serum calcium levels is important for maternal and fetal well being. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism. Phoslyra treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

Labor and Delivery. The effects of Phoslyra on labor and delivery are unknown.

Nursing Mothers. Phoslyra contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

Pediatric Use. Safety and effectiveness of Phoslyra in pediatric patients have not been established.

Geriatric Use. Clinical studies of calcium acetate 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, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE: Administration of Phoslyra in excess of the appropriate daily dosage may result in hypercalcemia *[see Warnings and Precautions]*.

HOW SUPPLIED/STORAGE AND HANDLING: Phoslyra for oral administration is a clear solution containing 667 mg calcium acetate per 5 mL. Phoslyra is supplied in a 473 mL (16 oz) amber-colored, multiple-dose bottle, packaged with a marked dosing cup. Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. The shelf life is 24 months.

PATIENT COUNSELING INFORMATION: Inform patients to take Phoslyra with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform patients about the symptoms of hypercalcemia *[see Warnings and Precautions and Adverse Reactions]*.

Advise patients who are taking an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after Phoslyra.

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INDICATION:

Phoslyra® (calcium acetate oral solution, 667 mg per 5 mL) is a phosphate binder (PB) indicated for the reduction of serum phosphorus in patients with end stage renal disease (ESRD). Phoslyra is administered orally with food.

IMPORTANT SAFETY INFORMATION:

- **Phoslyra is contraindicated in patients with hypercalcemia.**
- **Patients should have serum calcium levels closely monitored and their dose of Phoslyra adjusted or terminated to bring levels to normal.** No other calcium supplements should be given concurrently with Phoslyra.
- Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones.
- There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug 1 hour before or 3 hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range.
- The most common (>10%) adverse reactions experienced with Phoslyra are hypercalcemia, nausea, and diarrhea.
- Phoslyra may cause diarrhea with nutritional supplements that contain maltitol.

For additional important safety information, please see brief Prescribing Information on this page.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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New at ASN Kidney Week 2013

Changing the Focus: Innovation and Individualization

This year's Kidney Week includes exciting new features and resources.

Early Programs

ASN offers 17 Early Programs on Tuesday, November 5, and/or Wednesday, November 6, preceding the Annual Meeting (November 7–10). New Early Programs are:

- **Advances in Research Conference—From Molecules to Man to Main Street: The Impact of Innovations in Translational Science** explores concepts and best practices to familiarize participants with strategies that can optimize innovation and translation.
- **Business of Nephrology: Emerging Fronts and Opportunities** provides the basic knowledge and understanding of business skills to develop a successful practice of nephrology. *Jointly sponsored with the Renal Physicians Association*.
- **NephroPrevention** focuses on the prevention of (a) initiation of renal disease, (b) progression of disease, and (c) complications in patients with established renal disease.
- **Novel Biomarkers of Kidney Disease: False Dawn or New Horizon? (30th Arnold O. Beckman Conference)** provides a unique forum for clinicians and laboratorians to convene, discuss, and debate novel kidney biomarkers. *The conference is being presented by the American Association for Clinical Chemistry and ASN*.

Basic Science Content in the Mornings

This year, six basic science symposia have been added to the 10:30 a.m.–12:30 p.m. session slots on Thursday to Saturday:

- Magnesium Magnified: A Molecular Gateway toward Therapy (Thursday)
- mTOR in Immunity (Thursday)
- On Your Mark: How Can AKI Biomarkers Improve Outcomes? (Friday)
- Urinary Tract Development and Patterning (Friday)
- Endothelium in Control (Saturday)
- Maintaining Nephron Progenitors in Mice and Men (Saturday)

Kidney Week will also feature a Basic Science Symposium, "Clinomics: Diagnostics/Prognostics of Tomorrow, Available Now," on Saturday, 12:45 p.m.–1:45 p.m. Lunch will be served on a first-come, first-served basis to fully paid Annual Meeting registrants only.

Enhanced Kidney Week Mobile App

Access Kidney Week information in the palm of your hand. Use the mobile application for on-the-go access to meeting information on your smartphone or handheld device. Features include a customizable calendar and itinerary builder, all program information including oral/poster abstracts, expert disclosures, exhibitor listing with interactive booth map, social media interaction, special meeting alerts, and restaurant coupons/discounts. Download the app online at www.asn-online.org/KidneyWeek.

"Locate Me" Kiosks—Posters/Exhibitors

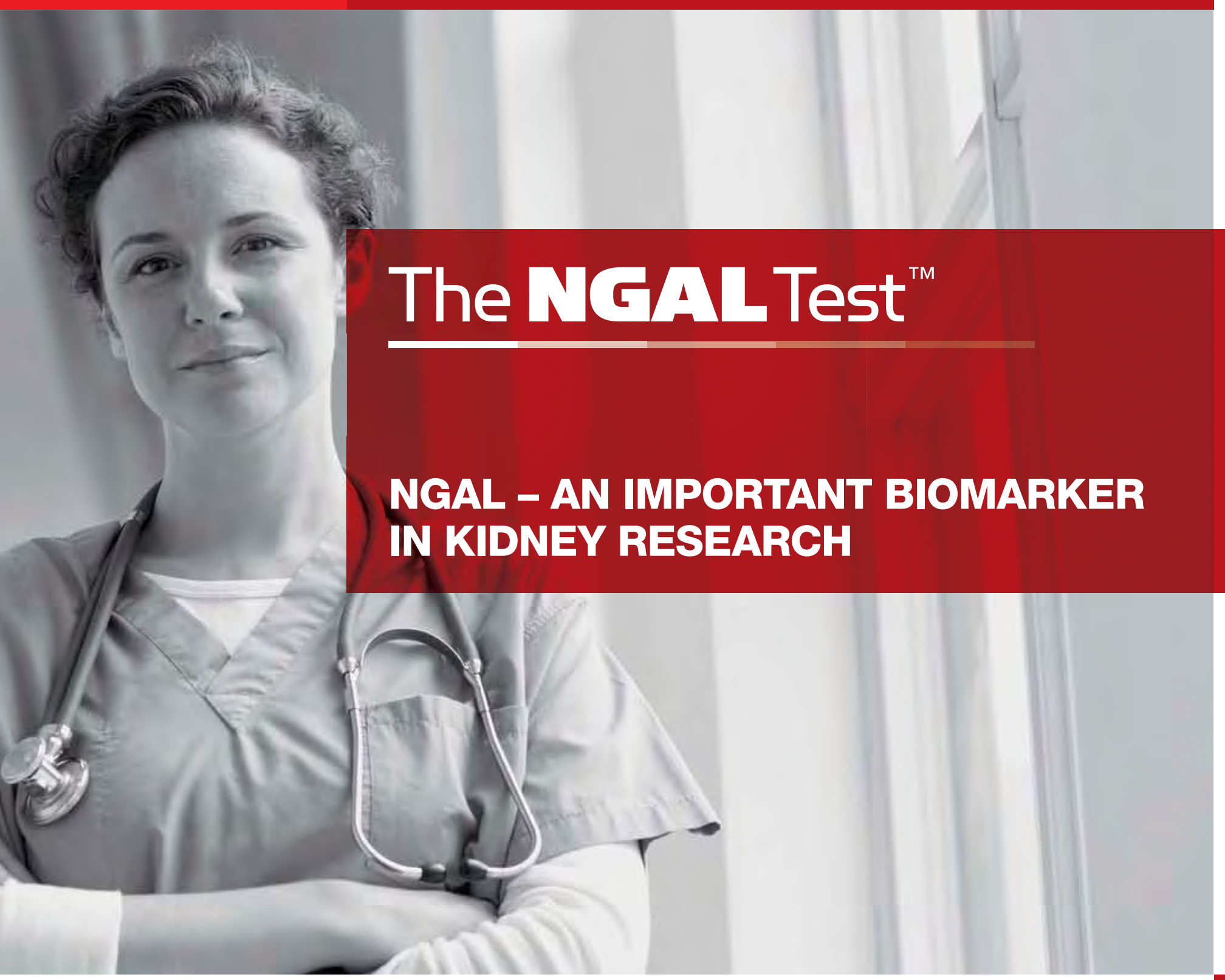
Poster and exhibit information can be found electronically at the "Locate Me" kiosks in Exhibit Halls B3/B4.

Expanded Innovators Place in Exposition

Innovators Place showcases the new products and services that have been developed for the nephrology market. This year's Innovators Place has been expanded to include drug and biologic research and development pipelines, display of investigational medical devices pending FDA clearance, information regarding developing food safety, and medical food technologies of interest to the nephrology medical community.

Atlanta, Georgia

For the first time ever, the ASN annual meeting is being held in Atlanta, GA. Located in the heart of downtown Atlanta, the Georgia World Congress Center will hold most Kidney Week functions and is complemented by the Georgia Dome and Centennial Olympic Park—the three facilities comprise one of the finest convention, sports, and entertainment complexes in the world. For more information about Atlanta, visit www.atlanta.net.



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ASN in Review

Since Kidney Week 2012, the American Society of Nephrology (ASN) broke new ground with its launch of the Kidney Health Initiative (KHI), developed programs to introduce young people to exciting aspects of studying and practicing nephrology, and initiated a diversity and inclusion program that will improve the society and the field. These activities and other new programs enhance ASN's ongoing commitment to providing the best professional education in the world, shaping policy to improve the lives of patients and professionals, providing research funding, and publishing the most widely read communications in kidney health and disease.

Improving patient care

In 2012, ASN and the U.S. Food and Drug Administration (ASN) launched a partnership to improve innovations in kidney treatment. Almost 50 organizations worldwide have already joined this effort to focus the kidney community on driving innovative therapies and improving the safety and quality of existing treatments. Pilot projects focus on lupus nephritis and pharmacokinetics in continuous renal replacement therapy, as well as an intensive review of barriers to innovation in kidney care. In addition, representative of KHI member organizations met recently to help develop the next round of KHI projects, activities, and educational offerings.

ASN is a world leader in shaping policies that affect kidney patients. ASN partnered with patient groups to talk with lawmakers about kidney disease and policy during a tremendously successful Kidney Health Advocacy Day, helped lead efforts to reevaluate the costs of lifetime immunosuppressive care and to advance the HOPE Act (legislation that will expand the number of available donor kidneys), and continued the society's longstanding commitment to increased funding for kidney research.

Other new programs this year include releasing a series of educational films on geriatric nephrology and launching an ASN Kidney Week early program in partnership with the Renal Physicians Association (RPA) focused on enhancing the ability of those in private practice to build and protect their practices and ability to provide the highest quality care.

Building the next generation of kidney professionals

Kidney disease affects more than 60 million people worldwide and this number will increase. Unfortunately, fewer young people are interested in becoming kidney professionals. This year, ASN initiated a new program for medical students: Kidney TREKS (Tutored Research and Education for Kidney Scholars) in partnership with the renowned Mt. Desert Island Biological Laboratories. Through this program, 24 first-year medical students spent a week studying renal physiology and began formal mentoring relationships with leading nephrologists.

ASN also partnered with the American Kidney Fund (AKF) to support a Kidney Action Day in Atlanta, GA, the day before Kidney Week. This successful partnership dovetails with a new ASN initiative, Kidney MAPS (Mentoring and Assessment Program for Students), designed to promote student interest in outreach programs that identify people at risk for diabetes and hypertension in medically underserved communities.

Since 1997, ASN has enabled more than 2,500 trainees with an interest in nephrology to attend ASN Kidney Week, and the ASN Medical Students and Residents Program adds new support for these students at every annual meeting. New this year, ASN piloted a program with Morehouse Medical School to provide a number of Morehouse students a close look at advances in kidney care and research by hosting a one-day program for them at Kidney Week.

ASN published an article this year on Recruiting the Next Generation of Nephrologists (doi 10.1053/j.ackd.2013.03.004) and presented a poster on workforce trends in nephrology at the American Association for Medical Colleges' Physician Workforce Research Conference.

Building diversity

ASN Councilors Jonathan Himmelfarb, MD, FASN, and Donald E. Wesson, MD, FASN, led a summit on increasing diversity and inclusion in all ASN programs and activities. In June, 10 nephrologists spent the day with Dr. Himmelfarb, Dr. Wesson, and ASN President-Elect Sharon M. Moe, MD, FASN, to discuss ways to broaden opportunities for underrepresented minority professionals and students.

This discussion resulted in a proposal that was approved by ASN leadership to develop a robust new program for advancing diversity and inclusion. Progress of efforts to increase diversity and inclusion will be overseen and monitored by ASN's newly appointed Diversity Champion, Eddie M. Greene, MD.

Accelerating kidney research

Also as part of the inclusion effort, ASN convened a summit focused on advancing basic research in kidney disease. ASN President Bruce A. Molitoris, MD, FASN, and Executive Director Tod Ibrahim met with 18 PhD investigators to discuss improving research support and career opportunities for basic researchers in kidney disease. The first step of a longer effort, the summit resulted in a series of recommendations, also approved by the ASN leadership, to create a more welcoming environment for PhDs, help foster PhD careers in kidney research, and raise awareness about the kidney and research.

Since 1996, ASN has awarded more than $25 million in research grants. In 2012, ASN expanded its funding program by launching the ASN Foundation for Kidney Research and the Ben J. Lipps Research Fellowship Program. During the past year, ASN has directed more than $3 million toward medical students, nephrology fellows, and junior investigators to help support those interested in kidney research.

ASN also conducted its second annual Research Advocacy Day in June and co-sponsored a congressional briefing on research conducted by the Veterans Administration.

ASN Year in Review, by the Numbers

- 14,000 members
- 4,500 abstracts submitted to Kidney Week 2013
- 13,000 participants in ASN Kidney Week 2012
- 1,200 instructional hours of professional education
- $3 million from ASN to kidney research
- 6 million visits to ASN's website and online journals

Disseminating knowledge

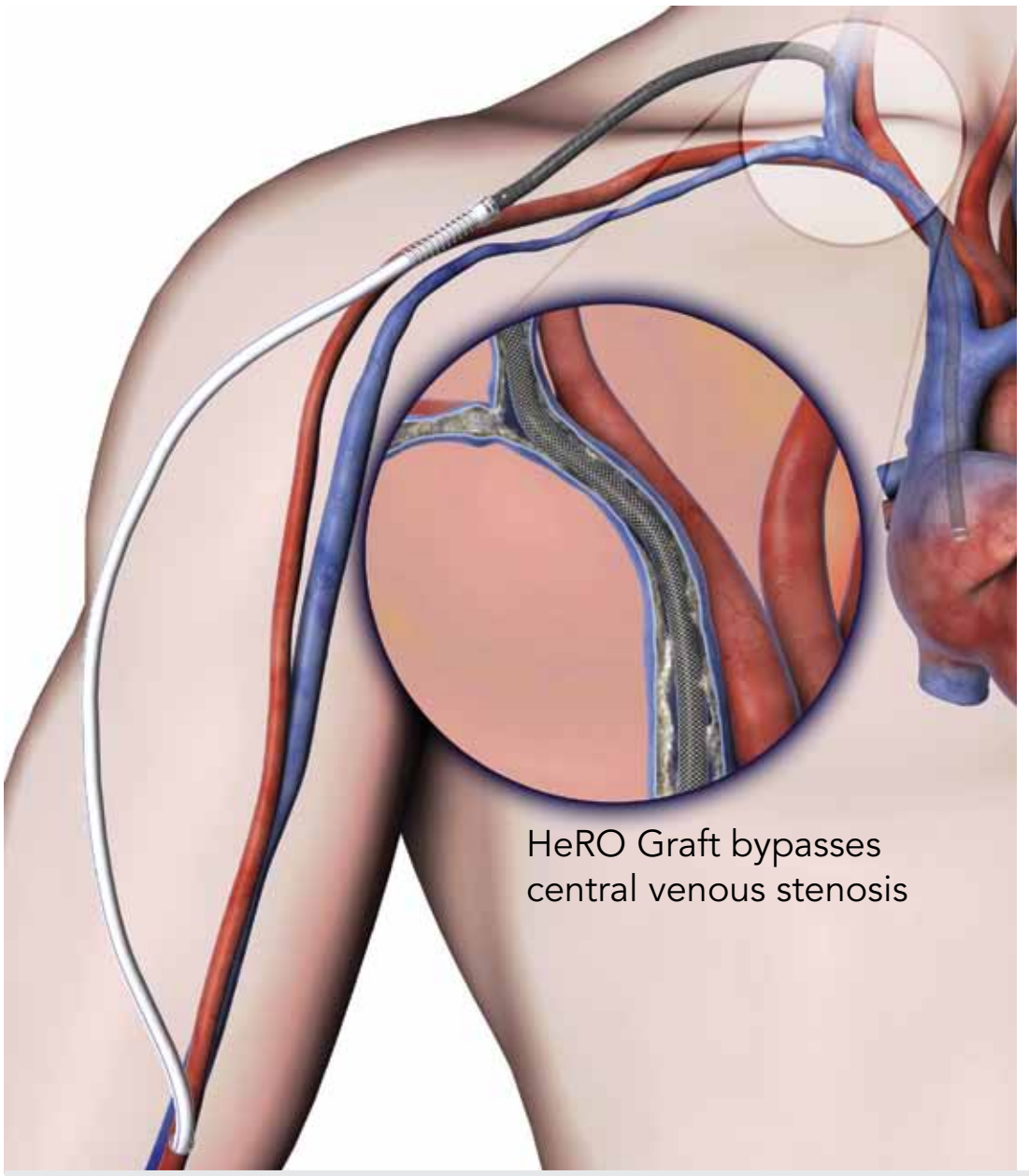
ASN's educational programs continue to provide the best educational opportunities in kidney care. Last year's annual meeting was a tremendous success, and Kidney Week 2013 will incorporate a number of new features and sessions. ASN continues to expand its educational offerings and venues: distance learning opportunities include an online version of ASN's Board Review Course and Update, a dialysis practice improvement module and a host of offerings to help members meet continuing education and certification requirements, Kidney Week content online, an updated curriculum on geriatric nephrology, and an evolving online presence for NephSAP, one of the most popular educational offerings in nephrology.

ASN continues to provide the best publications in kidney research and care. *JASN* and *CJASN* are the most referenced and most read journals in nephrology, respectively. *ASN Kidney News* reaches a vast audience, helping ASN become a leader among professional organizations with its social media presence. This year, the society launched an internally produced daily news briefing, ASN In The Loop.

Supporting professionals and the community

During Kidney Week 2013, ASN convened a leadership meeting with representatives from more than 20 U.S. kidney organizations. The ASN leadership sincerely hopes that this summit will result in increased communication, collaboration, and concrete deliverables among the associations that represent kidney patients and health professionals.

The annual achievements of the American Society of Nephrology reflect the collective efforts of its more than 14,000 members: physicians, researchers, pharmacists, nurses, and other health professionals who work daily to improve the lives of patients with kidney disease. ASN accomplishments depend upon the time and expertise of numerous volunteers and staff as well as the generous investment of organizations interested in advancing practice, research, and education to find cures for kidney disease.



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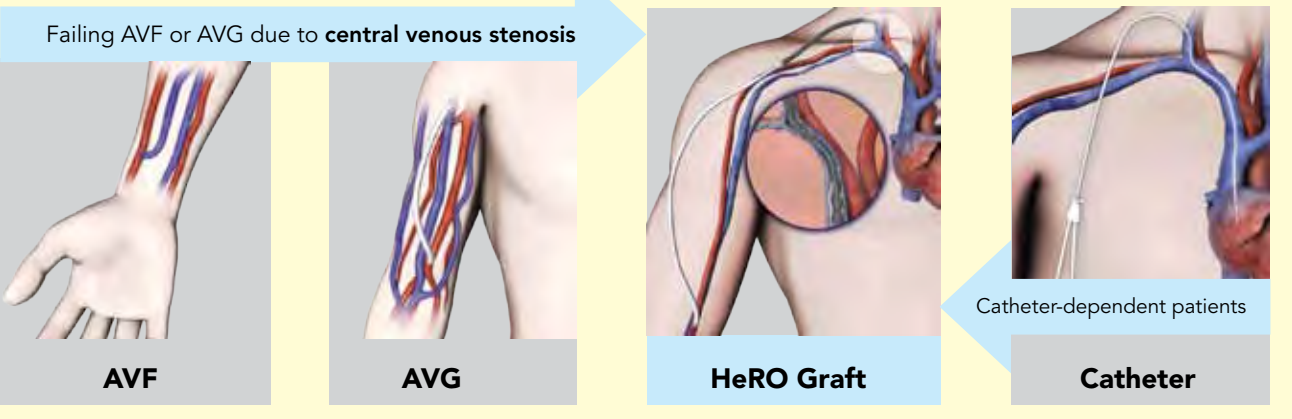

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

Indications for Use: The HeRO Graft is indicated for end stage renal disease patients on hemodialysis who have exhausted all other access options. See Instructions for Use for full indication, contraindication and caution statements. Rx only.

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  - CME Information, General Information, KHI, Membership Services, Publications, Foundation, and Web Services
- Career Fair
- Complimentary Refreshment Breaks
- Cyber Center
- Exhibitor Spotlights
- Innovators Place
- "Locate Me" Kiosks – Posters/Exhibitors
- Poster Sessions
- Wi-Fi Hotspots

Exhibitor Spotlights

ASN has built a special theater in the scientific exposition hall to spotlight industry's latest advances in nephrology practices, products, services, and technologies during 60 minute presentations (no continuing medical education credit). Seating is first come, first served and limited to 75 participants.

All presentations include breakfast (morning presentations) or lunch (afternoon presentations).

Schedule

Thursday, November 7

10:00 a.m. – 11:00 a.m.

Management of Hyponatremia due to SIADH in Patients with Cancer

Presented by Otsuka America Pharmaceutical, Inc.

12:30 p.m. – 1:30 p.m.

The Evolving Nephrology Landscape: Managing Anemia of CKD in Patients on Dialysis

Presented by AMGEN

Friday, November 8

10:00 a.m. – 11:00 a.m.

Urinary Function and Anemia Management Considerations for Improved Outcomes in CKD Patients

Presented by NIPRO MEDICAL CORPORATION

12:30 p.m. – 1:30 p.m.

Consider the Role of the Kidney in Type 2 Diabetes Mellitus

Presented by Janssen | Pharmaceutical Companies of Johnson & Johnson

Saturday, November 9

10:00 a.m. – 11:00 a.m.

Advances in aHUS: A Case-Based Approach to Management

Presented by ALEXION

12:30 p.m. – 1:30 p.m.

A Strategy to Manage SHPT in Hemodialysis

Presented by abbvie

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QUESTCOR PHARMACEUTICALS, INC. – **Booth 425**

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President's Address

Reflecting on a Year of Innovation: An Interview with Bruce A. Molitoris, MD, FASN

Bruce A. Molitoris

Bruce A. Molitoris, MD, FASN, ends his term as president the last day of Kidney Week, November 10, 2013. In this column Dr. Molitoris reflects on his year as president and on the most pressing issues for the kidney community.

Dr. Molitoris, what have you enjoyed most about this year as ASN President?

Working with members, volunteers, Council, and staff so closely has been a real pleasure and growth opportunity. ASN is a dynamic multifaceted organization and I have really enjoyed contributing to such key support of the kidney community. As ASN President, you receive feedback from all sorts of people and organizations interested in kidney disease and that has been a terrific learning experience.

What is the biggest challenge to kidney professionals?

Lack of awareness about kidney health, and inadequate funding to study kidney disease make it difficult to advance detection and treatment and to captivate the next generation of health care and research professionals. Medical students in many countries choose other specialties over nephrology. The situation is particularly bad in the United States, where medical student and resident interest in nephrology is at an all-time low. We must work across borders, to attract the best and the brightest to nephrology, and convey to students the range of patients seen by nephrology professionals and the satisfaction of making life better for people with complex and interesting problems.

What do you rank among ASN's most important achievements during the past year?

There are so many, but among the highlights:

- Two summits ASN convened this year represent exciting advances: one focused on improving diversity and inclusion in all ASN programs, the other on supporting careers of those engaged in basic research, primarily PhDs. Both summits yielded excellent recommendations that will develop into exciting programs that will enrich ASN and nephrology.
- We kidney professionals must enhance how we transmit the exciting and rewarding career nephrology can be. The ASN is committed to introducing more students to nephrology careers, and this year we commenced a very successful week-long renal physiology course focused on medical students. We are also funding over 180 students and residents to attend Kidney Week. Finally, we just completed a community screening in Atlanta, working with the American Kidney Fund to introduce students to nephrology by engaging their assistance in screening those who may be at risk for kidney disease.
- The Kidney Health Initiative (KHI), made huge strides in its first full year of existence. Fifty organizations have joined this ASN/FDA partnership as pioneer members; pilot projects are well underway, as is a comprehensive analysis of barriers to innovation in nephrology. ASN convened a very successful meeting of KHI members in September (see coverage, p. 12), and all members of KHI are committed to accelerating new diagnostics and treatments to improve patient care.
- On World Kidney Day we networked with two patient advocacy groups, for the first time ever, to educate House and Senate members about the breadth and extent of kidney disease, especially acute kidney injury (AKI). We initiated a survey of all kidney professionals in the U.S., asking for information about AKI cases. Participation was excellent and experts are currently analyzing the results to help develop a picture of acute kidney injury, the needs of AKI patients and of medical professionals who encounter AKI in their practices.
- One of my themes this year was to catalyze the nephrology community's working together to achieve mutual goals. All kidney organizations, whether representing patients, health care professionals or researchers, should work together for the good of the patient. In this vein the first joint leadership conference will be held at Kidney Week 2013 to identify areas of cooperation and future emphasis to advance kidney disease recognition and therapy.
- Last year ASN launched the ASN Foundation for Kidney Research, making a major commitment to funding research that will change lives. To date the ASN Research Foundation has raised $17 million and provided grant support to 56 medical students, fellows, and junior investigators. Focusing dollars on innovative research and enabling researchers to develop independent careers are vital to reducing the burden of kidney disease.
- Of course one of the most important achievements of any year is hosting the best meeting on nephrology in the world. It has been a real pleasure to see ASN Kidney Week Program Chair Anupam Agarwal, MD, and ASN Postgraduate Education Committee Chair Mark Rosenberg, MD, and their teams work together to produce such an exciting annual meeting. The cutting edge programming at Kidney Week 2013—from state-of-the-art lectures, to sessions on biomarkers, genomics, and emerging technologies in the kidney space, to the highest number of basic science sessions and early programs ever presented—reflect this year's theme of *Changing the Focus: Innovation and Individualization*. I'm particularly excited about Innovators Place, which this year has expanded to include drugs and biologics in development.

What do you know about ASN that you think most members do not?

Some members may be unaware of how strongly ASN figures in shaping kidney policy. ASN's Public Policy Board and policy staff members have made ASN a leader giving voice to all members of the kidney community. This year ASN helped advance the HOPE Act, legislation that will expand the pool of kidney donors, hosted congressional briefings on research, worked with the Rare Disease Caucus, and helped lead efforts to establish lifetime coverage for immunosuppressive drugs for kidney transplant recipients. We have also interacted with CMS on several clinical issues of importance to the kidney community, the NIH, and VA to support research, and the FDA through KHI to catalyze progress in development of new diagnostics and therapies.

What would most improve kidney care?

Kidney treatment and research has focused on patients with fairly advanced disease. If we are to make real advances in reducing the incidence and progression of kidney disease, we have to focus on individualizing care through diagnostics to improve prevention and treatment.

Kidney disease, like most other chronic disease conditions, is best treatable early in its course, but our ability to detect kidney disease early is limited. Increases in serum creatinine do not occur until approximately 50% of kidney function has been lost. Estimated glomerular filtration rates (GFR) are of value for population studies but of limited value for the individual patient. Furthermore, detectable proteinuria and fibrosis, signs of kidney dysfunction and progression, are not presently detectable in many disease states until progressive kidney disease is well underway. This lack of quantitative evaluation of kidney function also makes it challenging to determine the correct dose of a drug that is cleared by the kidney, often resulting in over- or undertreatment. Therefore, developing these diagnostics will allow for more appropriate therapies to be developed and started earlier in the course of disease than we are presently targeting. Although many different types of diagnostics are presently being investigated, the financial commitment to this area of research must be dramatically increased.

What will you do with your "extra" time when your presidential term ends?

Relax, reflect, refresh, reorient, relish the time spent, and Research.

Introducing President-Elect Sharon Moe

Sharon M. Moe, MD, FASN, will begin her term as ASN President November 10, 2013. Dr. Moe is Director of the Division of Nephrology at Indiana University School of Medicine, as well as the Stuart A. Kleit Professor of Medicine and an Adjunct Professor of Anatomy & Cell Biology. She is also Section Chief of Nephrology at the Roudebush Veterans Administration Medical Center in Indianapolis.

Dr. Moe will address readers in the December issue of Kidney News.

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KIDNEY HEALTH INITIATIVE

FDA Commissioner Addresses Stakeholders at Kidney Health Initiative Meeting

Commissioner of the Food and Drug Administration Margaret A. Hamburg, MD, spoke at the Kidney Health Initiative's first annual stakeholders meeting. In her opening remarks, Dr. Hamburg recognized ASN Past President Ronald J. Falk, MD, FASN, for his early leadership of the KHI initiative, KHI co-chairs Patrick Archdeacon, MD, of FDA's Office of Medical Policy at the Center for Drug Evaluation and Research and Prabir Roy-Chaudhury, MD, PhD, FASN, professor at University of Cinncinati, as well as Melissa West, KHI project director. Following are Dr. Hamburg's remarks to over 100 KHI members on September 11, 2013, in Rockville, MD

As you know, last year when ASN (the American Society of Nephrology) expressed concerns about the slow development of products related to kidney health, as well as safety issues involving other products that could have harmful effects on kidney health, we engaged in a number of discussions on the best ways to address these challenges and focused our attention on the opportunities and potential benefits of developing a public–private partnership model. Our talks resulted in the Memorandum of Understanding that Ron and I signed last year at this time, committing us to move forward together in pursuit of opportunities for collaborative education, research, and continuing dialogue.

Today's important forum is one outgrowth of that agreement, designed to facilitate scientific research and development, to inform regulatory science in the field of kidney health, and strengthen opportunities in clinical trial design, clinical pharmacology, and translational science. It is the beginning of what I expect will be a long, vibrant, and productive partnership.

That this effort has progressed so far, so fast is a testament not just to Ron's vision, but to the energy and commitment of all of those who are here today and to your understanding of what needs to be done to attract greater attention to kidney disease research and development.

We know all too well the catastrophic statistics relating to kidney disease: that one in nine Americans has chronic kidney disease and more than 570,000 have end stage renal disease; that the number of people with treated kidney failure reached a new high in 2010; that kidney disease actually kills more people than some other diseases like breast or prostate cancer that get far more attention; and that even when it is not fatal, the expense of treating kidney disease, in particular end stage kidney disease, is enormous, with profound implications for our society.

These statistics are extremely troubling. But just as frustrating is the disparity between the field of nephrology and other areas of medicine as it relates to the development of innovative approaches, new therapies, and an evidence base for promoting clinical practice and scientific advancement.

There are, of course, several reasons for this imbalance, including the disproportionately large range of products that have an impact on kidney health, as well as the wide range of diseases affecting or leading to end organ damage to the kidneys, such as lupus, diabetes, hepatitis, and heart failure. The difficulty of pinning down kidney diseases through well-defined and appropriate trial designs and regulatory pathways, and a shortage of multidisciplinary approaches are other significant factors. The bottom line, as several of my colleagues have described it, is that there exists both an awareness and, importantly, a "therapeutic gap" when it comes to kidney disease.

This initiative is designed to focus attention and resources on closing this gap and help ensure that kidney disease receives the focus it deserves. But even as we move forward in this effort, it is important to recognize and build on the real and continuing significant scientific, medical, and regulatory developments in the battle against kidney disease.

In 2011, for example, we approved the drug Nulojix to prevent acute rejection in adult patients who have had a kidney transplant. By blocking the costimulatory signal in T lymphocytes, this drug gives kidney transplant patients a new option. And in July of this year, FDA approved Astagraf, an extended-release formulation of the calcineurin-inhibitor tacrolimus, providing kidney transplant patients with the option of taking this once-daily (instead of Prograf, twice daily) to prevent acute rejection.

Even more exciting have been the strides we are making in the development of new technologies to address end stage kidney disease. And this moves us into the device domain.

As part of our groundbreaking Innovation Pathways Initiative, which is designed to reduce the time and cost of bringing safe and effective breakthrough medical device technologies to patients, we selected three products to help patients with end stage renal disease. These revolutionary new products—an implantable renal assist device, a wearable artificial kidney, and a hemoaccess valve system—all of which are being developed by small businesses dedicated to innovation—offer the potential to significantly change and improve the lives of many patients.

The FDA Center for Devices and Radiological Health (CDRH) team working on this project, in conjunction with the product sponsors, were able to move these innovative products forward into their next phase of development in a much more efficient and timely manner than would otherwise have occurred as a result of our collaborative "One-Team" concept.

It is all part of a broader enterprise by FDA to deepen public–private collaboration between FDA and scientific and medical innovators. The objectives of this effort, called the Critical Path Initiative (CPI), are simple, yet significant: to modernize the regulatory and product development process and to foster public–private collaboration so that new therapies can get to people who need them better, faster, and cheaper. The connection between CPI and the Kidney Health Initiative is a direct one, and I'd like to spend a few moments discussing how we got to where we are today.

CPI was launched in 2004 with the publication of a landmark report examining innovation and stagnation in the development of new medical products. The report sounded the alarm about the widening gap between scientific discoveries that have unlocked the potential to prevent and cure some of today's biggest killers and their translation into innovative medical treatments.

The Initiative catalyzed numerous collaborations with stakeholders to address specific areas where the science of product development had the greatest need for improvement and it continues to generate productive partnerships. One emphasis of the Initiative was the need to develop better evaluation tools, and, in particular, to find preclinical biomarkers that predict human kidney toxicity, which could help develop safer products and prevent kidney damage, as well as the publication of the first pilot framework for a preclinical regulatory biomarker qualification process.

Another successful example of collaboration that emerged from the Critical Path Initiative, and holds importance for kidney disease, is an ongoing partnership between FDA and the University of California at San Francisco that focuses on membrane transporters during drug development. Researchers there are gaining an increasing understanding of the vital role that membrane transporters—proteins that facilitate the movement of substances across cell and organ membranes—play in the body's response to some therapies and have discovered ways to prevent certain interactions and toxicity that can cause kidney poisoning.

It is this successful history that we are building on today with the Kidney Health Initiative, which, like CPI, recognizes that solutions to these immense scientific and medical challenges cannot readily be achieved by

Continued on page 14

Kidney Health Initiative

Continued from page 13

any one entity. Collaboration is the cornerstone for ending the stagnation in innovation and development.

KHI's potential is evident from the broad support it has already received—from the co-chairs of the Congressional Kidney Caucus, Congressmen Jim McDermott and Tom Marino, to the 40+ pioneer members—whose ranks include health care and dialysis providers, device manufacturers, patient groups, professional groups, pharmaceutical companies, academic research organizations, and representatives of the biotech industry.

It is precisely this kind of range and diversity that is critical to building a successful coalition, and that will generate a different kind of dialogue to shape and develop from the earliest stages through to finished products and new prescription and prevention strategies. That's why KHI is well positioned to kick start the kinds of innovative research and investment we need to eliminate the underlying disparities between kidney disease and to more effectively address the serious and under-recognized epidemic of kidney disease in this country.

I am confident that by working together across different fields and with a variety of perspectives, this public-private partnership can—and must—make a real difference. Now is the time to translate the opportunities in science and technology today—such as the dramatic advances in genomics, biotechnology, and material science—into meaningful breakthroughs for kidney disease.

And though the Kidney Health Initiative is still really quite new—after all, this is the first KHI Stakeholders meeting ever—real progress is being made. Besides the impressive membership of individuals and organizations, so many of whom are here today, important work is already underway.

By creating this kind of collaborative environment, the FDA and the greater scientific and stakeholder community committed to advancing kidney health, is engaged to support new understanding and achievements. The KHI clearinghouse, for example, a portal that allows timely and significant review of projects, offers enormous potential to optimize ideas and resources. I understand that several pilot projects are now moving forward. And there are exciting plans for think tanks, working groups, educational exchanges, and other events to promote discussion and enhanced awareness and updates related to kidney health.

In addition, KHI can bring together representatives from across FDA, as well as other relevant government agencies like CMS, NIH, and CDC, to strengthen opportunities for collaboration, which is particularly important in light of the vast expanse of research issues, regulatory concerns, and health care responsibilities associated with kidney disease. And our hope, of course, is that this new approach—and new thinking—can enable us to find more integrated strategies, and to pursue a path that with a realistic vision, broad engagement, and science-based strategies, can overcome barriers to innovation and optimize safety for the benefit of people with kidney disease.

In closing, I want to underscore one final important attribute of the Kidney Health Initiative—its good timing. The world of medical research and science today is in the midst of great changes. The rapid evolution of various technologies, the extraordinary forces of globalization, and the exciting emergence of new areas of science are having an enormous impact on the development of medical products, as well as on FDA's role in evaluating and regulating them. This "brave new world" offers significant opportunities to enhance and strengthen the traditional process by building new coalitions like this one to provide support for medical innovation and advances in public health.

An eminent surgeon and researcher, Dr. Quyen Nguyen commented that, "Successful innovation is not a single breakthrough. It is not a sprint. It is not an event for the solo runner. Successful innovation is a team sport, it's a relay race." It is creative collaborations like this one that are key to building just such a team that will identify and overcome the scientific challenges and generate the attention and innovation that chronic conditions such as kidney disease so richly deserve.

Making an Impact: The Kidney Health Initiative at Year One

At its one year anniversary, the Kidney Health Initiative has made great strides toward meeting its goal of building a collaborative environment with FDA to foster innovation and patient safety in kidney disease. During the past year, KHI developed its infrastructure with the selection of a Board of Directors, identified three pilot projects, and recruited 50 organizations and companies to join. With the successful conclusion of its first annual stakeholders meeting in September, the organization has now transitioned its focus to member-initiated and member-driven projects that focus on kidney health.

The aim of KHI's stakeholder meeting was to educate KHI members about FDA's public-private partnership model, to gather feedback on the upcoming white paper on the barriers and solutions to innovation in kidney disease, and to discuss nine project submissions from KHI members.

Of the 120 U.S. and international attendees, nearly a third represented FDA and government agencies like NIH, CMS, and CDC, a third were affiliated with industry, and a third represented patients and health care professionals. FDA Commissioner Margaret Hamburg, MD; Douglas Throckmorton, MD; Deputy Director for Regulatory Programs at FDA's Center for Drug Evaluation and Research; and Barry Straube, MD; Director at Marwood Group and former Chief Medical Officer at CMS, all provided thoughtful comments about the opportunities and challenges facing KHI.

Moving forward, KHI will gather members' ideas for projects via an online web portal on a cyclical basis. The portal will allow KHI members to submit brief project concepts and to discuss and refine submissions through this online forum. ASN members may submit project ideas for KHI by contacting the appropriate ASN Advisory Group.

Under the direction of the KHI Board of Directors, projects will be endorsed at the end of each submission cycle. Working groups consisting of KHI members will implement the projects. With members representing patient groups, professional organizations, industry partners, as well as key government agencies, KHI is poised to develop strategies that will help eliminate barriers to innovation in kidney disease and ultimately aim for a cure.

ENVISION NEW **POSSIBILITIES**

Invokana™
canagliflozin tablets

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

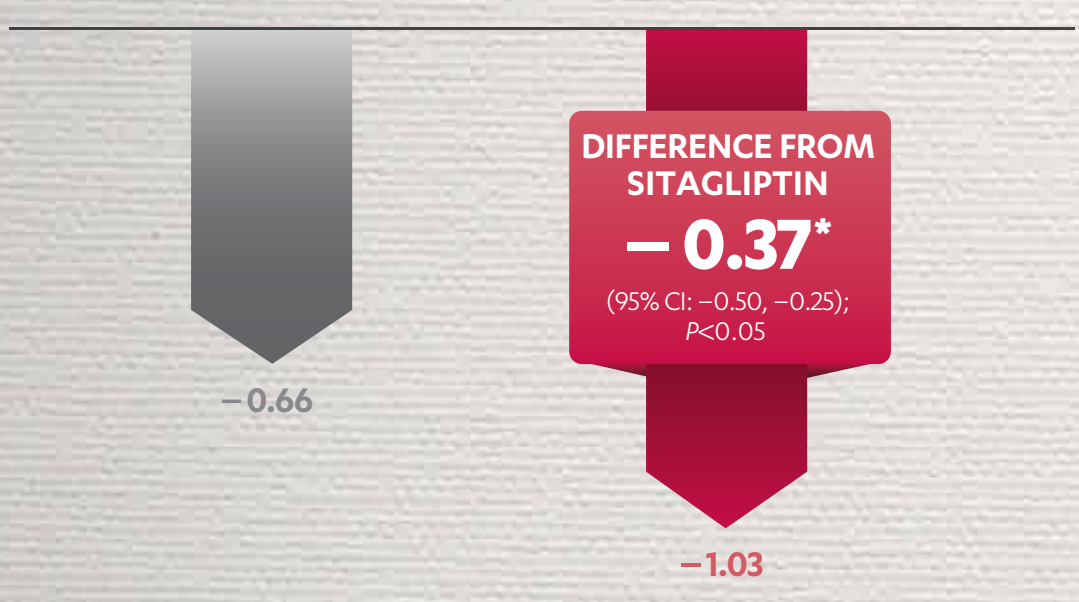
CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

INVOKANA™ 300 mg demonstrated greater reductions in A1C vs sitagliptin 100 mg at 52 weeks...

Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Sitagliptin 100 mg, Each in Combination With Metformin + a Sulfonylurea[1]



- **Sitagliptin 100 mg + metformin and a sulfonylurea** (n=378; mean baseline A1C: 8.13%)
- **INVOKANA™ 300 mg + metformin and a sulfonylurea** (n=377; mean baseline A1C: 8.12%)

Incidence of Hypoglycemia

With metformin + a sulfonylurea over 52 weeks: INVOKANA™ (canagliflozin) 300 mg: **43.2%**; sitagliptin 100 mg: **40.7%**[1]

- Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue[1]

Convenient Once-Daily Oral Dosing[1]

- Recommended starting dose: INVOKANA™ 100 mg
- Dose can be increased to 300 mg in patients tolerating 100 mg who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control

*INVOKANA™ + metformin is considered noninferior to sitagliptin + metformin because the upper limit of the 95% confidence interval is less than the prespecified noninferiority margin of 0.3%.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.
- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

*COVERED BY MORE THAN **75%** OF COMMERCIAL HEALTH PLANS*[3]

...as well as greater reductions in body weight† and systolic blood pressure (SBP)†

Change in Body Weight†

Significant reductions in body weight at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[1]

» Difference from sitagliptin‡:
300 mg: **–2.8%**

Change in SBP†

Significant lowering of SBP at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[2]

» Difference from sitagliptin‡:
300 mg: **–5.9 mm Hg**

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.

†Prespecified secondary endpoint.

‡Adjusted mean.

INVOKANA™ provides SGLT2 inhibition, reducing renal glucose reabsorption and increasing urinary glucose excretion.[1]

Adverse Reactions

In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.[1§]

References: 1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. **2.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. doi:10.2337/dc12-2491. **3.** Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ. Data as of 8/9/13.

SGLT2 = sodium glucose co-transporter-2.

§Included 1 monotherapy and 3 add-on combination trials with metformin, metformin + a sulfonylurea, or metformin + pioglitazone.

Learn more at **INVOKANAhcp.com/journal**

- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW
POSSIBILITIES

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.
- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.
- **Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

Janssen Pharmaceuticals, Inc.

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OVERDOSAGE

»There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

»The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

Please see brief summary of full Prescribing Information on the following pages.

K02CAN13149

Invokana™
canagliflozin tablets

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA or any other antidiabetic drug.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg

(N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups
† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population
† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were

evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

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ASN **Kidney Week** 2013

EDUCATIONAL SYMPOSIA SCHEDULE

Thursday, November 7 – Saturday, November 9

Omni Hotel at CNN Center

Continuing Education Credit

This live activity is eligible for continuing education credit. Please visit www.asn-online.org/KidneyWeek for more information.

Doors open 15 minutes prior to each session.

Breakfast or lunch will be served at each session.

Seating is limited and available on a first-come, first-served basis to fully paid Annual Meeting participants.

Thursday, November 7 • 12:45 p.m. – 1:45 p.m.

Biosimilar Pharmaceutical Agents in CKD and Dialysis
Support for this symposium is provided by an educational grant from Hospira

Dietary Phosphorus Burden and Adherence in Maintenance Dialysis Patients
Support for this symposium is provided by an educational grant from FRESENIUS MEDICAL CARE

Treating "Refractory" Nephrotic Syndrome
Support for this symposium is provided by an educational grant from QUESTCOR PHARMACEUTICALS, INC.

Update on Anemia Management in Dialysis Patients and Recent Trends
This activity is supported by an educational donation provided by AMGEN

Friday, November 8 • 6:45 a.m. – 7:45 a.m.

Kidney-Liver Cross-Talk: An Update on the Hepatorenal Syndrome
Support for this symposium is provided by an educational grant from IKARIA®

Transplant Immunosuppression: Make New Friends, But Keep the Old
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Treatment of ANCA Vasculitis: An Individualized Approach to Care
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Friday, November 8 • 12:45 p.m. – 1:45 p.m.

CKD-MBD: Getting to the Heart of the Matter
Support for this symposium is provided by an educational grant from SANOFI

Fluid Management in the Dialysis Patient
Support for this symposium is provided by an educational grant from FRESENIUS MEDICAL CARE

Hyponatremia and the Brain: Pathophysiology and Treatment
Support for this symposium is provided by an educational grant from Otsuka America Pharmaceutical, Inc.

Progress in the Pathogenesis and Management of Cystinosis
Support for this symposium is provided by an educational grant from raptor pharmaceuticals inc.

Saturday, November 9 • 6:45 a.m. – 7:45 a.m.

Monitoring and Treating Patients with Autosomal Dominant Polycystic Kidney Disease
Support for this symposium is provided by an educational grant from Otsuka America Pharmaceutical, Inc.

The Evolving Quality Incentive Program: Is It Getting It Right for Patients?
This activity is supported by an educational donation provided by AMGEN

Saturday, November 9 • 12:45 p.m. – 1:45 p.m.

Basic Science Symposium— Clinomics: Diagnostics/Prognostics of Tomorrow, Available Now
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Diagnosis and Treatment of Thrombotic Microangiopathies
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Severe Secondary Hyperparathyroidism in Hemodialysis Patients
This activity is supported by an educational donation provided by AMGEN

The Role of Iron in the Optimization of Anemia Management in CKD
Support for this symposium is provided by an educational grant from KERYX BIOPHARMACEUTICALS, INC

Plenary Session

State-of-the-Art Lecture

Regenerative Medicine Researcher to Describe Recent Progress

Anthony Atala

A pioneer in growing human body replacement parts will present a state-of-the-art lecture entitled "Regenerative Medicine: New Approaches to Healthcare" on Nov. 7. Anthony Atala, MD, will discuss current research generating new human cells, tissues, and organs.

Dr. Atala is the director of the Institute for Regenerative Medicine, the W.H. Boyce Professor and chair of the department of urology at Wake Forest University, and a practicing surgeon.

His research in regenerative medicine has been recognized in both the scientific and mainstream press. In 2011, Dr. Atala was named by *Scientific American* as a medical treatments leader of the year for his contributions to the fields of cell, tissue, and organ regeneration; by the *Huffington Post* as having one of 18 great ideas of the year; and by *Time Magazine* for making one of the top five medical breakthroughs of the year. In 2007, his achievements garnered attention as one of *Time Magazine*'s top 10 medical breakthroughs of the year, and as *Discover Magazine*'s "Top Science Story of the Year" in the field of medicine.

Dr. Atala heads a team of some 300 physicians and researchers. Ten technologies developed in his laboratory have been applied clinically.

Dr. Atala has led or served on several national professional and government committees, including the National Institutes of Health (NIH) working group on cells and developmental biology, the NIH bioengineering consortium, and the National Cancer Institute's advisory board. He is the editor of 12 books, including *Principles of Regenerative Medicine, Foundations of Regenerative Medicine, Methods of Tissue Engineering*, and *Minimally Invasive Urology*. He has published more than 300 journal articles and has applied for or received more than 200 national and international patents.

Dr. Atala serves as editor-in-chief of *Stem Cells—Translational Medicine, Current Stem Cell Research and Therapy, and Therapeutic Advances in Urology*. He is associate editor of *Tissue Engineering and Regenerative Medicine*, *The Journal of Rejuvenation Research*, and *Gene Therapy and Regulation*. He serves on the editorial boards of several journals.

Dr. Atala has received many awards, including the Christopher Columbus Foundation Award, the World Technology Award in Health and Medicine, the Samuel D. Gross Prize of the Philadelphia Academy of Surgery, the Barringer Medal from the American Association of Genitourinary Surgeons, the Gold Cystoscope Award from the American Urological Association, and the Innovation Award from the Society of Manufacturing Engineers.

Longtime Patient and Patient Advocate to Receive President's Medal

Lori Hartwell

Lifelong kidney patient Lori Hartwell will receive the President's Medal for her influential work in patient support and advocacy in a special presentation during the plenary session on Thursday, Nov. 7.

Hartwell has provided an inspiring model for living with chronic disease since her kidneys mysteriously stopped working at age 2. She has survived 13 years of dialysis and more than 40 surgeries. She is now living with her fourth transplanted kidney. The youngest person in California ever placed on dialysis, she continues to beat the survival odds, emerging as an example of how people with chronic illness can lead complete and productive lives.

She founded the patient-led Renal Support Network (RSN) in 1993 to instill "health, happiness, and hope" into the lives of fellow patients. As RSN president, Hartwell travels widely nationally and internationally, educating and inspiring people with kidney disease and health care professionals with her stories, insight, and humor. RSN's mission is to identify and meet the nonmedical needs of people affected by chronic kidney disease, whether they are in the early stages, on dialysis, or have received a kidney transplant. RSN provides service, support, and advocacy to patients and their families, and works to build coalitions within the renal community.

Hartwell has a long history of work in the field. She began her career as a technical sales specialist for HemaMetrics, developers of a hematocrit-controlled hemodialysis technology. She was western regional sales manager for Medcomp, distributors of vascular access catheters. In these positions, she visited more than 500 dialysis units in 30 states, which gave her a broad view of the renal patient population. She was editor of the medical journal *Contemporary Dialysis & Nephrology* and the lay journal, *For Patients Only*.

Her guidebook, *Chronically Happy: Joyful Living in Spite of Chronic Illness*, describes how to handle lifestyle and other nonmedical issues in the course of chronic disease. She wrote and produced a 60-minute video, "Communication Prescription for the Renal Care Professional," that shares practical advice, creative communication concepts, and stories of hope from people who live with CKD as well as from renal care professionals. The video won an Aegis Award for production quality.

In her public service positions, she has advised elected officials about how policies impact people with chronic illnesses. She served on the Governors Rehabilitation Council for the state of California. She chaired the Patient Advisory Committee for the Southern California Renal Disease Council and is a board of directors member of the California Dialysis Council and Kidney Care Partners. On the national level, she has advocated with congressional and state leaders about legislative issues affecting the kidney community and testified before the joint advisory committee of the Food and Drug Administration.

Medicare Official to Speak on Improving Outcomes

Jonathan Blum

An expert on Medicare will deliver the Christopher R. Blagg Endowed Lectureship in Renal Disease and Public Policy. Jonathan Blum's topic will be "Improving Standards and Quality Outcomes: The Federal Government in Action."

As acting principal deputy administrator and director of the Center for Medicare at the Centers for Medicare & Medicaid Services (CMS), Blum is responsible for overseeing the regulation and payment of Medicare fee-for-service providers, privately administered Medicare health plans, and the Medicare prescription drug program. These programs pay for health care for more than 50 million elderly and disabled Americans, with an annual budget in the hundreds of billions of dollars.

Over the course of his career, Blum has become an expert in the gamut of CMS programs. He served as an advisor to the Senate Finance Committee, where he worked on prescription drug and Medicare Advantage policies during the development of the Medicare Modernization Act of 2003. That act was one of the largest-ever overhauls of Medicare, and introduced Medicare Part D, the prescription drug benefit. He focused on Medicare as a program analyst at the White House Office of Management and Budget. Prior to joining CMS, he was a vice president at Avalere Health, overseeing its Medicaid and long-term care practice.

He holds a master's degree from the Kennedy School of Government and a bachelor's degree from the University of Pennsylvania.

ASN gratefully acknowledges the Northwest Kidney Centers and its contributors for support of the Christopher R. Blagg Endowed Lectureship in Renal Disease and Public Policy.

Plenary Session

State-of-the-Art Lecture

State-of-the-Art Lecture Addresses Vascular Disorders

Harry (Hal) Dietz

A state-of-the-art lecture will provide insights into vascular disorders on Nov. 8. Harry (Hal) Dietz, MD, will speak on "Found in Translation: New Insights into the Pathogenesis and Treatment of Marfan Syndrome and Related Disorders."

Dr. Dietz is Victor A. McKusick Professor of Pediatrics, Medicine, and Molecular Biology & Genetics in the Institute of Genetic Medicine at the Johns Hopkins University School of Medicine. He is also an investigator in the Howard Hughes Medical Institute.

Dr. Dietz heads a multidisciplinary clinic for the diagnosis and management of individuals with heritable forms of cardiovascular disease, with a special emphasis on Marfan syndrome and related connective tissue disorders. Dr. Dietz's research team has investigated the development and homeostasis of the arterial wall, with an emphasis on understanding the genetic factors that predispose patients to aortic aneurysm, a condition that accounts for up to 2 percent of deaths in industrialized countries. An understanding of Marfan syndrome could provide insight into vascular wall biology because it is caused by mutations in a single gene and its etiology includes aortic aneurysms.

Dr. Dietz's group linked an error in the gene that encodes fibrillin-1, a connective tissue protein, to Marfan syndrome, and has helped uncover genes underlying four other conditions that cause aortic aneurysms. Dr. Dietz is currently conducting a clinical trial of a drug approved for hypertension treatment to test its effectiveness in treating Marfan syndrome.

In addition to Marfan syndrome, his team is studying the vascular disorders familial tetralogy of Fallot, cerebral cavernous malformation, a premature aging syndrome, and Loeys-Dietz syndrome. The latter syndrome is named for Dr. Dietz and a Johns Hopkins colleague.

Dr. Dietz received his undergraduate training in biomedical engineering at Duke University and his medical degree from the Health Sciences University of Syracuse. He obtained clinical and research training in pediatrics, pediatric cardiology, and genetics at the Johns Hopkins University School of Medicine.

Dr. Dietz has received several prestigious awards, including the Curt Stern Award from the American Society of Human Genetics and the Taubman Prize for excellence in translational medical science. He is an inductee of the American Society for Clinical Investigation, American Association for the Advancement of Science, Institute of Medicine, Association of American Physicians, and the National Academy of Sciences.

Polycystic Kidney and Liver Disease Researcher to Receive Homer W. Smith Award

Stefan Somlo

Acclaimed researcher Stefan Somlo, MD, will receive the Homer W. Smith Award and deliver an address on Friday, Nov. 8, of Kidney Week. He will speak on "Polycystic Kidney and Liver Diseases: From Gene Discovery to Mechanism."

Dr. Somlo is C.N.H. Long Professor of Medicine (Nephrology) and professor of genetics at the Yale University School of Medicine. The Homer W. Smith Award recognizes individuals who contribute to our basic understanding of how the kidneys function in health and disease, and Dr. Somlo's contributions have greatly advanced our knowledge of human polycystic diseases.

Dr. Somlo's seminal contributions to the fields of polycystic kidney disease (PKD) and liver disease began with disease gene discoveries in the pre-genome era. His later studies yielded insights into the genetic mechanisms of PKD, the functions of polycystins, and the innovative application of genetically complex animal models to in vivo and preclinical discoveries in PKD. Dr. Somlo's laboratory identified the second gene for dominant polycystic kidney disease and two genes for familial forms of polycystic liver disease without kidney cysts. His group was part of a consortium that identified the recessive polycystic kidney disease gene.

Dr. Somlo's laboratory translated these gene discoveries into mechanistic studies of polycystic diseases using biochemical, cell biological, and in vivo approaches. Much of his laboratory's efforts have focused on defining disease pathogenesis using mouse models of polycystic diseases. Their work has also explored the effects of discrete signaling pathways in cyst formation and the genetic interrelationships between different polycystic disease genes.

Dr. Somlo has headed the section of nephrology at Yale since 2003. He has led a cross-disciplinary, multi-investigator polycystic disease research program at Yale and has developed clinical and translational components to implement his findings in basic science. He serves as an elected councilor for the Association of American Physicians and received the Lillian Jean Kaplan International Prize for Polycystic Kidney Disease Research.

Dr. Somlo is a graduate of Harvard College and the College of Physicians and Surgeons of Columbia University. He did his clinical training at the Albert Einstein College of Medicine and Yale and was on the faculty at Albert Einstein before returning to Yale.

Homer W. Smith

Homer W. Smith was chairman of physiology at the University of Virginia before moving in 1928 to New York University (NYU). As director of the Physiology Laboratories at NYU, he developed and refined the concepts of glomerular filtration and tubular absorption and secretion of solutes.

The clarity of Dr. Smith's logic and the skill with which he explained his ideas transformed them into vivid and powerful concepts that are the cornerstones of our present understanding of normal and abnormal renal function. He attracted the best and brightest to the field, to NYU, and to the Mount Desert Island Biological Laboratory, where he spent many summers studying renal physiology in fish.

The Homer W. Smith award recognizes individuals who contribute to our basic understanding of how the kidneys function in health and disease.

Coburn Lecture to Cover Endothelial Dysfunction and Vascular Calcification

Orson W. Moe

Orson W. Moe, MD, will present the Jack W. Coburn Endowed Lectureship on Friday during Kidney Week.

His topic will be the roles of fibroblast growth factor-23 (FGF-23) and the transmembrane protein Klotho in endothelial dysfunction and vascular calcification. Klotho mediates the role of FGF-23 in bone-kidney-parathyroid control of phosphate and calcium, and Dr. Moe has published studies showing that Klotho is an early biomarker for chronic kidney disease (CKD) and that Klotho deficiency contributes to soft-tissue calcification in CKD. Dr. Moe's research includes solute transport and metabolism, kidney stones, acid-base disturbance, and cardiovascular complications of CKD.

Dr. Moe is professor of internal medicine and physiology at the University of Texas Southwestern Medical Center in Dallas. He is the director of the Charles and Jane Pak Center of Mineral Metabolism and Clinical Research and is an active member of the nephrology division at Southwestern. He holds the Charles and Jane Pak Distinguished Chair in Mineral Metabolism Research and the Donald Seldin Professorship in Clinical Investigation.

Dr. Moe has an active practice in patient care and participates in the education of medical students, graduate students, residents, and fellows. He conducts both basic science and patient-oriented research on renal physiology and metabolism as well as epithelial biology. His research strives to cross from the level of the whole patient, to animal and cell culture models, and down to single molecules.

Dr. Moe serves on the editorial boards of the *American Journal of Physiology and Journal of the American Society of Nephrology*. He is the editor of *Current Opinions of Nephrology and Hypertension* and editor of the textbook *The Kidney by Seldin and Giebisch*.

He is a member of the American Society of Clinical Research, American Association of Physicians, American Society of Nephrology, and American Physiologic Society. Dr. Moe received his medical degree from the University of Toronto.

ASN gratefully acknowledges Amgen for support of the Jack W. Coburn Endowed Lectureship.

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Plenary Session

State-of-the-Art Lecture

Researcher Speaks on New Roles Found for Microbiota of the Human Body

David A. Relman

In recent years, research has revealed intriguing and important roles for the innumerable nonhuman species living in and on the human body. In recognition of these discoveries, David A. Relman, MD, will deliver a state-of-the-art lecture on "Diversity, Stability, and Function in the Human Microbiome" on Nov. 9.

Dr. Relman is the Thomas C. and Joan M. Merigan Professor in the department of medicine and the department of microbiology and immunology at Stanford University. He is also chief of infectious diseases at the Veterans Administration Palo Alto Health Care System in Palo Alto, Calif.

Dr. Relman's research focus is the indigenous human microbiome, and in particular, the nature and mechanisms of variation in microbial diversity within the human body as a function of time and space as well as in response to perturbations, such as exposure to antibiotics. He was one of the first researchers to employ modern molecular methods in this study and provided the first in-depth, sequence-based analyses of the microbial community in humans. His work includes studies of most major human microbial habitats.

Dr. Relman's research has also included the discovery of pathogens and the development of new strategies for identifying previously unrecognized microbial disease agents. One of his publications was cited by the American Society for Microbiology as one of the 50 most important microbiology papers of the 20th century.

Dr. Relman has served as an adviser to the U.S. government on microbiology, host-microbe interactions, emerging infectious diseases, and biosecurity. He co-chaired a widely cited 2006 study by the National Academies of Sciences (NAS) on "Globalization, Biosecurity, and the Future of the Life Sciences" and served as vice chair of a 2011 NAS study of the science underlying the FBI investigation of the 2001 anthrax mailings.

He currently serves as a member of the National Science Advisory Board for Biosecurity, chair of the Forum on Microbial Threats at the Institute of Medicine, and president of the Infectious Diseases Society of America. He received a National Institutes of Health director's Pioneer Award in 2006 and was elected a member of the Institute of Medicine in 2011.

Dr. Relman received an undergraduate degree from MIT and an MD from Harvard Medical School. He completed his clinical training in internal medicine and infectious diseases at Massachusetts General Hospital, served as a postdoctoral fellow in microbiology at Stanford University, and joined the Stanford faculty in 1994.

Mark Rosenberg to be Given Robert G. Narins Award for Contributions in Education

Mark E. Rosenberg

Mark E. Rosenberg, MD, FASN, will receive the Robert G. Narins Award, which honors those who have made substantial contributions to education and teaching.

In addition to being a professor of medicine, Dr. Rosenberg is vice dean for education at the University of Minnesota Medical School in Minneapolis. In this position, his many responsibilities for medical education include admissions, the four years of medical school, graduate medical education, and continuing medical education. Prior to joining the university, he was the chief of medicine and director of the primary and specialty medicine service line at the Minneapolis VA Health Care System from 2009 to 2012.

Dr. Rosenberg has been involved in medical education at many levels. He served as the fellowship director of the nephrology training program at the University of Minnesota, as founding and principal investigator of a National Institutes of Health training grant in nephrology, and as the senior fellowship coordinator of all fellowship programs in the department of medicine. For ASN, he chaired the executive committee of the nephrology training program directors, chaired the postgraduate education committee, served on the education committee, and is the outgoing education director for Kidney Week.

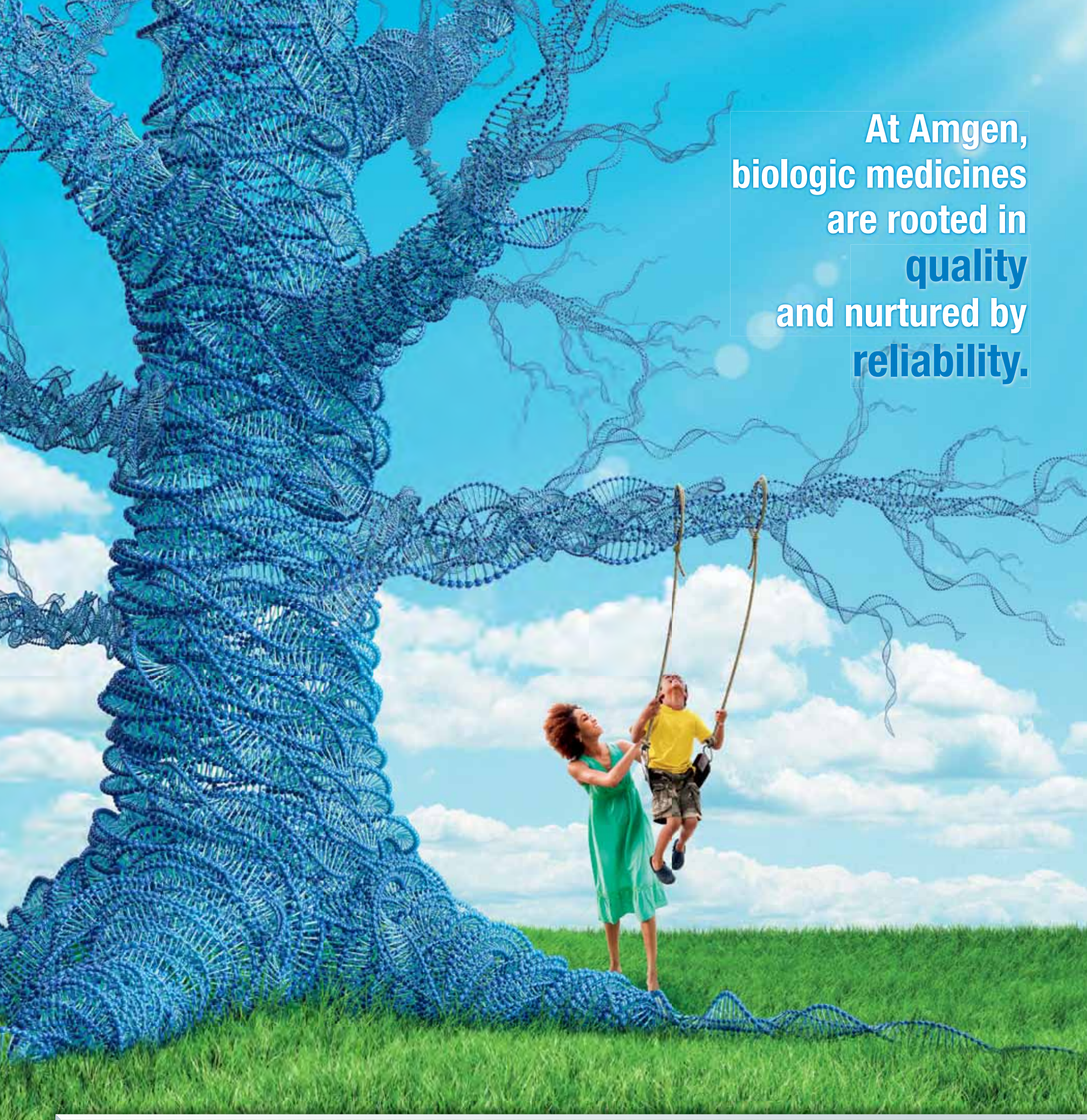
Dr. Rosenberg's other educational accomplishments include working on one of the first web-based evaluation systems for residency training programs, implementing the electronic residency application service (ERAS) and working on a specialty matching service for nephrology fellowship programs, and developing in-training examinations for fellowship programs. He developed the mobile nephrology handbook, Nephro-ToGo, initially as a program for personal assistant devices and later an app for Apple's iOS mobile operating system.

Dr. Rosenberg served on the council of the Association of Specialty Professors and chaired its education committee. He was associate editor of the Nephrology Self-Assessment Program (NephSAP) from 2001 to 2005. He received the distinguished professor award from the Association of Specialty Professors for contributions to specialty medicine, only the second nephrologist to receive this award.

He attended medical school at the University of Manitoba in Winnipeg, Canada, and did his internal medicine residency and nephrology fellowship at the University of Minnesota. He served as director of the division of renal diseases and hypertension at the University of Minnesota from 2000 to 2009.

Robert G. Narins

Robert G. Narins, MD, was the first recipient of the award now bearing his name. He taught and mentored countless students, serving on the faculties of the University of Pennsylvania, UCLA, Harvard University, Temple University, and Henry Ford Hospital. Well recognized for his contributions in the fields of fluid-electrolyte and acid-base physiology, Dr. Narins has also led numerous education efforts at the national and international levels. Among these, he has chaired the American Board of Internal Medicine's Nephrology Board and worked on the American College of Physicians' Annual Program Committee. From 1994 to 2006, he developed and guided ASN's educational programs, including working to expand educational programs during Renal Week (Kidney Week). In addition, he was instrumental in the development of the Nephrology Self-Assessment Program (NephSAP and the *Clinical Journal of the American Society of Nephrology*; and in establishing the Fellow of the American Society of Nephrology program. Dr. Narins is also credited with working with organizations in Europe and Asia to help promote education and teaching in nephrology.



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Plenary Session

John Peters Award to Honor David Salant

David J. Salant

ASN will recognize the wide-ranging contributions of David J. Salant, MD, with the presentation of the John P. Peters Award.

Dr. Salant is professor of medicine at Boston University Medical Center, where he has been chief of nephrology and director of the nephrology training program since 1987.

The John P. Peters Award is given for outstanding contributions to improving the lives of patients and to furthering the understanding of the kidney in health and disease, and Dr. Salant's research has added greatly to this understanding.

Supported by grants from the National Institutes of Health (NIH), he has conducted extensive research on immune disorders of the kidneys. His work has focused on mechanisms of immune deposition and the role of complement in glomerular diseases as well as the structural biology of the podocyte.

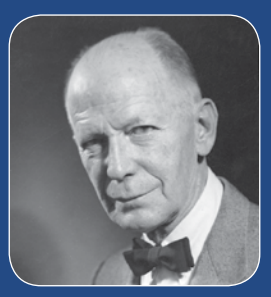
Dr. Salant was one of the earliest proponents of the notion that podocyte injury forms the basis of most, if not all, proteinuric kidney diseases. He was among the first to identify the podocyte as the primary target of injury in antibody-mediated glomerular disease.

In a landmark *New England Journal of Medicine* paper in 2009, Dr. Salant and his colleagues described their discovery that a high proportion of patients with idiopathic membranous nephropathy have circulating autoantibodies to the M-type phospholipase A2 receptor on human podocytes. He has authored more than 150 scientific papers, reviews, and book chapters.

Dr. Salant has received several awards and honors, including an investigator award from the American Heart Association, election to the American Society of Clinical Investigation and the Association of American Physicians, and the Jean Hamburger Award from the International Society of Nephrology. He has served on several NIH advisory panels and on the editorial boards of several major nephrology journals. He has also played a prominent educational role nationally as chair of the American Board of Internal Medicine in Nephrology.

Dr. Salant graduated from the Witwatersrand University Medical School in South Africa and completed his clinical training at the Johannesburg General Hospital. He received research training at Boston University with Dr. William Couser and joined the faculty in 1979.

John P. Peters



John P. Peters, MD, was one of the fathers of nephrology and former chief of the Metabolic Division in the Department of Medicine at Yale University. He transformed clinical chemistry from a discipline of qualitative impressions to one in which precise quantitative measurements of body fluids comprise a vital part of the patient examination and provide great explanatory value.

He advanced the view that disease is a quantitative abnormality of normal physiological processes and that, by understanding disease, one could gain a deeper understanding of normal physiology. His enduring scientific contributions paralleled his fervent mission to ensure that the physician be an advocate for the patient.

ASN to Bestow Belding Scribner Award on Andrew S. Levey

Andrew S. Levey

The Belding H. Scribner Award will be tendered to Andrew S. Levey, MD, for his career-long contributions to the practice of nephrology.

Dr. Levey is the Dr. Gerald J. and Dorothy R. Friedman Professor of Medicine at Tufts University School of Medicine and chief of the division of nephrology at Tufts Medical Center in Boston.

Established in 1995, the Belding H. Scribner Award is presented to individuals who have made outstanding contributions to the care of patients with renal disorders or have substantially influenced the clinical practice of nephrology. Dr. Levey has made significant contributions in patient care, research, clinical practice guidelines, training, and health care policy related to chronic kidney disease (CKD).

His involvement in patient care includes serving the Tufts Medical Center as director of the dialysis clinic from 1981 to 1990 and medical director for renal transplantation from 1983 to 2001.

His research spans a wide range, including serving as principal nephrologist co-investigator for the Modification of Diet and Renal Disease Study, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). He and his colleagues used this large database to develop an equation to estimate glomerular filtration rate (GFR) from serum creatinine. He also led the NIDDK effort to pool databases from studies to develop equations based on creatinine, cystatin C, and other filtration markers. The use of GFR equations to estimate kidney function and inform prognosis has transformed research and clinical practice in CKD.

An authority on clinical practice guidelines in CKD, Dr. Levey led the National Kidney Foundation (NKF) task force on cardiovascular disease in 1998. He chaired two NKF working groups on outcome quality initiatives. He led three global conferences on improving kidney disease outcomes. He directed the Tufts Center on Guideline Development and Implementation from 2003 until 2011.

Dr. Levey has been active in postgraduate fellowship training and mentoring of junior faculty. He directs a large research fellowship training program. He directed the Tufts University course for second-year medical students in renal pathophysiology from 1981 to 1988.

Dr. Levey's contributions to policy include serving as a member of the National Kidney Disease Education Program of the NIDDK. He co-chaired the Centers for Disease Control and Prevention 2007 expert panel that developed strategies for preventing development and progression of kidney disease.

Dr. Levey was associate editor of the *Annals in Internal Medicine*, and is currently editor-in-chief of the *American Journal of Kidney Diseases*.

Belding H. Scribner

Belding H. Scribner, MD, developed the arteriovenous shunt, which made possible long-term hemodialysis for chronic renal failure.

Dr. Scribner served as head of the University of Washington's Division of Nephrology in the Department of Medicine from 1958 to 1982. He and his co-workers at the Seattle university made numerous contributions to helping patients with end stage renal disease, including establishing the world's first out-of-hospital dialysis unit, developing a home hemodialysis program, improving techniques and equipment for hemodialysis and peritoneal dialysis, and studying the adequacy and complications of chronic renal disease treated by dialysis. Dr. Scribner's work made a significant contribution to transforming nephrology into a major subspecialty of internal medicine.

Salt Transport Authority to Describe Latest Research on Tubulopathies

David H. Ellison

An expert on salt transport by the kidney will deliver the Robert W. Schrier Endowed Lectureship on the topic, "Salt-Losing Tubulopathies."

David H. Ellison, MD, FASN, is professor of medicine, professor of physiology and pharmacology, and associate director of the Oregon Clinical and Translational Research Institute at Oregon Health and Science University. He headed its division of nephrology and hypertension for 13 years. He is also a staff physician at the Portland VA Medical Center.

Dr. Ellison's research centers on mechanisms of salt transport by the kidney, on the genetic basis of human blood pressure variation, and on diuretic treatment of edema. His work was translational before that term was even coined. A long-term focus of his research is the protein target of thiazide diuretics, drugs recommended as first-line antihypertensive agents. His early studies showed that the thiazide-sensitive Na-Cl transporter (NCC) is the dominant solute transport pathway along the distal convoluted tubule. This work led to the discovery that mutations in NCC cause Gitelman syndrome, a hypokalemic disease.

Dr. Ellison also showed that the antibiotic trimethoprim causes hyperkalemia by blocking sodium channels in the distal nephron, which is now a recognized side effect. Another one of his discoveries, that chronic treatment with high doses of loop diuretics activates solute transporters along the distal nephron, helped inform the use of combination diuretic treatment for resistant edema.

Recently, Dr. Ellison has been a leader in defining a novel kinase pathway in the kidney that, when mutated, causes familial hyperkalemic hypertension. His group has also demonstrated that the immunosuppressive drug tacrolimus causes hyperkalemia and hypertension by activating the NCC; this work is being used to design safer drugs for organ transplant recipients.

Dr. Ellison chairs the nephrology subspecialty board of the American Board of Internal Medicine, and is past chair of the American Heart Association's Council on the Kidney in Cardiovascular Disease. He was program chair for ASN's Renal Week in 2010. He is an elected member of the Association of American Physicians, and a standing member of the kidney molecular biology and genitourinary organ development study section of the National Institutes of Health. He recently completed service on the renal merit review study section for the Department of Veterans Affairs.

Dr. Ellison also has an active clinical practice in nephrology, and is a dedicated teacher and mentor to medical students, residents, nephrology fellows, and postdoctoral scientists.

ASN gratefully acknowledges Otsuka America Pharmaceutical, Novartis, Astellas Pharma US, and several individuals for support of the Robert W. Schrier Endowed Lectureship.

Plenary Session

State-of-the-Art Lecture

Genetics Advances Offer Hope in Treatment of Hypertension

Julie A. Johnson

The potential for using genetics to guide hypertension therapy will be the subject of a state-of-the-art lecture on Nov. 10. Julie A. Johnson, PharmD, will describe advances in hypertension pharmacogenomics.

Dr. Johnson is the V. Ravi Chandran Professor of Pharmaceutical Sciences and distinguished professor of pharmacy and medicine at the University of Florida Colleges of Pharmacy and Medicine. She is also director of the Center for Pharmacogenomics and director of the Shands Personalized Medicine Program at the University of Florida.

Dr. Johnson is a leader in the field of cardiovascular pharmacogenomics, having published more than 200 peer-reviewed publications. She leads a research group focused on pharmacogenomics of antihypertensive drugs as part of the National Institutes of Health (NIH)-supported Pharmacogenomics Research Network. She also leads the University of Florida's effort in clinical translation of pharmacogenomics, which launched its clinical implementation program in June 2012.

Dr. Johnson has served on the Nonprescription Drugs Advisory Committee of the Food and Drug Administration, the Xenobiotic and Nutrient Disposition and Action Study Section at NIH as well as the National Heart, Lung, and Blood Institute's Pediatric Heart Network Protocol Review Committee and Heart Failure Network Data Safety Monitoring Board. She was also a member of the American Heart Association committee on scientific sessions programming and co-chair of the 2009 International Congress on Genetics and Genomics of Cardiovascular Disease. She has had numerous other leadership roles in a variety of national organizations.

She is on the editorial boards of *Clinical Pharmacology and Therapeutics, Pharmacogenetics and Genomics, Journal of the American Heart Association, Psychosomatic Medicine, and Pharmacogenomics*.

Before joining the faculty at the University of Florida in 1998, Dr. Johnson spent 9 years on the faculty of the University of Tennessee College of Pharmacy. She received her bachelor's degree in pharmacy from the Ohio State University and her PharmD from the University of Texas at Austin and the University of Texas Health Science Center at San Antonio.

Dr. Johnson has received numerous awards including teaching awards from the University of Tennessee and the University of Florida, the Ohio State University Alumni Association William Oxley Thompson Award for early career achievement, the Young Investigator Award from the American Society for Clinical Pharmacology and Therapeutics, the Distinguished Alumnus Award from the Ohio State University College of Pharmacy, the Paul Dawson Biotechnology Research Award from the American Association of Colleges of Pharmacy, and a therapeutic frontiers award and award for contributions to the literature from the American College of Clinical Pharmacy.

Research Pioneer Will Outline Potassium Regulation Findings

Lisa M. Satlin

A leading researcher in ion transport and other areas will deliver the Barry M. Brenner Endowed Lectureship on Sunday, Nov 10. Lisa M. Satlin, MD, FASN, will speak on "Shear-Mediated K Channel Regulation."

An internationally known pioneer in pediatric nephrology, Dr. Satlin has made important discoveries, including how the developmental expression of specific proteins responsible for sodium absorption and potassium excretion in the kidney allow for growth and maintenance of blood pressure during postnatal life, and how high urinary flow rates, such as those caused by diuretics, lead to potassium losses.

Dr. Satlin is professor and chair of the department of pediatrics at the Mount Sinai School of Medicine, where she is also an associate director of the MD/PhD Training Program. She directs the Center for Patient Oriented Research, Training, Education and Development (CePORTED), the innovative educational arm of Mount Sinai's Institutes for Translational Sciences, known as Conduits. She was recruited to Mount Sinai in 1997 to lead the division of pediatric nephrology.

She built an internationally respected pediatric nephrology division and an accredited pediatric nephrology fellowship training program, which has attracted both physician and research trainees.

Dr. Satlin runs a laboratory supported by the National Institutes of Health (NIH) focused on defining the mechanisms leading to the acquisition, maintenance, and regulation of ion transport in the renal collecting duct, the nephron segment responsible for the regulation of salt and water homeostasis.

She is currently serving a second term as an associate editor of the *American Journal of Physiology: Renal Physiology*, and has served as a member of multiple study sections and grant review groups of the NIH, American Heart Association, and Polycystic Kidney Disease Foundation. Her leadership positions include serving as president of the American Society of Pediatric Nephrology, on the board of advisors of ASN, and as councilor of the International Society of Pediatric Nephrology. Her research accomplishments have been recognized by her election to membership in the Society for Pediatric Research, American Pediatric Society, and Association of American Physicians.

Dr. Satlin received her medical degree from Columbia University College of Physicians and Surgeons, completed a pediatrics residency at the Babies Hospital of Columbia University, and a pediatric nephrology fellowship at the Albert Einstein College of Medicine.

ASN gratefully acknowledges Monarch Pharmaceuticals for support of the Barry M. Brenner Endowed Lectureship.

Young Investigator Recognized for Fibrogenesis Research

Jeremy S. Duffield

The ASN will present its Young Investigator Award to Jeremy S. Duffield, MD, PhD, for his groundbreaking research on fibrogenesis. He will describe his recent findings in an address, "New Insights into Mechanisms and Consequences of Fibrogenesis: An Avenue to Novel Therapeutics for Kidney Disease."

Dr. Duffield is associate professor of medicine at the University of Washington Medical School in Seattle, where he also directs the inflammation research laboratory at the Kidney Research Institute.

An established National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) investigator, he heads a laboratory focused on the role of the innate immune response cells called monocytes in injury and repair and on the role of the mesenchymal cells known as pericytes and fibroblasts in microvascular remodeling and fibrosis. This research has led to several candidate therapeutics now being tested in clinical trials.

Dr. Duffield received young investigator awards from the British Renal Association, the U.K.'s Medical Research Society, and the NIDDK; a Gottschalk Award from the American Society of Nephrology; and a challenge grant from the National Institutes of Health.

In 2011 he was elected a member of the American Society for Clinical Investigation. He also serves on scientific study sections at the NIDDK and the National Heart, Lung, and Blood Institute. He is on the scientific advisory boards of Promedior and Regulus Therapeutics, companies dedicated to the development of antifibrotic therapies.

He also practices nephrology at the University of Washington Medical Center with special interests in systemic lupus erythematosus, systemic vasculitis, and pregnancy-related kidney disorders.

Dr. Duffield studied medicine and developmental biology at Oxford University and obtained a doctorate in medicine and immunology at Edinburgh University in the U.K. He moved to the United States in 2003 and worked as assistant professor of medicine at Harvard medical school until 2010.

Time out.

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

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Reengineering Dialysis

In 2011, the Mayo Clinic Dialysis System initiated a quality and design methods approach to improve ESRD patient outcomes by creating high-value patient-centered care across all settings. The implementation and expansion of bundled payments for dialysis and the Quality Incentive Program (QIP) created a challenge and an opportunity to reengineer care for patients on dialysis by focusing on best practices as well as outcomes important to patients. Here, Amy Williams, MD, Division of Nephrology and Hypertension, Medical Director of the Eisenberg Dialysis unit, Medical Director of Hospital Operations, Mayo Clinic Rochester, MN, and Krisa Ryan, Designer, Center for Innovation, Mayo Clinic, describe the Mayo Clinic's Reengineering Dialysis Project.

KN: What did you hope to accomplish with the Reengineering Dialysis (RED) Project?

Williams: Our hope was to design a system that would better meet the needs of our patients, leading to a decrease in emergency room (ER) visits and hospitalizations and improvements in patient compliance and success. We aimed for seamless transitions of care across all care settings and improvements in our patients' overall well-being. This would also allow us to meet metrics set forth by the Centers for Medicare & Medicaid Services (CMS) while decreasing the total cost of patient care. The Mayo Clinic Dialysis Services already had a shared medical record and standard processes and procedures for dialysis, but we needed to take it a step further to include the total care of our patients. We just did not realize exactly what the step would look like.

KN: When and why did Mayo begin to collaborate with the Center for Medicare and Medicaid Innovation on the project?

Williams: As we began our project, the expanded multidisciplinary team—including nephrologists (who were medical directors of dialysis units and had inpatient and intensive care unit practices), dialysis nurses (inpatient and outpatient), social workers, dieticians, nurse practitioners, physician assistants, administrators, technicians, quality experts, and resources from the Mayo Clinic, such as project managers—began putting together our future state. We all thought we knew what this "accountable care organization" or "medical home" for dialysis patients would look like. Then the Department of Medicine approached us to engage the resources of the Mayo Clinic Center for Innovation (CFI). They realized the importance of defining valued care for this patient population with complex chronic disease as it could then be translated to other complex chronic disease populations, such as heart failure. After our initial meeting with CFI, we collectively decided they would help us better understand what was needed or what was important from the patients' viewpoint. This information could inform the rest of our project and help define tactics.

KN: As the project got underway, a patient shared this statement with Krisa Ryan: "Patients don't get vacations." Why did this become the guiding principle for the RED project?

Williams: Through her qualitative research, Krisa Ryan—a CFI designer—was able to redefine our future state by giving us insight into what really influenced our patients' abilities to be successful. She gathered many powerful quotes, but "Patients don't get vacations" truly touched every team member at our core. How true, these individuals and their families never get a vacation from their complex chronic disease—never. How sobering. With that understanding, our goal was to decrease the overall burden of their disease to give patients more overall capacity to manage all of the aspects of their life, whether dialysis- or ESRD-related or not.

KN: You performed research to understand the "interwovenness" of dialysis care with what else is going on in patients' lives. How did you go about this?

Ryan: I took a standard design approach and tried to meet the patients where they were. Part of this process was meeting them through all of their care touchpoints, whether in an outpatient, inpatient, or home setting. I conducted interviews, observations, and inquiries about what was working for them and where potential opportunities stood. Caregivers and family members also had opportunities to share their stories. It was in the stories where we found the link to missing pieces of the redesign process.

KN: How did Krisa's research determine how the Mayo team reconsidered its delivery of dialysis care?

Williams: First, Krisa's current and future state from the patient standpoint was not a straight line as we imagined, but a complicated trajectory with many transition points and loops. We realized that at every transition point—whether from CKD to starting dialysis, dialysis to transplant or back to dialysis, inpatient setting to outpatient setting, changes in independence, or making end-of-life decisions—we needed to concentrate support and resources. The personas were an aha moment for the team. Every advanced CKD or ESRD patient I have known fit into one of the personas. And the five influencers or patient needs that were common to each patient became the "compass" for the team as we designed tactics to reach our goals. Even now, as we test and fine tune our tactics we trial them against the personas. If the tactic does not support the influencers or needs, we do not implement it.

Her research also supported the theory that for an ESRD patient to be successful and make well-informed decisions about health care and treatment options based on their preferences and goals, education and seamless care needs to start when they have CKD and before they need renal replacement therapy. One example of Krisa's findings is that patients want consistent, honest information throughout the course of their disease—information about their options and how these options will impact things important to them such as symptoms, travel, quality of life, cost, employment, and prognosis. Based on her findings, we restructured and refocused all of our patient education for those with CKD through renal replacement therapy. This includes patient-focused decision aids and just-in-time information critical for those starting in-hospital dialysis and transitioning to outpatient dialysis centers.

KN: Krisa, how did you work with Amy's quantitative data and patient information regarding their movement within the system, what you term transitions from touchpoint to touchpoint?

Ryan: All of Amy's data was very meaningful. It told us what was happening in a distinct way and what to look for. We could take this data and ask: Why is this happening? How is it originating? What does this mean long term for patients and their well-being? That's where the patients' and caregivers' stories really created context for us. As long as we could map this, then we could change it.

KN: Based on what you have learned in RED, how do you hope to influence CMS to promulgate more meaningful measure of quality?

Williams: Understanding what outcomes are important to the patient is a first step. Staying healthy enough to meet their personal goals, to not need acute hospitalization or ER care, to successfully manage their chronic illness in partnership with their health care team, to understand their health care options and make informed decisions based on their health care goals and preferences— these are important and patient focused.

Quality measures are important and should positively impact patient outcomes. Yet wasting resources gathering data that does not influence meaningful outcomes can be a distraction and prevent dialysis systems from focusing on the patient needs that would help the patient be more successful managing their chronic disease, life, and dialysis. We need systems that have seamless transitions throughout the complicated disease trajectory of those with advanced CKD/ESRD. We need a process that identifies high-value care and will not penalize those centers that care for high-risk or complex patients. We hope to influence the definition of high-value care for ESRD patients.

2013 Kidney Legislative Activity in the States

Most states have wrapped up their legislative sessions for the year. Several kidney-related bills were signed into law in 2013.

Utah became one of a handful of states with laws allowing posthumous organ donation by inmates. The "Inmate Medical Donation Act" requires the Utah Department of Corrections to make document-of-gift forms available to inmates that state inmates' willingness to have organs donated if they die while in custody of the department.

New Jersey passed a bill that prohibits discrimination against organ transplantation solely on the basis of a mental or physical disability, unless that disability is determined to specifically affect the provision of an organ. Individuals who are unable to comply with posttransplant medical requirements may be cleared for transplant if they have the "necessary support system" to help.

Maine and Idaho will now have a $2 check-off box on driver's license applications and renewal forms for drivers to indicate their intent to donate to their respective state organ donation funds.

Texas has continued appropriations for its "Love Your Kidneys" campaign, a multimedia statewide effort launched in 2007 to educate citizens about risk factors for chronic kidney disease.

Delaware passed legislation to ensure that Medicare supplemental insurance (Medigap) is available to individuals under the age of 65 who are eligible for the Medicare program due to age or disability. Medigap is used to cover costs not covered under original Medicare. Insurers who provide these supplemental plans are only required to offer them to beneficiaries over the age of 65. Over 25 states have similar statutes in place.

Are Lower Blood Pressure Targets Beneficial in Chronic Kidney Disease?

Intensive blood pressure reduction slows the progression of chronic kidney disease (CKD), but only in patients with proteinuria, suggests a meta-analysis in the *Canadian Medical Association Journal*.

A systematic review identified 11 randomized trials in which CKD patients were assigned to different blood pressure reduction targets. A meta-analysis included data on more than 9000 patients; blood pressure targets in the intervention groups varied widely. Outcomes of interest were a composite of doubling of serum creatinine level and a 50 percent decline in GFR, and the progression of ESRD.

Intensive blood pressure reduction was associated with a lower rate of both renal outcomes: hazard ratio 0.82 for the composite outcome and 0.79 for ESRD. However, there was a significant modifying effect of proteinuria. The reduction in kidney failure was significant only in patients with proteinuria at baseline: hazard ratio 0.73.

The effect on renal outcomes also appeared stronger in studies with lower markers of trial quality. The rates of cardiovascular events, all-cause mortality, and severe adverse events were similar between the intervention and usual care groups.

The current CKD guidelines recommend a blood pressure target of less than 130/80 mm Hg, but the strength of evidence behind this recommendation has been questioned. The new meta-analysis finds a reduced risk of kidney failure events with intensive blood pressure lowering, but mainly in patients with baseline proteinuria. Further study would be needed to show a similar protective effect in CKD patients without proteinuria [Lv J, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ* 2013; 185:949–957].

Policy Update

ASN Launches Grassroots Campaign to Protect Medical Research Funding

By Grant Olan

Despite shrinking funding for kidney research and a record low grant application success rate at the National Institutes of Health (NIH), more cuts are set to take effect in 2014 unless Congress takes action to prevent them.

As part of ASN's response to this continued threat to research, the society asks members to meet with congressional offices in their home districts in November and December to highlight the value and importance of continued investments in medical research. This district-level advocacy is a crucial corollary to the society's advocacy work.

ASN recently surveyed its U.S. members to collect feedback on the impact of budget cuts on their research laboratories, institutions, and patients. Nearly 70 members responded. This feedback has been invaluable in helping ASN build the case in Congress that cuts have, and will continue to have, a negative effect on the United States' position as the global leader in research.

Through congressional briefings, office visits, and community sign-on letters to Congress, ASN is aiming to ensure Congress hears the message about cuts to research funding. ASN also supports six coalitions committed to protecting federal investments in medical research, including NDD United, which represents 3200 organizations advocating for a balanced approach to deficit reduction. For more information, visit http://www.nddunited.org/.

ASN members can access all the directions and tools necessary to meet with local congressional offices, including talking points and fact sheets, at http://www.asn-online.org/policy/. It is important for members of Congress to hear from those on the ground, their own constituents who have been affected or will be affected by budget cuts.

"It doesn't make sense to cut investments like medical research that grow the economy," ASN Research Advocacy Committee Chair John R. Sedor, MD, said. "Discretionary programs have already sustained significant cuts and there is no more fat to trim. Even eliminating all federal discretionary funding won't eliminate the deficit. Congress needs to find a balanced approach to debt reduction, and your elected representatives need to hear that from you this November and December. Please help yourself by helping ASN. Visit http://www.asn-online.org/policy/ today to take action."

In Their Own Words

Kidney professionals describe the impact of budget cuts

I am a practicing nephrologist with a small clinical research program in autosomal dominant polycystic kidney disease (ADPKD), a rare genetic disease. One of my key collaborators may no longer be able to run his laboratory. He has spent decades amassing expertise in this disease. Once he is gone our ability to address innovative questions is dramatically reduced. – Neera Dahl, MD, PhD, Yale University School of Medicine

Diabetes is the number one cause of progressive kidney injury and ESRD, and increases the risk of heart disease, heart attacks, and strokes. Cuts in my federal funding will mean losing staff members whose work is critical to our ability to find ways to slow or reverse the progression of kidney disease in diabetes. – Raymond Harris, MD, Vanderbilt University Medical Center

My laboratory supports work that advances treatment for a number of diseases of glomerular function. These diseases affect young and old, have no therapies, and often result in the need for life-saving dialysis. The cost to American taxpayers is more than $30 billion a year. Brilliant young scientists in our training program are turning away from a career in science because they view this career as too risky. The future of kidney research and patient care is being seriously and rapidly eroded. – Lawrence Holzman, MD, University of Pennsylvania

Our research focuses on understanding polycystic kidney disease and glomerular disease. Our present grants have been cut back, decreasing our ability to pursue this research and the potential treatments that may result. We are facing a time where prominent scientists in the field of nephrology are unsure how and if they will be able to maintain their laboratories. The field was already in crisis before the sequester. Now it is in uncharted territory. – Jordan Kreidberg, MD, PhD, Boston Children's Hospital and Harvard Medical School

We develop therapies to treat people with food-borne infections that cause acute kidney injury and coagulation problems, organ damage, and increased risk for kidney complications. We have had to release one technician, move another to part time, and cannot bring in new graduate students and the new knowledge they bring. As a result, our work developing better treatments has slowed significantly. – DJ Stearns-Kurosawa, PhD, Boston University School of Medicine

Proposed Cuts to ESRD Program: ASN Responds

By Mark Lukaszewski

A proposal to cut the End-Stage Renal Disease (ESRD) Program by nearly 10 percent may have unintended consequences for people on dialysis. This was ASN's key message to the Centers for Medicare & Medicaid Services (CMS) in comments on the proposed rule regarding the Medicare ESRD Prospective Payment System (PPS) and Quality Incentive Program (QIP).

ASN's Quality Metrics Task Force, Public Policy Board, and Dialysis Advisory Group assessed the proposed rule to determine what effects it could have on patient care and access to dialysis before the society submitted feedback to CMS.

Previous ASN comment letters have focused on the quality portion of the proposed rule instead of the payment component. But given the magnitude of the proposed cuts, ASN leadership felt strongly that the society should focus on both sections of the rule, highlighting the effect the potential cuts could have on patient access to care. This article summarizes ASN's main recommendations to CMS (Table 1).

This year Congress directed CMS to reexamine the ESRD base rate based on changes in drug utilization. In response to this mandate CMS proposed to decrease total payments to ESRD dialysis facilities by 9.4 percent. ASN is concerned about the potential serious adverse effects on the quality of care and patient access to dialysis that the proposed reduction in payment for ESRD services would have, especially if implemented at once.

"It's troubling that Congress mandated a payment reduction at the same time that CMS is using the ESRD program as a model for bundled payment, a quality-incentive program, and a specialty-specific integrated care delivery model," noted Thomas H. Hostetter, MD, chair of the ASN Public Policy Board. "The kidney community is working diligently on achieving the goals of the Quality Incentive Program (QIP), which was also mandated by Congress and implemented by CMS, in order to avoid further cuts in reimbursement."

According to a 2012 Medicare Payment Advisory Commission's report, the two largest dialysis providers saw Medicare margins of 3.4 percent on nearly 70 percent of spending, compared with 0.1 percent for 31 percent of spending for all other providers. In 2010, rural facilities operated on a –3.7 percent Medicare margin. This suggests many dialysis facilities risk closing, especially in rural and urban areas where few are covered by commercial insurers.

If any substantial base rate reductions occur, ASN strongly recommends cuts are phased in over several years, which would allow CMS to monitor for adverse effects on dialysis patients' access and quality of care before implementation of further reductions.

CMS also recommended a "holdback" policy for home dialysis training, in which dialysis facilities would not be reimbursed for training patients who are unsuccessful in transitioning to home dialysis. ASN strongly recommended CMS eliminate this proposed policy. The society is concerned that the proposal would discourage attempts at home dialysis dissemination to more infirm individuals, who, if they are able to successfully perform home dialysis, may derive greater benefits. Moreover, the holdback appears to conflict with CMS' stated goal of using the PPS as a mechanism to promote increased home dialysis utilization.

Evaluating quality of care as well as patient access to dialysis services and medications is of utmost importance within a bundled payment system, and is especially necessary in light of proposed changes to the base rate. Nonetheless, given the limited scientific evidence currently available regarding what comprises optimal care for patients on dialysis, the society expressed reservations about some aspects of the proposed modifications to the QIP program.

ASN noted existing and proposed QIP measures are not as relevant as others. Some are focused on processes—monitoring and collecting data—rather than on outcomes. Ample evidence shows most providers meet or exceed quality standards for several measures, such as hemoglobin. ASN plans to work with stakeholders and CMS to strengthen the QIP and expand the evidence base for meaningful new measures.

The proposed clinical hypercalcemia measure was of greatest concern. CMS would penalize facilities if a percentage of patients don't meet the serum calcium target of 10.2 mg/dL or below. However, ASN believes there is insufficient scientific evidence to substantiate this target. No hypercalcemia performance gap currently exists and calcium management is the care standard. ASN recommended CMS not finalize the hypercalcemia measure, stating that it would create a reporting burden without benefitting patients.

CMS will likely release a final rule in early November, and ASN, with other kidney stakeholders, will continue to advocate to CMS and Congress until then. "More than 20 million Americans have kidney disease, and the Medicare ESRD program provides lifesaving care to nearly 400,000 beneficiaries with kidney failure," said ASN President Bruce A. Molitoris, MD, FASN. "People with kidney disease, among the most vulnerable patients, are disproportionately underrepresented minorities, and such a large cut may reduce access to care and quality of treatment. ASN, the kidney community, and CMS must work together to provide the highest quality care possible to the millions of Americans with kidney disease, including those on dialysis whose lives are saved daily by the Medicare ESRD Program." ASN's comment letter is available at http://bit.ly/18en5BA.

Table 1

Key ASN recommendations to CMS

- Assess the significant negative effect a cut of the proposed magnitude would likely generate on patient access to quality care.
- Provide the option to phase in any PPS bundle rebase over a 4-year period in equal parts.
- Implement and publicly describe a comprehensive monitoring program to identify any unintended consequences that could arise as a result of any PPS bundle rebase, including consolidation of the dialysis market.
- Eliminate the concept of a "holdback" for home dialysis training.
- Maintain a reporting-only hypercalcemia measure instead of transitioning it to a clinical measure.
- Collaborate with ASN and other stakeholders in the kidney care community to update the 2728 form and corresponding annual comorbidity reporting list.

Policy Update

ESRD Seamless Care Organizations: Where Do We Go from Here?

By Rachel Shaffer

The deadline for nephrologists and dialysis facilities to apply to become an ESRD Seamless Care Organization (ESCO)—the first-ever disease-specific Medicare Shared Savings Program—has come and gone. As of press time, it appears that the Centers for Medicare and Medicaid Services (CMS) received fewer applications than the agency and the community had once hoped.

CMS had originally stated that it expected between 10 and 15 unique ESCOs to participate, with representation from all dialysis provider organizations/facility types and geographic areas—and that it would consider making more than 15 awards "if a compelling reason exists to do so." No official count of the number of applications has yet been announced, but a number of complications—including a CMS proposal to reduce the ESRD Prospective Payment System base rate by 9.4% and outstanding questions such as what quality measures will be used to evaluate the program—suggest a lower participation rate.

It is still unclear how financially viable the shared savings model would be, especially in light of the proposed cuts to the ESRD payment system.

Since CMS announced the Comprehensive ESRD Care Initiative in February 2013, there were several changes along the way. In addition to pushing back deadlines, the agency also shared information it previously indicated could not be made public regarding how many dialysis patients are currently attributed to traditional Accountable Care Organizations. (CMS' ESCO Request for Proposal specifies that patients who are already being attributed to traditional Accountable Care Organizations are not eligible for attribution to an ESCO.) Another key change was the lifting of the requirement that nephrologists and dialysis facilities must apply jointly with a "third Medicare eligible provider," thereby making it easier to form an ESCO.

Despite these changes, many uncertainties with the model remain. Table 1 summarizes ASN's top concerns and recommendations for improvement.

At press time, ASN was set to meet with CMS and Center for Medicare and Medicaid Innovation leaders to talk about the future of the ESCO program. Other patient and health professional organizations expected to attend included the American Association of Kidney Patients, the American Kidney Fund, the American Nephrology Nurses Association, the American Society of Pediatric Nephrology, Dialysis Patient Citizens, and the Renal Support Network.

Table 1

Top ASN Recommendations for the ESCO Program

1. Continue to emphasize the leadership role of nephrology health professionals in ESCOs.
2. Develop quality metrics that are appropriate for patients on dialysis in a transparent manner that allows for input from the entire kidney community.
3. Prospectively specify the criteria that determine whether an ESCO is deemed "successful" or "unsuccessful," and include patient perceptions of experience of care in that assessment.
4. Facilitate research into and better understanding of optimal dialysis care by sharing de-identified ESCO patient data with qualified investigators, similar to the National Institutes of Health.
5. Develop a plan to ensure consistent access to transplantation, recognizing that the best candidates for transplant are also often likely to be the healthiest patients on dialysis, and will not be attributed to the ESCO posttransplant.
6. Establish and explain safeguards to monitor and address "cherry picking" or potential changes in patient outcomes.
7. Reconsider the goal of rebasing the program in years four and five, recognizing that this approach penalizes the highest performing ESCOs.

Journal View

Integrated Pharmacy Service Shows Benefits in Patients Receiving Dialysis

Integrated pharmacy services are associated with lower mortality and hospitalization rates in patients receiving hemodialysis, reports a study in the *American Journal of Kidney Diseases*.

The study evaluated the outcomes of an integrated pharmacy program created in 2005 by a large dialysis organization in the United States. The voluntary program offered patients services including medication delivery, refill management, medication list reviews, medication management via telephone, and help with prior authorizations.

The researchers compared outcomes in 8864 patients receiving hemodialysis who received integrated pharmacy services versus 43,013 propensity score-matched control individuals. The patients in both groups had concurrent Medicare and Medicaid eligibility. The relative rates of death and hospitalization were compared between groups.

The patients who opted for integrated pharmacy services had significantly lower mortality: hazard ratio (HR) 0.92 on intention-to-treat analysis and 0.79 on as-treated analysis. Integrated pharmacy services were also associated with lower rates of hospital admissions: relative rate 0.98 (nonsignificant) on inten-

Continued on page 40

Journal View

Integrated Pharmacy Service

Continued from page 39

tion-to-treat analysis and 0.93 on as-treated analysis. For hospital days, the relative rates were 0.94 and 0.86, respectively.

For patients enrolled in the integrated pharmacy program, the cumulative disenrollment rates were about 24 percent at 1 year and 37 percent at 2 years. Enrollees were much more likely to fill prescriptions for cinacalcet and phosphate binders, and they were somewhat more likely to fill prescriptions for antihypertensive drugs.

Medication management for patients receiving hemodialysis is a challenging problem. The current evaluation suggests that an integrated pharmacy program can help to lower mortality and hospitalization rates in dialysis recipients. The authors call for further studies evaluating the use of program services and providing more detailed information on clinical and economic outcomes [Weinhandl ED, et al. Clinical outcomes associated with receipt of integrated pharmacy services by hemodialysis patients: a quality improvement report. *Am J Kidney Dis* 2013; 62:557–567].

Variations in Antithrombotic Use Affect Bleeding Risk in Hemodialysis

The data from a large international study of patients receiving hemodialysis show a wide variation in antithrombotic therapy, along with an increased risk of bleeding among patients receiving oral anticoagulants (OACs), reports *Kidney International*.

In more than 48,000 patients enrolled in the worldwide Dialysis Outcomes and Practice Patterns Study, the researchers assessed variations in antithrombotic therapy and major bleeding events. The study also sought to identify risk factors for stroke and bleeding events in this very large hemodialysis population.

The use of all categories of antithrombotic agents varied widely among countries: from 0.3 percent to 18 percent for OACs, 3 percent to 25 percent for antiplatelet agents (APAs), and 8 percent to 36 percent for aspirin. The rates of major bleeding events also varied widely: from 0.05 to 0.22 events per year. In adjusted analyses, patients receiving OACs were at increased risk of all-cause and cardiovascular mortality as well as bleeding events requiring hospitalization. Antiplatelet agents were also associated with increased all-cause and cardiovascular mortality.

In patients with atrial fibrillation, the CHADS2 score was a significant predictor of stroke risk. Gastrointestinal bleeding within the past year was a strong predictor of bleeding risk: for patients with such a history, the bleeding rate was at least twice as high as the stroke rate. This was so at all levels of CHADS2 score and among patients at high risk of stroke.

The results show a wide variation in the use of antithrombotic agents in patients receiving hemodialysis, with increased bleeding risk in patients receiving OACs. Both OACs and APAs are associated with increased mortality. "Appropriate risk stratification and a cautious approach should be considered before OAC use in the dialysis population," the researchers conclude [Sood MM, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. *Kidney Int* 2013; 84:600–608].

Copper Deficiency Plays Role in Cysteamine Toxicity

Patients with cystinosis and cysteamine toxicity show evidence of copper deficiency—suggesting that copper supplementation might prevent cysteamine toxicity, reports a study in the *Journal of Pediatrics*.

Laboratory tests for copper deficiency were performed in 36 patients with cystinosis. Of these, 22 had renal Fanconi syndrome (FS), including seven with signs of cysteamine toxicity, including bruise-like lesions and/or red skin striae. Twelve patients had undergone kidney transplantation, one was receiving hemodialysis, and one had ocular cystinosis.

Urinary copper excretion was increased in all 22 patients with FS. Nine patients—including the seven with cysteamine toxicity—had decreased serum copper and ceruloplasmin levels and urinary copper/creatinine ratio. Genetic tests, including tests of the copper transporter, lysyl oxide, and type I procollagen genes, showed no specific variations associated with cysteamine toxicity. There were no differences in fibroblast (pro)collagen synthesis in a comparison of three patients with and two without cysteamine toxicity.

Cysteamine toxicity was recently described as a complication of high-dose cysteamine therapy in patients with cystinosis. There are clues that cysteamine may interfere with collagen cross-linking.

The new study shows that cysteamine toxicity is associated with copper deficiency, with no evidence of relevant genetic abnormalities. Copper deficiency may cause decreased activity of lysyl oxidase, which plays a critical role in collagen cross-linking. The researchers conclude, "[T]he administration of copper supplements should be considered in patients with cystinosis, especially in those with FS" [Besouw MTP, et al. Copper deficiency in patients with cystinosis with cysteamine toxicity. *J Pediatr* 2013; 163:754–760].

Continued on page 43

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Journal View

Pazopanib vs. Sunitinib for Metastatic Renal Cell Cancer

Although pazopanib and sunitinib have similar survival benefits in patients with metastatic renal cell carcinoma, pazopanib offers lower rates of adverse events and higher quality of life, reports a head-to-head trial in the *New England Journal of Medicine*.

The multicenter, international trial included 1110 patients with clear-cell, metastatic renal cell carcinoma. Patients were randomly assigned to open-label treatment in 6-week cycles with pazopanib, 800 mg once daily; or sunitinib, 50 mg once daily for 4 weeks (followed by 2 weeks off). Progression-free survival and overall survival were compared, along with safety outcomes and quality-of-life scores.

In terms of progression-free survival, pazopanib was noninferior (clinically similar) to sunitinib: median 8.4 and 9.5 months. The median overall survival was 28.4 and 29.3 months, respectively.

Certain adverse events were more frequent with sunitinib, including fatigue, 63 percent versus 55 percent; hand-foot syndrome, 50 percent versus 29 percent; and thrombocytopenia, 78 percent versus 41 percent. Pazopanib was superior to sunitinib in most domains of health-related quality of life, with the largest differences in fatigue, hand-foot syndrome, and mouth sores. Some measures of medical resource use, including emergency department visits, were lower with pazopanib.

Tyrosine kinase inhibitors are recommended first-line therapy for patients with metastatic renal cell carcinoma. Previous studies have suggested improved safety with pazopanib; this phase 3 trial is the first direct comparison of pazopanib versus sunitinib.

Although the two drugs are similarly effective, pazopanib is associated with improved safety outcomes and quality of life. The authors note that such outcomes "assume special importance in comparative-effectiveness research when clinically similar treatments are being considered" [Motzer RJ, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013; 369:722–731].

Impact of Albuminuria on Coronary Heart Disease Differs by Race

A higher urinary albumin-to-creatinine ratio (ACR) is more strongly related to incident—but not recurrent—coronary heart disease (CHD) in black versus white Americans, reports a study in the *Journal of the American Medical Association*.

The analysis included data on black and white adults in the United States enrolled in the prospective Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Urinary ACR was evaluated for association with CHD outcomes, including possible differences between racial groups. Incident CHD was evaluated in about 23,000 participants initially free of this condition, and recurrent CHD in nearly 5000 individuals with CHD at baseline. The mean follow-up time was 4.4 years.

Higher ACR had a greater impact on incident CHD in black participants. At an ACR above 300 mg/g, the age-adjusted and sex-adjusted incidence of CHF was 20.59 per 1000 person-years in black participants versus 13.60 per 1000 person-years in white participants. After adjustment for cardiovascular risk factors and medications, the risk of incident CHD was threefold higher (hazard ratio 3.21) in black adults with ACR greater than 300 mg/g (versus less than 10 mg/g). The association was no longer significant in white participants.

By contrast, the risk of recurrent CHD events associated with high ACR did not differ by race. At an ACR above 300 mg/g, adjusted hazard ratios for first recurrent CHD event were 2.21 for black and 2.48 for white participants.

High urinary ACR is more frequent in black than in white adults. Previous REGARDS data have shown that albuminuria is a stronger risk factor for stroke in black than in white individuals.

The new results suggest that the association extends to CHD. The relative risk of incident CHD associated with high ACR appears two times greater in black than in white individuals. No such difference is apparent for recurrent CHD risk. The investigators conclude, "Future studies should examine whether addition of ACR can improve the diagnosis and management of CHD in black individuals" [Gutierrez OM, et al. Association between urinary albumin excretion and coronary heart disease in black vs white adults. *JAMA* 2013; 310:706–714].

ASN Foundation for Kidney Research

Time for a Cure

Mission: To prevent and cure kidney diseases through research and innovation

Established in 2012, the ASN Foundation for Kidney Research funds the Career Development Grants Program, the Ben J. Lipps Research Fellowship Program, and the Student Scholar Grants Program awarding over $3,000,000 annually to young investigators, fellows, and medical students.

The ASN Foundation for Kidney Research congratulates the talented group of researchers who were awarded grants in 2013.

Career Development Grants Program - Funding for New Investigators

Advancing the independent careers of young investigators in biomedical research, grants are awarded to applicants within seven years of their initial faculty appointment.

Carl W. Gottschalk Research Scholar Grants

Matthew Abramowitz, MD
Albert Einstein College of Medicine
Metabolic Acidosis and Insulin Resistance in Chronic Kidney Disease

Michelle Gumz, PhD
University of Florida
Role of the Kidney in Blood Pressure Regulation by the Circadian Protein Per1

Tamara Isakova, MD
University of Miami Leonard M. Miller School of Medicine
Longitudinal Assessments of Sclerostin in Chronic Kidney Disease

Pinelopi Kapitsinou, MD
Vanderbilt University Medical Center
Role of Endothelial Oxygen Sensing in Kidney Injury and Repair

Mara Mcadams-DeMarco, MD
Johns Hopkins University
Frailty and Adverse Health Outcomes of Aging in Older Adults with Kidney Failure

Jennifer Pluznick, PhD
Johns Hopkins University School of Medicine
Elucidating the Function of Renal Olfactory Receptor 1393

Aylin Rodan, MD, PhD
UT Southwestern Medical Center
Mechanisms of NKCC Regulation in the Drosophila Renal Tubule

Norman Siegel Research Scholar Grant

Katherine Wesseling-Perry, MD
University of California, Los Angeles
Pathogenesis of Defective Skeletal Mineralization in CKD

The Halpin Foundation - ASN Foundation for Kidney Research Grant

Ying Chen, MD, PhD
Washington University
Chemical Chaperone Impact on Defective Glomerular Laminin Secretion and Congenital Nephrotic Syndrome

The NephCure Foundation - ASN Foundation for Kidney Research Grant

Jeffrey Hodgin, MD, PhD
University of Michigan
Deep Sequencing and Cross-Species Analysis of the Glomerular and Podocyte Transcriptome in Focal Segmental Glomerulosclerosis

Student Scholar Grants Program

The ASN Foundation for Kidney Research enables medical students with an interest in either basic or clinical research to spend time engaged in work on a kidney research project.

Samuel Allred
University of North Carolina at Chapel Hill
Characterization of Two Novel Isoforms of Proteinase-3 (PR3)

Divya Chalikonda
George Washington University
Development and Standardization of a Furosemide Stress Test for Patients with Acute Kidney Injury

Edward Cuaresma
Nationwide Children's Hospital
Markers of Renal Injury

Susan Dewolf
Columbia University Medical Center
Mechanism of T Cell Tolerance in Patients Receiving Combined Kidney and Bone Marrow Transplantation

Kieran Feeley
Research Institute at Nationwide Children's Hospital
Physiological Determinants of HNP1-3's Activity Against Uropathogens

Ryan Gillihan
University of Kansas Medical Center
Impact of Chronic Kidney Disease on Circulating Osteoblast Progenitor Cells

Elizabeth Hendren
St. Paul's Hospital/University of British Columbia
Use of Compatible Living Kidney Donors in Living Donor Paired Exchange

Roger Kim
Yale School of Medicine
The Effects of Dopamine and Angiotensin-II on NHE3 Patterns of Phosphorylation

Ioannis Konstantinidis
Mount Sinai School of Medicine
Complex Comorbidity and Adherence to Therapy for Chronic Kidney Disease: Disease Perceptions and Adherence in Patients with Comorbid HIV

Tanya Kuper
Toronto General Hospital/ University Health Network
Proteinuria and the Risk of Cardiovascular Disease in Kidney Transplant Recipients

Ayodele Odutayo
University of Toronto
Pregnancy Outcomes in Glomerular-Based Kidney Diseases

Thomas Clark Powell
University of Alabama School of Medicine
Multicenter Validation of a Novel Acute Kidney Injury Staging System

Pavel Roshanov
London Health Sciences Centre
Predicting Perioperative Acute Kidney Injury

Natjalie Salas
Ponce School of Medicine and Health Sciences/ Vanderbilt University
IL-1 Trap and Vascular Health in Chronic Kidney Disease

Monica Schwartzman
Mount Sinai School of Medicine
Regulation and Functional Significance of YAP Signaling in Podocytes

Ann Zalucky
University of Calgary
The Effect of Sustained Hypoxia on the Vascular and Renal Hemodynamic Responses to Angiotensin II Infusion in Humans

Ben J. Lipps Research Fellowship Program

Funding ten new research applicants and ten continuing projects annually, the program distributes $50,000 a year per fellow for two years to conduct original, meritorious research.

Ben J. Lipps Research Fellows

Yongen Chang, MD, PhD
University of California, San Francisco
The Important Role of Renal Myofibroblast Alphav Integrins in Tubulointerstitial Fibrosis

Katharina Hopp, PhD
Mayo Clinic
Identification of Modifier Genes that Cause Early-Onset Autosomal Dominant Polycystic Kidney Disease Using Next-Generation Sequencing

Daria Ilatovskaya, PhD
Medical College of Wisconsin
TRPC6 Channel as a Target for Treatment of the Nephrotic Syndrome

Steven Kim, MD
University of California, San Francisco
A Novel Array of Silicon Nanopore Membranes: Transport & Biocompatibility Studies

Omar Maarouf, MD
Brigham and Women's Hospital
The Role of Wnt Signaling in Kidney Pericyte to Myofibroblast Transition

Sharon Anderson Research Fellow

Nwamaka Eneanya, MPH, MD
Massachusetts General Hospital
Discussing End-of-Life: Racial Disparities in End-of-Life Preferences in Chronic Kidney Disease Patients Due to Limited Health Literacy

Dimitrios G. Oreopoulos Research Fellow

Tripti Singh, MD
University of Pittsburgh Medical Center
Role of Innate Activation of B Cells in Alloimmunity and Graft Rejection

George B. Rathmann Research Fellow

Jie Cui, MD
Massachusetts General Hospital
Prediction of Arteriovenous Fistula Stenosis and Failure Via In Vivo Inflammation and Fibrin Molecular Imaging

ASN Foundation for Kidney Research Fellows

Colin Lenihan, MD
Stanford University
The Effectiveness and Safety of Cardiovascular Medications in Kidney Transplant Recipients

Meghan Sise, MD
Columbia University Medical Center
Molecular Networks Mediating HIV-associated Nephropathy

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Index to Advertisers

Industry Spotlight

New Anemia Drug Could Debut in 2014

Rockwell Medical completed a second late-stage study in September (the earlier, identical late-stage trial ended in July) and announced that its experimental drug has met the main goal of improving hemoglobin levels in adult patients with chronic kidney disease, Reuters reported.

Carol Werther, a Summer Street research analyst, said that the company will be able to file for marketing approval in 6 months or less. She noted that soluble ferric pyrophosphate (SPF) perhaps could be approved in the second half of 2014. Werther predicted that the drug could generate annual sales of $225 million in 2017.

The administration of SFP is different from that of conventional iron therapies for dialysis patients who need iron. SFP is given along with the fluid used in dialysis, whereas the standard care is to give iron therapy intravenously to patients with chronic kidney disease.

Summer Street's Werther said that the drug's unique method of administration allows for maintenance of hemoglobin levels and lowers the risk of iron overload, which could increase infection rates in patients receiving dialysis. Patients lose several milligrams of iron during a dialysis treatment.

The company reported positive results from the first study of SFP in July.

A separate study in February showed that regular treatment with the drug reduced the need for erythropoiesis-stimulating agents.

Chief Executive Officer Rob Chioini said that he has great confidence in getting approval from the U.S. Food and Drug Administration for the drug and that "SFP could become the new standard of care in iron therapy," Reuters reported.

Renal Denervation on Way to United States Soon?

The renal denervation device market has several systems approved for use in Europe, but none so far has been approved by the U.S. Food and Drug Administration (FDA). Renal denervation is a catheter-based ablation procedure used to treat patients with high blood pressure resistant to drugs.

In June, the first clinical trial for a renal denervation device started enrolling in the United States, according to the Endovascular Today website. St. Jude Medical, Inc., reported that it won FDA approval to begin the EnligHTN IV renal denervation study, under an investigational device exemption. The EnligHTN IV study is a randomized, single-blind, controlled, multicenter (about 80 sites) trial that should enroll about 590 patients between the ages of 18 and 80 who have a systolic blood pressure of 160 mm Hg or greater and who take three or more antihypertensive medications, including a diuretic.

The European market is already full of contenders in the renal denervation marketplace. Overall, the predicted marketplace for renal denervation devices is about $30 billion, according to experts at manufacturer Vessix, *Bloomberg News* reported.

In early September, St. Jude Medical announced the CE Mark (European region) approval of its next-generation EnligHTN Renal Denervation System for treating patients with drug-resistant, uncontrolled hypertension. The system features an advanced generator that delivers simultaneous ablations with a multielectrode catheter and lowers the total ablation time from about 24 minutes to 4 minutes with the new system.

Device makers that have received approval to sell hypertension devices in Europe include the field's leader, Medtronic Inc.; St. Jude Medical, Inc.; Covidien Plc; ReCor Medical; and Vessix. Vessix also has won approval to be sold in Australia.

Boston Scientific bought Vessix last October and tabled its plans to produce its own renal denervation system. Under the terms of the deal, Boston Scientific made an upfront payment of $125 million and will make milestone payments of up to $400 million between 2013 and 2017, according to *Bloomberg News*.

Medtronic paid $800 million, plus milestone payments equal to the annual growth in sales through 2014 for Ardian, a maker of a renal denervation system.

Bernstein Research analyst Derrick Sung said that Boston Scientific is paying high in comparison with the most recent renal denervation deals. He said that Ardian's high price is justified by the fact that the intellectual property gives Medtronic a 2-year to 3-year lead in the United States. Covidien recently paid $60 million for Maya Medical, plus up to $170 million in milestone payments.

The new question is this: exactly when will these devices be approved for sale in the United States?

Test for Early Rejection of Transplanted Organs

For years, medical researchers have sought an early test to determine how well a transplant patient's body is accepting an organ. Half of kidney recipients have organ failure within 10 years of a transplant.

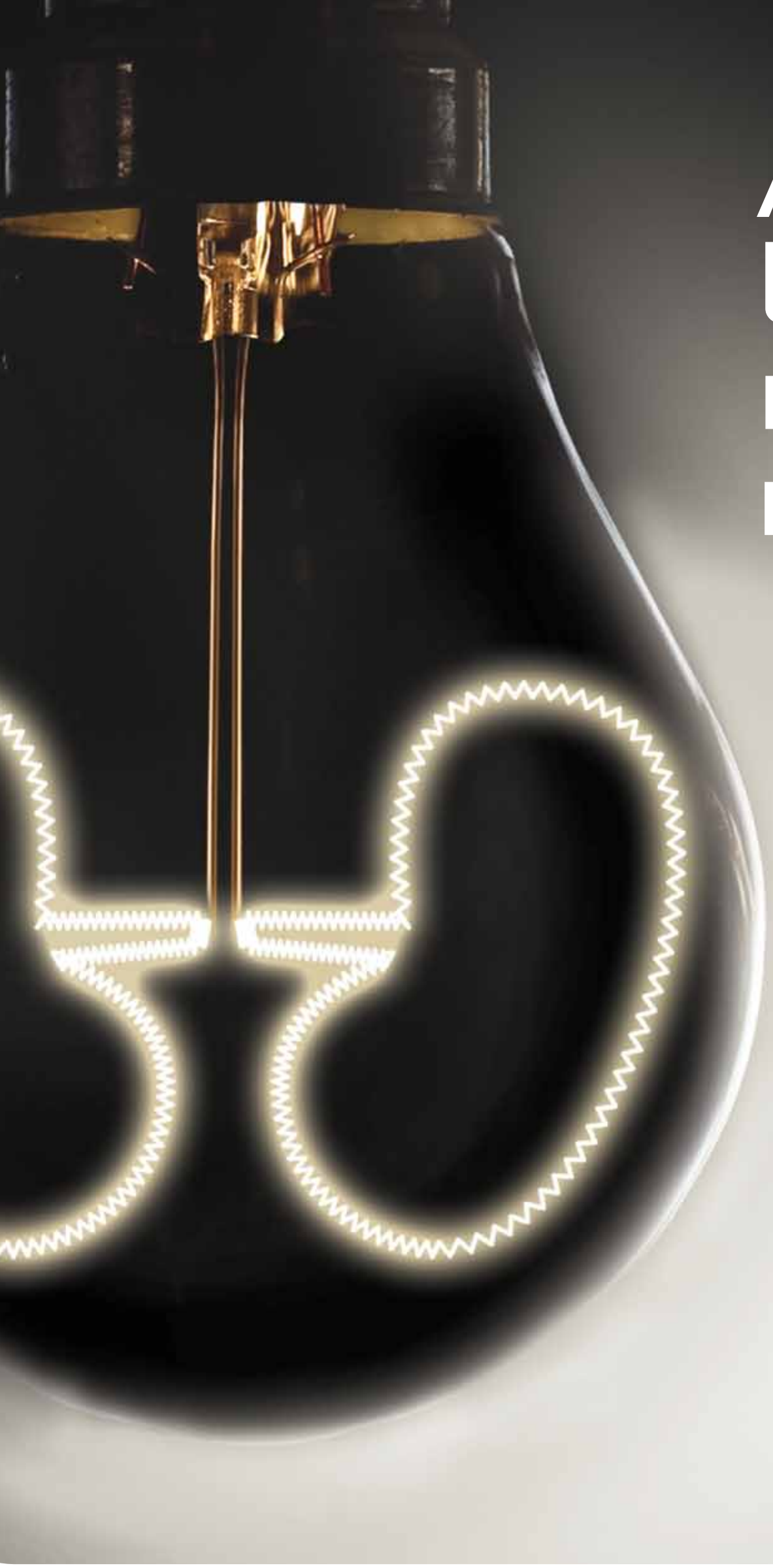
Now, two companies have produced a test that may help to solve the problem of detecting early rejection.

Graft-derived, cell-free DNA (GcfDNA) in the blood of transplant recipients is considered a potential biomarker for organ rejection. Previous attempts to determine GcfDNA levels, which required sequencing of both donor and recipient DNA, have been expensive, required a long turnaround, and also meant donor DNA specimens were necessary.

Chronix Biomedical researchers, along with research partner University Medical Center Göttingen, wanted to develop a new method that would address these drawbacks. As described by the team of scientists, the new method uses Bio-Rad Laboratories' Droplet Digital PCR (ddPCR) technology to overcome obstacles of earlier tests, which were both time-consuming and costly.

The new method reduces test time from 3 days or more to 1 day and cuts costs by 90 percent, the authors said. They were able to address the past need for donor DNA by preselecting single nucleotide polymorphisms (SNPs, small, comparable differences in sections of DNA) that ensure enough difference between donor and recipient DNA as to be detectable.

The method was presented at the American Association of Clinical Chemistry 2013 annual meeting.



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